

## Comparison of lung ultrasound with transpulmonary thermodilution in assessing extra-vascular lung water

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**Background:** Increased extra-vascular lung water (EVLW) is common in critical care and correlates with the severity of acute lung injury, length of intensive care unit stay and mortality. Lung ultrasound (LUS) can assess EVLW by determining the amount of 'B-lines': artefacts signifying alveolar-interstitial oedema. This study's aim was to determine whether EVLW estimation with the help of LUS correlates with the more accurate PiCCO<sub>2</sub><sup>®</sup> cardiac output system utilising transpulmonary thermodilution.

**Methods:** This prospective observational study was undertaken at Universitas Academic Hospital, Bloemfontein. Patients were scanned according to a fixed protocol, followed by transpulmonary thermodilution. The cumulative B-line count was compared with the EVLW index generated by the PiCCO<sub>2</sub><sup>®</sup> system.

**Results:** Four males and six females were enrolled. The mean EVLW index was 9.1 ml/kg/m<sup>2</sup> (standard deviation 1.45), and the median cumulative B-line count was 14 (interquartile range 6–25). A positive, but not statistically significant, correlation was found ( $r = 0.40$ ,  $p = 0.25$ ) between the B-line count and EVLW index.

**Conclusion:** This study investigated a possible correlation between LUS interpretation and transpulmonary thermodilution in assessing EVLW. Results seem promising, but the small sample could indicate only that LUS might be of use for the assessment of EVLW. Further studies are needed.

**Keywords:** B-lines, critical care, extra-vascular lung water, lung ultrasound, thermodilution

### Introduction

Extra-vascular lung water (EVLW) refers to the amount of fluid within the lungs but outside the vascular compartment. Increased EVLW is frequently observed in critical care patients, often associated with various pulmonary conditions as well as cardiac and renal disease. It can be thought of as a marker of pulmonary congestion, not just haemodynamic congestion. Increased EVLW has been linked to worse patient outcomes, increased intensive care unit (ICU) length of stay and ICU mortality.<sup>1</sup> There are also recent reports that EVLW estimation may be used as a prognostic risk stratification tool in patients presenting with dyspnoea and/or chest pain syndromes in the emergency department.<sup>2</sup> In clinical settings EVLW can be estimated by physical examination, imaging (chest radiography (CXR), chest computerised tomography (CT), or lung ultrasound (LUS)), or by invasive cardiac output (CO) monitoring utilising transpulmonary thermodilution.

The clinical estimation of increased EVLW is affected by transmitted sounds during auscultation and significant inter-observer variation. One study reported a diagnostic accuracy of only 55% for alveolar-interstitial syndrome (equivalent to raised EVLW).<sup>3</sup> As such, imaging modalities are usually employed in quantifying EVLW.

Chest radiography is frequently performed in the critical care setting but, although easily accessible, it lacks the sensitivity to provide an adequate indication of EVLW (75% accuracy vs. 93% for LUS).<sup>3</sup> A Greek study showed significant accuracy rates for LUS when compared with CXR.<sup>4</sup> This finding can also be extrapolated to other pulmonary diagnoses, such as pneumonia, where there

was a 60% versus 95% sensitivity rate in favour of LUS.<sup>5</sup> The reason for this poor sensitivity in the critical care setting is largely technical and includes factors such as patient rotation, the supine position, and an X-ray beam originating anteriorly at a shorter distance than recommended. Inter-observer variability also remains a major problem. Lichtenstein *et al.*<sup>3</sup> reported that in more than a third of cases chest radiographic images remain suboptimal and expose the patient to a small but cumulative amount of ionising radiation.

Chest CT is regarded as the diagnostic gold standard in the assessment of EVLW, having been compared with lung gravimetry (the experimental gold standard) and the pulmonary artery catheter. Unfortunately, it is costly, requires transportation to a radiology suite and exposes patients to significant amounts of ionising radiation, with or without contrast media. Repeatability remains a major problem, and as a result the response to treatment cannot be ascertained by this method alone. In a recent pilot study, a statistically significant correlation between LUS and CT assessment of lung water was found.<sup>6</sup>

Lung ultrasound in the critical care setting is becoming more prevalent, assisting in decision-making regarding diagnosis, fluid therapy and ventilation strategies. The review by Ashton-Cleary<sup>7</sup> compared LUS with CXR and CT in the diagnosis of common pulmonary conditions (pleural effusion, pneumothorax, increased EVLW and consolidation) and found that, in expert hands, diagnostic thoracic ultrasonography proved just as effective as the other modalities. It offers the advantage of real-time bedside monitoring, reproducibility, and does not expose patients to ionising radiation.

An increase in EVLW is diagnosed by the amount of B-lines (Figure 1) seen while scanning. First described in 1994, B-lines are defined as 'discrete laser-like vertical hyperechoic reverberation artefacts that arise from the pleural line, extend to the bottom of the screen without fading, and move synchronously with lung sliding'.<sup>8</sup> B-lines have replaced the historical 'ultrasound-lung rockets' and 'comet-tail artefacts' and are significant when three or more<sup>9</sup> are noted per scanning site. In one study, 27% of healthy subjects had up to two B-lines in the last lateral intercostal space below the diaphragm.<sup>10</sup> In another study, the presence of B-lines resulted in a sensitivity of 85.7%, and specificity of 97.7% for the diagnosis of radiological alveolar-interstitial syndrome.<sup>11</sup> B-lines have also been compared with gravimetry in assessing lung water. Jambrik *et al.*<sup>12</sup> showed in a porcine acute lung injury/acute respiratory distress syndrome (ALI/ARDS) model that B-lines correlate very well ( $r = 0.91$ ,  $p < 0.001$ ) with the wet/dry ratio obtained by gravimetry. Lung ultrasound is also increasingly used for the evaluation of oxygenation and ventilation, i.e. evaluating the degree of positive end-expiratory pressure (PEEP),<sup>13</sup> alveolar consolidation<sup>14</sup> and to assess weaning failure.<sup>15,16</sup> An Italian group recently described a correlation between  $\text{PaO}_2/\text{FiO}_2$  and the number of B-lines seen.<sup>17</sup> In an observational controlled study evaluating over 300 patients, Peris *et al.*<sup>18</sup> found that the routine use of LUS in the critical care setting was associated with a significant reduction in the number of CXR and CTs performed. Automated B-line scoring software is now being tested in clinical practice to eliminate human error or bias.<sup>19</sup>

The limitations of LUS are the same as for any emerging point-of-care imaging modality; it is heavily dependent on operator skill and there is a relative lack of well-defined institutional diagnostic criteria. Lung ultrasound, however, is much easier to perform than, for example, abdominal ultrasound or echocardiography. There are a number of conditions that make LUS and the analysis of B-lines challenging, including thoracic trauma, extensive dressings, pneumothorax and major subcutaneous emphysema.<sup>9</sup>

The PiCCO<sub>2</sub><sup>®</sup> system (Pulsion Medical Systems SE, Feldkirchen, Germany) combines pulse contour analysis with transpulmonary thermodilution to determine a number of parameters, one of which is the EVLW index (ELWI). It requires both a specialised arterial line and a central venous cannula. It has been shown to



Figure 1: B-lines in a LUS image taken with the Samsung® Medison UGEO PT60A ultrasound system used in the local clinical imaging setting.

be accurate and reliable in comparison with other CO monitors, and the gold standard of CO monitoring, the pulmonary artery catheter (PAC).<sup>20,21</sup> The PiCCO<sub>2</sub><sup>®</sup> system is less invasive than the PAC, equating to fewer complications. Studies showed that patients managed with a PiCCO<sub>2</sub><sup>®</sup> have lower morbidity rates and length of ICU stay when compared with patients managed with a PAC,<sup>22</sup> while others suggest no particular benefit.<sup>23</sup> There is good evidence, however, that the PiCCO<sub>2</sub><sup>®</sup> system outperforms the older type CO monitors, such as the FloTrac™ (Edwards Lifesciences Corp, Irvine, USA).<sup>21</sup> Despite this, the search for a consistently reliable method to assess a patient's fluid status in the critical care set-up is still ongoing.<sup>24</sup> There are a number of circumstances where the measurements may be inaccurate though. These include significant intracardiac shunts, aortic stenosis, aortic aneurysmal disease, pneumonectomy and during extra-corporeal circulation.<sup>20</sup>

Currently, at the multidisciplinary unit in Universitas Academic Hospital, EVLW is estimated based on physical examination and routine CXR. Chest CT is performed only if additional pathology, such as pulmonary embolism or trauma, is suspected. At Universitas Academic Hospital, LUS is only occasionally used for diagnosing and treating pleural effusions. Even though invasive CO monitoring provides intensivists with accurate information regarding a patient's fluid status, not all critical care patients qualify for its use due to limited resources.

### Objectives

The aim of this study was to explore whether a non-invasive, cost-effective technique such as LUS can accurately estimate EVLW when compared with minimally invasive CO monitoring in a resource-limited setting.

### Methods

This project was structured as a prospective observational study, conducted at a multidisciplinary ICU at Universitas Academic Hospital in Bloemfontein. The hospital receives patients from the Free State, Northern Cape and parts of the Eastern Cape. The multidisciplinary ICU at Universitas Academic Hospital is a six-bed unit and has an admission rate of approximately 20 to 25 patients per month. Ten patients were included in the study, and data were collected over a three-month period (June 2014 to August 2014). Patients older than 18 years and scheduled for an arterial line replacement (either due to malfunction, or if the existing arterial line was suspected of being an infective focus) were eligible for inclusion in the study.

Informed consent was obtained from the patient or a legally authorised representative. Exclusion criteria were patients who lacked informed consent, LUS not possible (severe thoracic trauma, burns), patients who lacked a central venous catheter (CVC), and the moribund or haemodynamically unstable patient. Patients with significant intracardiac shunts, aortic aneurysms, aortic stenosis, pneumonectomy, macro lung embolism, intra-aortic balloon pumps, and undergoing extracorporeal circulation were also excluded, as these are contraindications for PiCCO<sub>2</sub><sup>®</sup> monitoring.

Data collected included age, gender, length of ICU stay, height and weight. The admission diagnosis and ventilator settings were also noted (PEEP, mean and peak airway pressures [ $\text{Mean}_{\text{aw}}$  and  $\text{Peak}_{\text{aw}}$ ], tidal volume [ $V_T$ ] and inspired oxygen concentration [ $\text{FiO}_2$ ]).

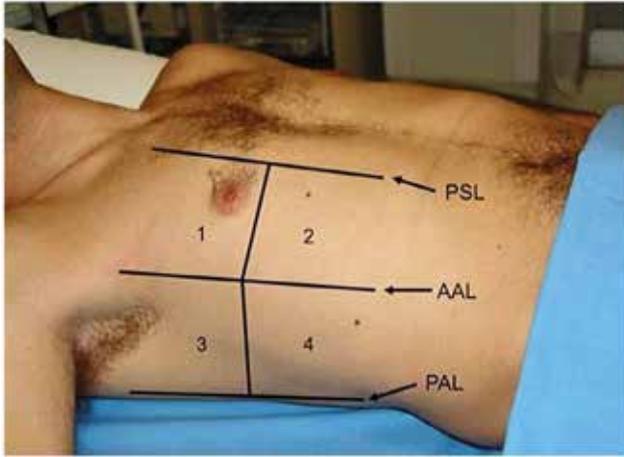


Figure 2: Volpicelli's zones<sup>8</sup> (used with permission).

All patients were scanned by one researcher trained in point-of-care ultrasonography. A Samsung<sup>®</sup> Medison UGEO PT60A ultrasound system equipped with a LN5-12 Linear (8.5 MHz) and a C2-5 Convex (3.35 MHz) probe (Samsung Medison Co, Seoul, South Korea) was used for arterial cannulation and lung scans, respectively. The chest was scanned for B-lines according to international evidence-based recommendations for point-of-care lung ultrasound (Figure 2). The sonographic images were analysed, and an average cumulative B-line score was calculated for each patient. The examination did not interfere with routine ICU care, and did not last for more than 20 minutes.

A 5F thermistor-tipped arterial PiCCO<sub>2</sub><sup>®</sup> catheter was then placed within two hours of the lung scan, after confirming that the existing arterial line was scheduled for replacement. This procedure was performed aseptically and under direct ultrasound guidance according to good clinical practice. After the necessary calibration checks were performed, a bolus of 15 ml of iced saline was injected in the CVC, while the resultant drop in temperature was analysed by the arterial catheter. The mean of three consecutive boluses was used. The following parameters were obtained: cardiac index (CI), ELWI, systemic vascular resistance index (SVRI) and stroke volume variation (SVV). The arterial catheter then remained *in situ* for the continued use of the critical care physicians. Typically, patients with femoral CVCs will have false elevated global end-diastolic volume (GEDV) and intra-thoracic blood volume (ITBV) readings by approximately 75 ml. It is worth noting that the location of the CVC has no effect on the EVLW readings.<sup>25</sup>

Data were analysed by the Department of Biostatistics, Faculty of Health Sciences, University of the Free State. The comparison between the cumulative B-line scores and PiCCO<sub>2</sub><sup>®</sup> ELWI values was then performed using Pearson correlations. Because of the small sample size, 95% confidence intervals (CI) are also provided.

Institutional ethics approval was obtained (ECUFS NO 64/2014), and the study was registered at the South African National Health Research Ethics Council (DOH-27-1014-478).

## Results

Ten patients (four male, six female) were enrolled in this study, and there were no withdrawals. Patient characteristics are outlined in Table 1. Patient height was measured by the researchers, and weight was obtained from an averaged value as

Table 1: Patient characteristics

Measurement	Range	$\bar{X}$ with 95% CLs	SD
Age (years)	26–64	37.8   47.2   56.6	13.13
Weight (kg)	60–100	70.0   78.7   87.3	12.04
Height (cm)	155–185	163.3   170.5   177.7	10.12
Average ICU stay (days)	0–39	3.5   11.8   20.3	11.81

Notes: SD = standard deviation;  $\bar{X}$  = mean; CL = confidence limits.

the critical care beds do not have a weighing function. Estimating patient weight in critical care is difficult, and despite various anthropometric equations, many units still use the averaged value.<sup>26</sup> The median number of days spent in ICU was 6.5.

A summary of working diagnoses at the time of investigation is shown in Figure 3. The most common diagnoses were sepsis and hypertension. Sepsis was diagnosed according to current Surviving Sepsis Campaign<sup>®</sup> guidelines.<sup>27</sup>

The values derived from the PiCCO<sub>2</sub><sup>®</sup> system are shown in Table 2. The mean cardiac index was 3.65 l/min/m<sup>2</sup>, while the mean SVRI was 1 969.1 dynesec/cm<sup>5</sup>/m<sup>2</sup>. The EVLW estimate was also indexed to body weight, resulting in a mean of 9.1 ml/kg/m<sup>2</sup>.

One of the inclusion criteria was that patients needed to be ventilated as data based on pulse contour analysis become less accurate in spontaneously breathing patients. Synchronised intermittent mandatory ventilation (SIMV-VC) was the preferred

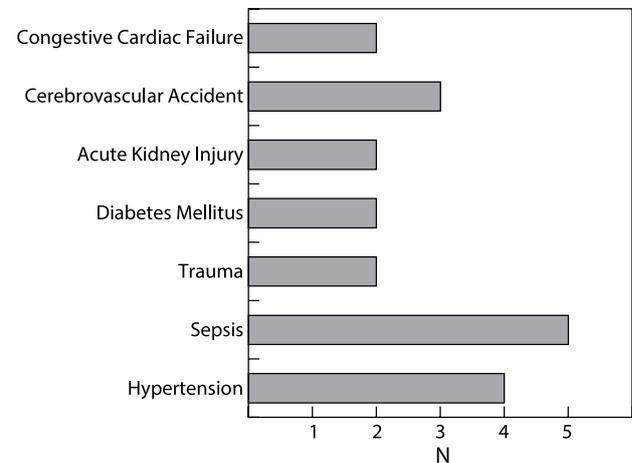


Figure 3: Working diagnoses of the patients at the time of investigation.

Table 2: PiCCO<sub>2</sub><sup>®</sup> measurements

Measurement	PiCCO <sub>2</sub> <sup>®</sup> ranges	$\bar{X}$ with 95% CLs	SD
Cardiac index (l/min/m <sup>2</sup> )	1.72–6.30	2.7   3.65   4.6	1.36
Extra-vascular lung water index (ml/kg/m <sup>2</sup> )	7–12	8.1   9.1   10.1	1.45
Systemic vascular resistance index (dynesec/cm <sup>5</sup> /m <sup>2</sup> )	1184–3353	1493.2   1969.1   2445.0	665.26
Stroke volume variation (%)	3–26	4.1   9.6   15.1	7.14

Notes: SD = standard deviation;  $\bar{X}$  = mean; CL = confidence limits.

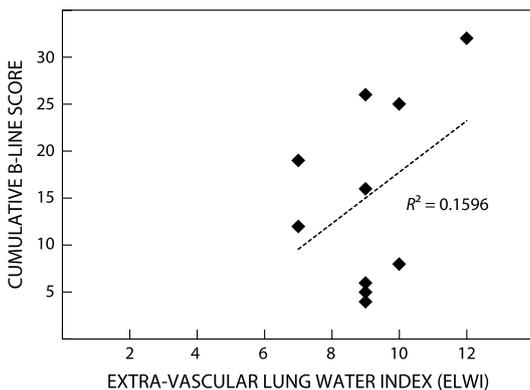


Figure 4: Correlation between extra-vascular lung water index (ELWI) and B-line scores.

mode of choice with a mean PEEP of 10 cmH<sub>2</sub>O (95% CI: 8.2–11.8) and mean Peak<sub>aw</sub> of 22.5 cmH<sub>2</sub>O (95% CI: 17.8–27.3).

The cumulative B-line count was an aggregate of the number of B-lines seen in the eight Volpicelli zones, four over each hemithorax. B-line counts of less than three per scanning zone were considered normal. A confluent image (due to frank pulmonary oedema) was noted as 10 B-lines, which is thus the maximum count per scanning zone. This occurred in only one patient's scan. The cumulative B-line count ranged from 4 (already above normal) to 32, with a median of 14 (95% CI 5–26; interquartile range (IQR) 6–25). The correlation between the B-line count and the EVLW was 0.40 ( $p = 0.25$ ; 95% CI –0.31–0.82) (Figure 4). While this is a moderate correlation, it was not statistically significant.

## Discussion

To our knowledge, this is the first South African study comparing LUS with transpulmonary thermodilution in the assessment of EVLW. The first international trial evaluating these modalities was performed by Agricola *et al.*<sup>28</sup> They enrolled 20 post-cardiac surgery patients and compared a 'comet score' (cumulative) with wedge pressure, chest radiography and PiCCO<sub>2</sub><sup>®</sup>. They found a statistically significant positive linear correlation ( $r = 0.42$ ;  $p = 0.01$ ) between the comet score and the ELWI generated by transpulmonary thermodilution. It should be noted, though, that even in their study, the 95% CI for the correlation ranged from a very weak correlation (0.18) to a moderately strong correlation (0.61), and thus the uncertainty about this remains. An Italian group investigated the relationship of B-lines and pulmonary artery occlusion pressure as well as EVLW.<sup>29</sup> They also found a linear correlation, but they focused more on the evaluation of haemodynamic congestion, not pulmonary congestion. Our study reiterated the positive correlation ( $r = 0.40$ ;  $p = 0.25$ ), although it did not prove to be statistically significant. The lack of significance may be affected by two factors: the small sample size, and the restriction of range caused by having very few low B-line scores (none within the normal range) and no low EVLW values.

Repeat CXR and CT imaging remain the cornerstone in diagnosing pulmonary conditions. In the past 20 years, LUS has become increasingly popular in critical care, cardiology and emergency departments. There is a growing body of evidence that LUS is more accurate than clinical examination and CXR, equally as sensitive as CT and, recently, comparable with invasive CO monitoring, whether by the PAC or the PiCCO<sub>2</sub><sup>®</sup>. Various protocols<sup>8,30–33</sup> for diagnosing pneumothorax, interstitial syndrome and consolidation have been published, and it would

seem prudent to implement these in our critical care units. Without a doubt, LUS has a steep learning curve, but in resource-limited settings it should seriously be considered as a viable, cost-effective and safe diagnostic instrument.

## Limitations

Sponsorship could only be obtained for 10 thermistor-tipped catheters (together with the monitor itself); this resulted in a small sample size. While this is problematic, it is not, in absolute terms, much smaller than other studies (e.g. Agricola *et al.*<sup>28</sup>). Furthermore, the correlation found may have been weakened by the restriction in range, but conducting a study as invasive as this on healthy patients so as to extend the range of measurements obtained would be ethically questionable, as well as extremely costly. The results, however faint they may be, should then be seen in this context and not slighted because of the practical limitations on the size of the sample.

Another limitation was the possibility of intra-observer and inter-observer variability when assessing the lung scans for B-lines. In the near future, software capable of automated B-line counting may be available worldwide, which would standardise the practice.

The ELWI takes predicted body weight into account and we used an averaged value. This practice, although not ideal, is performed in many units worldwide where there are no beds capable of weighing functions. This may have affected the results of the study, although the precise effect would be impossible to determine, and the practical difficulties involved with obtaining accurate weights for these patients dictates that, under the circumstances, this was the best course of action to follow.

## Conclusion

Our aim was to investigate the correlation between LUS and CO monitoring utilising transpulmonary thermodilution, two modalities not frequently used in local critical care units. Recent literature indicates that the measurement of EVLW is an important prognostic indicator and this needs to be assessed in every critical care patient. The role of minimally invasive CO monitors has grown in this field, but unfortunately proves to be limited by excessive cost. Therefore in a resource-limited facility, not all patients can be monitored with this modality.

In conclusion, this study has shown that the assessment of EVLW using LUS may correspond with the PiCCO<sub>2</sub><sup>®</sup> system. However, studies using larger samples, which include patients with 'normal' values, are needed to support this statement.

**Acknowledgements** – Ms E. le Roux (Tau Medical<sup>®</sup>) for the sponsorship of the 10 arterial catheters and the PiCCO<sub>2</sub><sup>®</sup> monitor. Mr S. Cole (SSEM Mthembu<sup>®</sup>) for providing the ultrasound equipment. Ms S. Sefatsa for the setting up of equipment, monitoring and logistics. The medical and nursing staff of the ICU at Universitas Academic Hospital, Bloemfontein, who ultimately care for the patients. Ms T. Mulder, medical editor, School of Medicine, University of the Free State, for technical and editorial preparation of the manuscript.

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Received: 26-11-2015 Accepted: 20-07-2016