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Original Research Article

A Study to Assess how Effective Extravascular Lung Water Measurement is in Controlling Lung Damage in Critical Care Units

Ranjeet Kumar[1], Shashi kant[2]

[1]Assistant Professor, Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, India

[2]Assistant Professor, Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, India

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Corresponding author: Dr. Shashi kant
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Abstract

Aim: To evaluate the use of extravascular lung water measurement in managing lung injury in intensive care unit. **Methods:** This was a prospective observational study conducted in the Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, India for 12 months. 50 critically ill patients between 18 and 65 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. EVLW indexed to the predicted body weight, EVLWI, was measured by injecting 20ml of ice-cold saline through the central venous catheter, through thermistor manifold three times, and the average of the three readings was noted. Simultaneously with EVLWI measurements, PaO_2:FiO_2 and alveolar-arterial gradient of oxygen ($AaDO_2$) were also recorded. EVLWI values with corresponding PaO_2:FiO_2 and $AaDO_2$ readings were obtained for correlation. **Results:** Mean baseline EVLWI and PVPI were higher in ARDS patients, but the difference was not statistically significant ($P > 0.05$). 30 patients died during their ICU stay, 20 patients were successfully treated and shifted out to the ward. There was no statistically significant difference in mean EVLWI ($P = 0.81$) and PVPI ($P = 0.61$) between the two groups. The chest radiograph scores from both radiologists strongly correlated with EVLWI ($r = 0.69$ and 0.64 for observers 1 and 2, respectively, $P < 0.0001$ for both observers). A moderate correlation between chest radiograph scores and PVPI was obtained ($r = 0.57$ and 0.55 for observers 1 and 2, respectively, $P < 0.0001$ for both observers). **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: ICU, Mechanical Ventilation, Lungs.

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 and critically ill patients[3,4]. For many years, this variable of paramount importance in the pathophysiology of critical illness could only be measured ex vivo. The emergence of trans pulmonary thermodilution has opened up the area of EVLW investigation in the clinical setting. In 1994 the American Thoracic Society and the European Society of Intensive Care Medicine co-published the proceedings of a consensus conference on ARDS, and defined ALI and ARDS as an American-European Consensus Conference (AECC) definition[5,6]. Although many clinical trials performed after the publication of the proceedings used the AECC definition, this definition has been suggested to have various issues, including a lack of explicit criteria for defining what is acute, the sensitivity of the PaO_2/FiO_2 (P/F) ratio to different ventilator settings, poor reliability of the chest radiograph criterion, and difficulties distinguishing hydrostatic edema[7]. These criteria are also not sensitive predictors of disease severity and outcomes[8-10] because: the P/F ratio varies considerably across different FiO_2 levels, particularly when $FiO_2 < 0.5$, $PaO_2 > 100$ mmHg, or when the shunt fraction is low; many patients who initially fulfill the ARDS criteria might improve the P/F ratio > 200 mmHg after application of positive end-expiratory pressure for a short time or the use of higher FiO_2; and hypoxemia in ARDS may also be related to atelectasis or a low cardiac output. Based on these limitations, a novel definition has been proposed that takes into account the clinical and physiologic characteristics of ALI/ARDS[11].

During recent years, many studies have been dedicated to EVLW in the field of critical care and ARDS research. They have focused on the validation of its measurement and on its value for the characterisation of lung oedema, for the prognostic stratification of critically ill patients, for the evaluation of lung-targeted treatments and for the strategy of fluid management.

Material and Methods

This was a prospective observational study conducted in the Department of Anaesthesia, Netaji Subhas Medical College and Hospital, Bihta, Patna, India for 12 months.

Methodology

50 critically ill patients between 18 and 65 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.

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 0.89 (height in centimeters -152.6) +50 for males or 0.89 (height in centimeters -152.6) +45.7 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 peri hilar 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[12]. Simultaneously with EVLWI measurements, PaO_2:FiO_2 and alveolar-arterial gradient of oxygen ($AaDO_2$) were also recorded. $AaDO_2$ was derived using alveolar gas equation ($AaDO_2$= $[FiO_2 * [P_{atm}-P_{H_2O}]-PaCO_2/R]-PaO_2$, P_{atm} – atmospheric pressure, 760 mmHg, P_{H_2O} − saturated water vapor pressure, 47 mmHg, R – respiratory quotient, PaO_2 and $PaCO_2$ - 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, PaO_2:FiO_2 and $AaDO_2$ were measured at least twice a day, and chest radiographs were obtained along with EVLWI measurements when clinically indicated. A total of 135 sets of EVLWI values with corresponding PaO_2:FiO_2 and $AaDO_2$ 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, PaO_2:FiO_2 ratio, and $AaDO_2$.

Statistical analysis

We correlated between EVLWI and PVPI with chest radiograph scores and oxygenation parameters. Correlation between variables was tested by Pearson's coefficient of correlation. The significance of each of the correlation coefficients was tested with Student's t-test, and $P < 0.05$ was considered the cut-off for statistical significance.

Results

We included 50 patients whose baseline parameters show in Table 1. All patients were mechanically ventilated with lung protective ventilation with median baseline positive end-expiratory pressure of 5 cm H_2O. 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 ($P > 0.05$). 30 patients died during their ICU stay, 20 patients were successfully treated and shifted out to the ward. There was no statistically significant difference in mean EVLWI ($P = 0.81$) and PVPI ($P = 0.61$) between the two groups. One patient took leave against medical advice and was not included in any of the outcome groups.

The chest radiograph scores from both radiologists strongly correlated with EVLWI ($r = 0.69$ and 0.64 for observers 1 and 2, respectively, $P < 0.0001$ for both observers) (Table 2). A moderate correlation between chest radiograph scores and PVPI was obtained ($r = 0.57$ and 0.55 for observers 1 and 2, respectively, $P <$

0.0001 for both observers) (Table 2). The chest radiograph scores from the two independent observers correlated strongly with each other (r = 0.81, P < 0.0001). There was a good inter-observer agreement between the two radiologists with a kappa value of 0.74 (95% confidence interval: 0.71–0.91). A moderately negative correlation was found between EVLWI and PaO_2:FiO_2 ratio (r = −0.29, P = 0.0003) (Table 2). The EVLWI values correlated moderately with $AaDO_2$ values (r = 0.27, P = 0.0013) (Table 2). There was a moderate correlation between PVPI and PaO_2:FiO_2 (r = −0.42, P = 0.0001) and $AaDO_2$ (r = 0.29, P = 0.0012) (Table 2). However, there was a good correlation of EVLWI with PaO_2:FiO_2 (r = −0.69, P < 0.0001) and $AaDO_2$ (r = 0.62, P = 0.0001) among ARDS patients [Table 3]. PVPI among ARDS patients was better correlated with PaO_2:FiO_2 (r = −0.62, P = 0.0001) and $AaDO_2$ (r = 0.41, P = 0.0019) than non-ARDS patients [Table 3]

Table 1: Baseline characteristics of study population

Age	39.5 (27-53)
Male sex	30 (60%)
Medical vs post surgical patients	42 vs 8
ARDS	25 (50%)
Baseline CI (ml/m^2)	4.12±1.52
Baseline SVRI (dyne-s-m^2/cm^5)	1479.87±719.63
Baseline EVLWI (ml/kg)	13.9 (7.53-17.59)
Baseline PVPI	3.49 (2.82-4.25)
Baseline GEDI (ml/m^2)	532.69±161.11
APACHE II score	20.9 (21-24.6)
SOFA score	12(9-13)
MODS score	9 (5-11)
PaO :FiO ratio	187.29 (99-264.7)
$AaDO_2$	156.87 (120.97-365.13)
Chest Radiograph score (Observer 1)	182 (120-251)
Chest Radiograph score (Observer 2)	122 (22-230)
Thoracic Fluid Content	42(27-48)
Mechanical ventilation requirement	50 (100%)
Baseline V_T (ml/kg)	9 (6-9)
Baseline PEEP (cm H_2O)	6 (5-8)

Data are expressed as Mean±standard Deviation, or, Median (Interquartile range) or specified otherwise. EVLWI: Extravascular lung water index; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment score; MODS: Multiple Organ Dysfunction Score; PEEP: Positive end - expiratory pressure

Table 2: Correlation coefficients and P values of correlation

		No. of values (n)	**Correlation coefficient (r)**	***P***
EVLWI	Chest radiograph score (Observer 1)	66	0.69	<0.0001
EVLWI	Chest radiograph score (Observer 2)	66	0.64	<0.0001
EVLWI	PaO_2/FiO_2	121	-0.29	0.0003
EVLWI	$AaDO_2$	121	0.27	0.0013
EVLWI	PVPI	103	0.91	<0.0001
PVPI	Chest radiograph score (Observer 1)	61	0.57	<0.0001
PVPI	Chest radiograph score (Observer 2)	61	0.55	<0.0001
PVPI	PaO_2/FiO_2	101	-0.42	0.0001
PVPI	$AaDO_2$	101	0.29	0.0012

EVLWI: Extravascular lung water index; PVPI: Pulmonary Vascular Permeability Index

Table 3: Acute respiratory distress syndrome and non-acute respiratory distress syndrome subgroup analysis

	ARDS patients (N=21)	Non-ARDS patients (N=29)	P-value
Baseline EVLWI (ml/kg)	15.12±6.31	12.37±6.39	0.38
Baseline PVPI (%)	4.27±2.09	3.52±1.62	0.45
Correlation between EVLWI and PaO_2:FiO_2	*n*=47, r=0.68(*P*<0.0001)	*n*=69, r=0.21 (*P*=0.0397)	0.0021
Correlation between EVLWI and $AaDO_2$	*n*=47, r=0.62 (*P*<0.0001)	*n*=69, r=0.17 (*P*=0.21)	0.0007
Correlation between PVPI and PaO_2:FiO_2	*n*=38, r=0.62(*P*=0.0001)	*n*=62, r=0.31 (*P*=0.047)	0.0587
Correlation between PVPI and $AaDO_2$	*n*=38, r=0.41 (*P*=0.0019)	*n*=62, r=0.21 (P=0.11)	0.14

Baseline EVLWI and PVPI are expressed as Mean±standard deviation, *N*: Number of patients; *n*: Number of observations; r: Correlation coefficient; EVLWI: Extravascular lung water index; PVPI: Pulmonary vascular permeability index

Discussion

We studied 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[12] 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[13-16]. Though it is costly and cumbersome to initiate in critical care settings, measuring EVLWI by TPTD gives a repeatable quantitative measure of pulmonary edema that is sensitive to small changes in lung water[17]. Qualitative interpretation of chest radiographs by clinicians is susceptible to inter-observer variability and disagreement[18]. 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 dilution[12] or thermodilution (PiCCO®, Pulsion Medical System, Munich, Germany) technique[18,19] also showed moderate correlation with chest radiograph scores similar to our findings. The present study showed a moderate negative correlation between EVLWI and PaO_2:FiO_2 ratio. This finding was similar to the results of several previous studies[19,20]. We found a moderate correlation between EVLWI and $AaDO_2$ as found in earlier studies[21,22] but in contradiction with the findings of a study[23] 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[24]. 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[25]. 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 PaO_2:FiO_2 ratio and $AaDO_2$. In the present study, baseline EVLWI and PVPI were higher among ARDS patients than non-ARDS patients, but it was not statistically significant. This finding can be attributed to the confounding effect of sepsis and multiorgan dysfunction on the permeability and extravascular water content as all of our patients were in septic shock with multiorgan dysfunction. Indeed, in a previous study by Martin et al., 27% of patients with clinical ARDS never had raised EVLWI and 57% of patients with severe sepsis had raised EVLWI in the absence of clinical ARDS, suggesting an unrecognized form of lung injury as a part of multiorgan dysfunction that does not fulfill the Berlin definition[19]. This can be further supported by the findings of a previous study where EVLWI and PVPI were higher in patients with sepsis-induced multiorgan dysfunction syndrome than patients without. Statistically significant higher values were obtained on both days 1 and 3 in sepsis of pulmonary and non pulmonary origin, indicating the role of sepsis-induced increased permeability with or without ARDS[26]. In the subgroup analysis of patients with ARDS, we found a better correlation of EVLWI and PVPI with PaO_2:FiO_2 and $AaDO_2$. 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.[16] reported lack of decrease in EVLW indexed to PBW (EVLWp) at maximum values of dead space ventilation. Indices of oxygenation and EVLWI are independent predictors of ARDS with their own physiological importance. PVPI and EVLWI as independent predictors of mortality indicate different pathogenesis of ARDS. While PVPI quantifies the alveolocapillary barrier permeability, EVLWI measures the impact of this on pulmonary capillary leak[27]. Earlier studies had found a good correlation between PVPI and prognosis of ARDS patients and it was established as an independent mortality indicator[25] in the present study, the base line EVLWI and PVPI were not different significantly. In 200 ARDS patients, Jozwiak et al.[25] 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 Our study has some limitations. First, the sample size was relatively small. However, the measurements were done at several points on each patient to provide adequate power. This could have led to bias which can be prevented by a larger sample size. Second, there may be concerns regarding the reliability of TPTD in severe ventilation–perfusion mismatch hampering access to the poorly perfused pulmonary vascular bed[28]. Third, even though we excluded three chest radiographs due to evident pleural effusion, we could not use ultrasound or CT scan to rule out minimal pleural effusion. Fourth, due to small study population, we could not assess the prognostic value of EVLWI in terms of mortality outcomes and the impact of negative fluid balance aiming at reduction of EVLWI on oxygenation and other

physiologic variables. Lastly, fluid balance could not be recorded in a protocolized manner due to increased physician and nursing workload.

Conclusion

According to the findings of this investigation, EVLWI and PVPI may have predictive value in the evaluation of lung damage in septic shock patients with ARDS. More study is needed to determine the use of EVLWI as a fluid resuscitation endpoint in the therapy of septic shock with ARDS.

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