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Original Research Article

A Prospective Study to Assess the Correlation between EVLWI and PVPI with the Severity of Lung Injury in Patients Admitted with Septic Shock in Intensive Care Unit

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Abstract

Aim: The aim of the present study was conducted in the Intensive Care Unit (ICU) of our institute, with an aim to assess the correlation between EVLWI and PVPI with the severity of lung injury in patients with septic shock.

Methods: The present study was conducted in the Department of Critical Care medicine (Anesthesiology), IGIMS, Patna, Bihar, India for 1 year .

Results: The chest radiograph scores from both radiologists strongly correlated with EVLWI ($r = 0.75$ and 0.70 for observers 1 and 2, respectively, $P < 0.0001$ for both observers). A moderate correlation between chest radiograph scores and PVPI was obtained ($r = 0.64$ and 0.60 for observers 1 and 2, respectively, $P < 0.0001$ for both observers). The chest radiograph scores from the two independent observers correlated strongly with each other ($r = 0.78$, $P < 0.0001$).

Conclusion: EVLWI and PVPI may have a prognostic significance in the assessment of lung injury in septic shock patients with ARDS. Further research is required to reveal the usefulness of EVLWI as an end point of fluid resuscitation in the management of septic shock with ARDS.

Keywords: Acute respiratory distress syndrome, critically ill patients, extravascular lung water, septic shock

Introduction

Extravascular lung water (EVLW) is the amount of water that is contained in the lungs outside the pulmonary vasculature. It corresponds to the sum of interstitial, intracellular, alveolar and lymphatic fluid, not including pleural effusions. [1] An increase in EVLW is the pathophysiological hallmark of hydrostatic pulmonary oedema and acute respiratory distress syndrome (ARDS). [2] EVLW is

also high in many septic shock [3] and critically ill [4] patients. For many years, this variable of paramount importance in the pathophysiology of critical illness could only be measured ex vivo. The emergence of transpulmonary thermodilution has opened up the area of EVLW investigation in the clinical setting.

The transpulmonary thermodilution technique provides an estimation of both EVLW and the pulmonary blood volume, and the ratio of these two parameters -the pulmonary vascular permeability index (PVPI) – has been shown to reflect the pulmonary microvascular permeability. [5,6]

A lot of critical conditions can be associated with the assemblage of lung water resulting in pulmonary edema. During systemic inflammation and sepsis, acute respiratory distress syndrome (ARDS), multiple trauma with severe blood loss, burns, pancreatitis, ischemia-reperfusion damage, and other conditions, the discharge of pro-inflammatory agents may increase pulmonary microvascular permeability and pressure, therefore, cause to fluid gathering in the lungs. [7-10] In contrast to hyperpermeability occurrences, increase in hydrostatic pressure in pulmonary circulation, during cardiac failure, is the main mechanism for edema. However, enhance in extravascular lung water index (EVLWI) is a common sign in both noncardiogenic and cardiogenic sources of airway edema.[7] Several categories of both pediatric and adults critically ill patients including anyone who has noncardiogenic or cardiogenic airway edema, extensive fluid shifts, and serious alternations in microvascular permeability have been shown to benefit from monitoring EVLWI.

Physiologically, there is a normal leakage of fluid and solutes from the pulmonary microvessels into the pulmonary interstitial tissue. Fluid and solutes do not reach the alveoli because of the tight junctions of the alveolar epithelium. This net outward fluid filtration from micro vessels to the interstitium is governed by Starling's law, which mainly includes the gradient of hydrostatic and oncotic pressures between the vascular and interstitial spaces and the filtration coefficient of the alveolocapillary barrier. [11,12]

While EVLW is the absolute amount of lung water measured, EVLWI is the ratio of EVLW with the patient's actual or predicted body weight to nullify the variation due to patient's anthropometric measures. The primary goal of septic shock management is maintenance of organ perfusion. [13] The conventional end points of resuscitation seldom include volumetric parameters. Parameters of fluid responsiveness cannot always guide us about the adequacy of fluid administration and adverse effects of over resuscitation.

The aim of the present study was conducted in the Intensive Care Unit (ICU) of our institute, with an aim to assess the correlation between EVLWI and PVPI with the severity of lung injury in patients with septic shock.

Materials and Methods

The present study was conducted in the Department of Critical Care medicine (Anesthesiology) , IGIMS, Patna, Bihar, India, for 1 year The study included 50 patients.

Inclusion & exclusion criteria

Following written informed consent, twenty critically ill patients between 20 and 60 years of age with an admission diagnosis of septic shock with or without ARDS with Acute Physiology and Chronic Health Evaluation II ≥20 requiring mechanical ventilation were included in this study. The exclusion criteria included pregnant patients, patients with coagulopathy (international normalized ratio >1.5 or platelet count <100,000 per cubic millimeters or both), history of pneumonectomy/lobectomy, peripheral

arterial disease, contraindication for femoral artery catheterization, patients with a diagnosis of deep vein thrombosis, and pulmonary embolism. None of our patients needed extracorporeal membrane oxygenation support.

Methodology

EVLW indexed to the predicted body weight, EVLWI, was measured by injecting 20 ml of ice-cold saline through the central venous catheter, through thermistor manifold three times, and the average of the three readings was noted. For this purpose, Volume View® and EV1000® Clinical Platform (Edwards Life Sciences, Irvine, California, USA) were used. Predicted body weight (in kilograms) was calculated as 0.91 (height in centimeters - 152.4) +50 for males or 0.91 (height in centimeters - 152.4) +45.5 for females. Central venous catheters were inserted through the right internal jugular vein, and catheter tip position in the lower part of superior vena cava was confirmed by chest radiograph (above carina and below sternoclavicular junction).

The anteroposterior chest radiographs were obtained along with the EVLW measurements. The radiographic exposure time was minimized to decrease motion artifacts, due to respiratory and cardiac motions. Two radiologists, who were blinded to the volumetric and oxygenation parameters, interpreted each of the radiographs. Each lung was divided into three zones – upper, lower, and perihilar zones. Each of the six zones was given a score from 0 to 65 as follows: 0 – normal, 10 – mild pulmonary vascular congestion, 20 – moderate pulmonary vascular congestion, 30 – severe pulmonary vascular congestion, 40 – interstitial edema without septal lines, 45 – interstitial edema with septal lines, 50 – mixed interstitial and alveolar edema, sparing some areas, 55 – mixed interstitial and alveolar edema, involving the entire lung zone, 60 – alveolar edema with sparing, and 65 – alveolar edema involving the entire lung zone. Summations of scores from the six zones, ranging from 0 to 390, were the final chest radiograph scores.[14]

Simultaneously with EVLWI measurements, PaO2:FiO2 and alveolar-arterial gradient of oxygen (AaDO2) were also recorded. AaDO2 was derived using alveolar gas equation (AaDO2= [FiO2* [Patm-PH2O]-PaCO2/R]-PaO2, Patm atmospheric pressure, 760 mmHg, PH2O – saturated water vapor pressure, 47 mmHg, R – respiratory quotient, PaO2 and PaCO2 - partial pressures of arterial oxygen and carbon dioxide as measured by arterial blood gas) while taking respiratory quotient as 0.8 for all measurements. EVLWI, PVPI, PaO2:FiO2, and AaDO2 were measured at least twice a day, and chest radiographs were obtained along with EVLWI measurements when clinically indicated. A total of 117 sets of EVLWI values with corresponding PaO2:FiO2 and AaDO2 readings were obtained for correlation. After rejecting three chest radiographs due to presence of pleural effusion, 64 chest radiographs were scored by the two radiologists and correlated with the corresponding EVLWI readings. Ninety-nine readings of PVPI were recorded and correlated with EVLWI, chest radiograph scores, PaO2:FiO2 ratio, and AaDO2.

Statistical analysis

In this study, we correlated between EVLWI and PVPI with chest radiograph scores and oxygenation parameters. Patients were grouped into ARDS and non-ARDS for subgroup analysis. Baseline parameters were described as mean ± 2* standard deviation or median (interquartile range). Normality of data was checked with D'Agostino-Pearson test. Correlation between variables was tested by Pearson's coefficient of correlation and graphed as scatter plots. Inter-observer agreement for the two chest radiograph scores was measured by Cohen's kappa test. The significance of each of the correlation coefficients was tested with Student's

t-test, and P < 0.05 was considered the cutoff for statistical significance. The statistical analysis was done using the statistical software MedCalc® (v.12.5.0.0) (Ostend, Belgium).

Results

Table 1: Baseline characteristics of study population

Baseline characteristics	n=50
Age	40 (25-50)
Male sex	30 (60%)
Medical vs post-surgical patients	40 vs 10
ARDS	20 (40%)
Baseline CI (ml/m2)	4.20±1.50
Baseline SVRI (dyne-s-m2/cm5)	1555.50±780.98
Baseline EVLWI (ml/kg)	14.4 (7.45-17.45)
Baseline PVPI	3.60 (2.7996-4.2404)
Baseline GEDI (ml/m2)	550.55±158.09
APACHE II score	20.9 (20-23.5)
SOFA score	11 (9-12)
MODS score	8 (6-10)
PaO2:FiO2 ratio	190.5 (100-262.5)
AaDO2	158.2 (121.15-364.45)
Chest Radiograph score (Observer 1)	190 (121-244)
Chest Radiograph score (Observer 2)	140 (23-228)
Thoracic Fluid Content	41 (28-47)
Mechanical ventilation requirement	20 (100%)
Baseline VT (ml/kg)	8 (6-8)
Baseline PEEP (cm H2O)	5 (5-7)

This study included twenty patients whose baseline parameters are summarized in Table 1. All patients were mechanically ventilated with lung protective ventilation with median baseline positive end-expiratory pressure of 5 cmH2O. Baseline parameters were found to be normally distributed (P > 0.05), but the distributions of the measurements used for correlation were not normal. Mean baseline EVLWI and PVPI were higher in ARDS patients, but the difference was not statistically significant (P > 0.05). Fifteen patients died during their ICU stay, four patients were successfully treated and shifted out to the ward. There was no statistically significant difference in mean EVLWI (P = 0.8581) and PVPI (P = 0.5744) between the two groups.

Table 2: Correlation coefficients and P values of correlation

		No. of values (n) EVLWI	Correlation coefficient (r)	P
EVLWI	Chest radiograph score (Observer 1)	64	0.75	<0.0001
EVLWI	Chest radiograph score (Observer 2)	64	0.70	<0.0001
EVLWI	PaO2/FiO2	117	-0.35	0.0003
EVLWI	AaDO2	117	0.30	0.0012
EVLWI	PVPI	99	0.85	<0.0001

PVPI	Chest radiograph score (Observer 1)	57	0.64	<0.0001
PVPI	Chest radiograph score (Observer 2)	57	0.60	<0.0001
PVPI	PaO2/FiO2	99	-0.40	0.0001
PVPI	AaDO2	99	0.34	0.0017

The chest radiograph scores from both radiologists strongly correlated with EVLWI (r = 0.75 and 0.70 for observers 1 and 2, respectively, P < 0.0001 for both observers). A moderate correlation between chest radiograph scores and PVPI was obtained (r = 0.64 and 0.60 for observers 1 and 2, respectively, P < 0.0001 for both observers). The chest radiograph scores from the two independent observers correlated strongly with each other (r = 0.78, P < 0.0001). There was a good inter-observer agreement between the two radiologists with a kappa value of 0.77 (95% confidence interval: 0.67–0.88). A moderately negative correlation was found between EVLWI and PaO2:FiO2 ratio (r = −0.32, P = 0.0004). The EVLWI values correlated moderately with AaDO2 values (r = 0.29, P = 0.0014) [Table 2].

Discussion

Although ARDS has been recognized as an acute, diffuse inflammatory lung damage resulting in enhanced pulmonary vascular permeability, loss of airway tissue, and increased lung weight, none of the proposed signs assessed the indication of ARDS, enhance in airway microvascular permeability. [15] Both American-European Consensus Conference definition and the Berlin definition may involve a wide range of respiratory deficiency without an addition in pulmonary microvascular permeability. Diagnosis of ARDS would be more realistic using more precise physiological indicators. EVLW is one probable marker and is associated to lung function and death in patients with sepsis. Increased EVLW suggests further diagnostic value for airway damage. Increased EVLW enhances the probability of death.

In this study, we tested the correlation between TPTD parameters (EVLWI and PVPI) and severity of lung injury in terms of oxygenation parameters. We also tried to assess pulmonary edema noninvasively by chest radiograph scoring, [14] and their correlation with EVLWI and PVPI measurements. EVLW was indexed to predicted body weight, instead of the actual body weight, as it has been found to be better reflective of the patient's prognosis.

Chest radiograph interpretation is often hindered by positioning of the patients and other conditions such as pleural effusion, consolidation, and atelectasis. Indeed, three chest radiographs were rejected due to the presence of pleural effusion in our study. Our rationale to correlate EVLWI values and chest radiograph scores is that chest radiographs are cheaper and easier to obtain. Previous studies where EVLWI was derived by single dye dilution14 or thermodilution (PiCCO®, Pulsion Medical System, Munich, Germany) technique3,16 also showed moderate correlation with chest radiograph scores similar to our findings.

The present study showed a moderate negative correlation between EVLWI and PaO2:FiO2 ratio. This finding was similar to the results of several previous studies. [16,17] We found a moderate correlation between EVLWI and AaDO2 as found in earlier studies [18,19] but in contradiction with the findings of a study [20] where double indicator dilution system was used.

Increases in EVLWI and PVPI are the indicators of common physiological derangements in septic shock and ARDS due to increased capillary leakiness which allows protein-rich fluid to escape through

the capillary endothelium. [21] PVPI is calculated as the ratio of EVLWI and PBV. This may explain the strong correlation between PVPI and EVLWI in our study. Clinical studies have shown significantly higher PVPI in ARDS than in hydrostatic pulmonary edema. [22] An increase in pulmonary vascular permeability leads to increased EVLW and hence decreased lung compliance. Alveolar flooding due to increased permeability causes intrapulmonary shunt-related hypoxemia. However, we found only a moderate correlation of PVPI with PaO2:FiO2 ratio and AaDO2.

In the subgroup analysis of patients with ARDS, we found a better correlation of EVLWI and PVPI with PaO2:FiO2 and AaDO2. This is a strong reflection of the innate pathophysiology of ARDS, where intrapulmonary shunting is a major contributor of hypoxemia as explained earlier. Whereas in non-ARDS patients along with sepsis-induced increased permeability, there are many other causes of hypoxemia including ventilation–perfusion mismatch. The above finding does not agree with the hypothesis of the negative effect of dead space ventilation, which is a part of ARDS pathophysiology, on the validity of TPTD parameters, but further studies with higher number of patients are needed to strengthen this fact. In an earlier study, Phillips et al. [23] reported lack of decrease in EVLW indexed to PBW (EVLWp) at maximum values of dead space ventilation. [24]

Earlier studies had found a good correlation between PVPI and prognosis of ARDS patients and it was established as an independent mortality indicator. In the present study, the base line EVLWI and PVPI were not different significantly. In 200 ARDS patients, Jozwiak et al. [22] had reported a poor predictive value of EVLWI on day-1 compared to the value on day-3 and EVLWI value reached maximum within 3 days on average. Similar to above findings, we had a good correlation between TPTD parameters and oxygenation indices among ARDS patients when all the measurements were taken into account.

Conclusions

Even though we have found a modest correlation of TPTD parameters with oxygenation, the correlation was significant in the subgroup of patients with ARDS. Thus, we conclude that EVLWI and PVPI may have a prognostic significance in the assessment of lung injury in septic shock patients with ARDS, and targeting fluid management towards decreasing EVLWI may improve oxygenation in patients with ARDS. Further studies with larger sample size are required to confirm these findings and to reveal the usefulness of EVLWI and PVPI as end points of fluid resuscitation in the management of septic shock with ARDS.

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