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Original Article

Measurement of extravascular lung water to diagnose severe reperfusion lung injury following pulmonary endarterectomy: a prospective cohort clinical validation study*

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Summary

The measurement of extravascular lung water is a relatively new technology which has not yet been well validated as a clinically useful tool. We studied its utility in patients undergoing pulmonary endarterectomy as they frequently suffer reperfusion lung injury and associated oedematous lungs. Such patients are therefore ideal for evaluating this new monitor. We performed a prospective observational cohort study during which extravascular lung water index measurements were taken before and immediately after surgery and postoperatively in intensive care. Data were analysed for 57 patients; 21 patients (37%) experienced severe reperfusion lung injury. The first extravascular lung water index measurement after cardiopulmonary bypass failed to predict severe reperfusion lung injury, area under the receiver operating characteristic curve 0.59 (95% CI 0.44–0.74). On intensive care, extravascular lung water index correlated most strongly at 36 h, area under the receiver operating characteristic curve 0.90 (95%CI 0.80–1.00). Peri-operative extravascular lung water index is not a useful measure to predict severe reperfusion lung injury after pulmonary endarterectomy, however, it does allow monitoring and measurement during the postoperative period. This study implies that extravascular lung water index can be used to directly assess pulmonary fluid overload and that monitoring patients by measuring extravascular lung water index during their intensive care stay is useful and correlates with their clinical course. This may allow directed, pre-empted therapy to attenuate the effects and improve patient outcomes and should prompt further studies.

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Introduction

Chronic thromboembolic pulmonary hypertension is a complication of pulmonary embolism, leading to precapillary pulmonary hypertension and right heart failure [1]. Surgical pulmonary endarterectomy is recognised as the definitive treatment and, in higher volume centres, operative mortality is below 5% [2]. Reperfusion lung injury (RLI) is common in pulmonary endarterectomy patients and has been identified as an important cause of postoperative morbidity and mortality [3, 4]. Reperfusion lung injury results in high permeability pulmonary oedema occurring with varying severity in 10–40% of patients [2–7]. Reperfusion lung injury is defined by arterial partial pressure of oxygen to inspired fraction of oxygen ratio (PaO_2/F_IO_2 ratio) < 39.9 kPa and opacity on chest radiography [4]. Patients with pulmonary vascular resistance (PVR) > 1000 dynes.s.cm^{-5} have a higher morbidity and mortality risk and there is a greater risk of RLI if the fall in PVR after endarterectomy is substantial [5, 6]. In its most severe form, RLI can present as profound hypoxaemia and is associated with significant increases in duration of invasive mechanical ventilation, length of intensive care unit (ICU) stay and mortality [5, 8]. Early prediction of severe RLI and directed therapy may diminish its negative effects on patient outcome and allow patients without risk of severe RLI to progress to earlier tracheal extubation and discharge from ICU.

Extravascular lung water (EVLW) is promising as an early marker of pulmonary oedema and may offer a timely therapeutic target. It is the amount of water contained in the lungs outside the pulmonary vasculature: the sum of interstitial, alveolar, intracellular and lymphatic fluid, except pleural effusions [9]. However, it has not yet been well validated peri-operatively and its clinical utility is poorly understood. Extravascular lung water indexed to predicted body weight (EVLWi) has been identified as an early indicator of lung injury in severe sepsis and a marker of disease severity in patients with established acute respiratory distress syndrome (ARDS) [10–12]. It has been correlated with late markers of ARDS such as PaO_2/F_IO_2 ratio, lung injury scores and radiographic pulmonary infiltrates [13, 14]. Recent studies have demonstrated that the maximum value of EVLW during episodes of high permeability pulmonary oedema independently predicts 28-day mortality [15–17]. In critically ill adults with systemic inflammatory response syndrome and shock, EVLW measured early in the course of disease correlates with pulmonary function, and the combination of EVLW and diagnosis of lung injury increases the post-test odds of ICU mortality [18].

We decided to assess the value of high peri-operative EVLWi in predicting clinically significant (severe) RLI. We also investigated the correlation between EVLWi and PaO_2/F_IO_2 ratio, duration of invasive mechanical ventilation, ICU and hospital length of stay and in-hospital mortality. We studied patients undergoing pulmonary endarterectomy because RLI is common after this surgery and therefore offers a model for validating EVLWi clinically.

Methods

We performed a prospective observational cohort study of all patients undergoing pulmonary endarterectomy at Royal Papworth Hospital, UK. National Research Ethics Committee approval was obtained before study commencement. Patients were considered eligible if over the age of 18 years, undergoing elective pulmonary endarterectomy surgery and managed as part of an established protocol at Royal Papworth Hospital, including patients undergoing a combined procedure with coronary artery bypass grafting. Patients requiring peri-operative mechanical circulatory support (intra-aortic balloon pump, veno-arterial extracorporeal membrane oxygenation or veno-venous extracorporeal membrane oxygenation) were excluded. Written consent was obtained before study enrolment.

Anaesthetic and surgical techniques were not affected by patient participation in the study and were standardised according to a local protocol. Anaesthesia was induced with midazolam, fentanyl and propofol, and pancuronium administered for neuromuscular blockade. Maintenance of anaesthesia was by continuous propofol infusion. Doses were titrated to clinical requirement at the discretion of the anaesthetist. Patient monitoring followed a standardised protocol that included insertion of a central venous catheter, pulmonary artery flotation catheter, a radial artery catheter and a thermistor-tipped catheter placed in the femoral artery (Edwards Lifesciences, Irvine, CA, USA). The femoral arterial catheter data were displayed and recorded as part of the routine anaesthetic monitoring. For the study, this was spliced to supply data to the VolumeView$^{(TM)}$ system (Edwards Lifesciences, Irvine, CA, USA), which was used solely for EVLW measurements.

Mechanical ventilation of the lungs was commenced during the rewarming phase after deep hypothermic circulatory arrest. A peri-operative lung-protective strategy (tidal volumes of 5 ml.kg^{-1} predicted body weight and low peak airway pressure) was targeted in the protocol [19]. On completion of surgery, patients were transferred to the ICU. Postoperative ventilatory, circulatory and fluid management was protocolised for the first 48 h. The

pulmonary artery and femoral arterial catheters were removed on the morning of the second postoperative day.

Thermodilution measurements were performed by injection of 20 ml cold saline (< 8 °C) into a central vein in the superior vena cava territory. The VolumeView system was used to provide EVLWi measurements, using the average of three consecutive injections. VolumeView uses the slope of the transpulmonary thermodilution curve to calculate intrathoracic fluid volume and intrathoracic blood volume. The difference between these volumes is the EVLW, and is explained in greater detail elsewhere [20]. The value of EVLWi considered normal was < 7 $ml.kg^{-1}$ of predicted body weight [21]. A pre-operative EVLWi measurement was conducted after induction of anaesthesia but before sternotomy. Subsequent measurements were made after discontinuation of cardiopulmonary bypass at sternal wound closure and at 2 h, 4 h, 6 h, 12 h, 24 h, 36 h and 40 h after sternal wound closure. The majority of patients were discharged from the ICU on the second postoperative day, precluding a 48-h measurement. Chest radiographs on the second postoperative day were evaluated by an experienced radiologist (BA).

Pre-operative PVR, right ventricular function, cardiopulmonary bypass time, aortic cross-clamp time, and deep hypothermic circulatory arrest time were recorded. Arterial blood gases and F_IO_2 were recorded together with duration of mechanical lung ventilation (including non-invasive ventilation).

The primary objective was to evaluate EVLWi after discontinuation of cardiopulmonary bypass at sternal wound closure as a predictor of severe RLI. Severe RLI was defined as opacity on chest radiograph in a reperfused lung region, severe hypoxaemia (PaO_2/F_IO_2 ratio < 39.9), in keeping with the Berlin Criteria stratifying severe hypoxaemia in ARDS [22]) and no other identified cause for severe hypoxaemia. Secondary objectives included the correlation between EVLWi and worst PaO_2/F_IO_2 ratio, duration of mechanical ventilation, ICU length of stay, hospital length of stay and in-hospital mortality.

Comparison for pairs of continuous variables was performed using a two-tailed Student's t-test or a Wilcoxon test, as appropriate. Pearson's coefficient was used to measure correlation between variables. For every time-point, the area under the receiver operating characteristic curve (AUC) was used to evaluate each EVLWi measure's ability to classify patients according to the development of severe RLI. We report the cut-point that optimises each EVLWi measure's differentiating ability when equal weight is given to sensitivity and specificity [23–25]. Statistical analyses were performed using R software (version 3.5.0, https://www.r-project.org/about.html). Data were reported according to a per protocol analysis where missing EVLWi measurements were excluded. In a prospective cohort study of critically ill patients with sepsis, Martin et al. found a median EVLWi of 15 $ml.kg^{-1}$ and 7 $ml.kg^{-1}$ in patients with and without lung injury, respectively [10]. In a randomised controlled trial comparing salbutamol with placebo in patients with ARDS, the mean (SD) EVLWi at baseline was 14 $ml.kg^{-1}$ (8 $ml.kg^{-1}$) [26]. Assuming a common SD of peak EVLWi of 8 $ml.kg^{-1}$ with 80% power using a two-sided t-test at a 5% significance level, we planned to recruit 56 patients based on a power calculation to detect a between-group difference of 6.5 $ml.kg^{-1}$ (0.8 SD units) in the mean EVLWi between patients with RLI and those without [27].

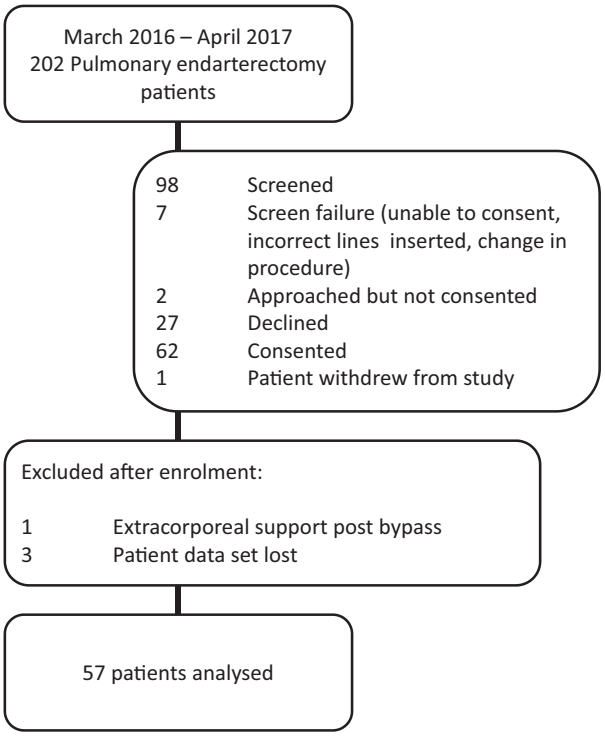

Figure 1 Flow diagram showing number of patients enrolled in the study and subsequently analysed.

Results

From March 2016 to April 2017, we recruited a total of 61 patients. This represents 30% of the total number of patients undergoing pulmonary endarterectomy in this time period, and was determined by researcher and equipment availability. Three patients' data could not be analysed and one patient was excluded due to postoperative extracorporeal support; data from 57 patients were therefore analysed (Fig. 1). As per protocol, patients were subdivided into two groups based on whether they

Table 1 Baseline characteristics of patients undergoing pulmonary endarterectomy. Values are mean (SD), number (proportion) or median (IQR [range]).

	All patients n = 57	Severe RLI n = 21	Severe RLI not present n = 36	p value[a]
Age; years	59.1 (13.9)	60.0 (14.0)	58.5 (14.1)	0.80
Sex; men	37 (65%)	14 (67%)	23 (64%)	1.00
Height; cm	172 (8.8)	171 (7.8)	172 (9.4)	0.80
Weight; kg	87.1 (19.6)	90.4 (21.0)	85.21 (18.7)	0.34
PVR; dynes.s.cm^{-5}	558 (342–838 [139–1700])	557 (400–892 [174–1445])	579 (342–735 [139–1700])	0.39
Pre-operative PVR > 1000 dynes.s.cm^{-5}	10 (17%)	5 (24%)	5 (14%)	0.56
Right ventricular function				0.66
Good	11 (19%)	5 (24%)	6 (17%)	
Mildly impaired	11 (19%)	3 (14%)	8 (22%)	
Moderately impaired	16 (28%)	5 (24%)	11 (31%)	
Severely impaired	19 (33%)	8 (38%)	11 (31%)	
Cardiopulmonary bypass time; min	320 (46)	322 (45)	319 (47)	0.83
Aortic cross-clamp time; min	66 (31)	74 (39)	61 (24)	0.13
Deep hypothermic circulatory arrest time; min	35 (27–43 [6-87])	36 (31–56 [6–65])	35 (25–42 [8–87])	0.39
Quality of endarterectomy clearance				0.61
Excellent	20 (35%)	10 (48%)	10 (28%)	
Good	36 (63%)	11 (52%)	25 (69%)	
Poor	1 (2%)	0 (0%)	1 (3%)	

RLI, reperfusion lung injury; PVR, pulmonary vascular resistance.
[a]Severe RLI vs. Severe RLI not present.

experienced severe RLI as a complication of surgery. There were no differences in their baseline characteristics compared with those patients who did not experience severe RLI (Table 1) and this result persisted when corrected for multiplicity.

During the first 40 h postoperatively, 40 (70%) patients met criteria for RLI, and 21 (37%) met criteria for severe RLI (Table 2). Extravascular lung water index data predicted severe RLI most strongly at 24 h and 36 h (Figs 2 and 3).

At sternal wound closure (after discontinuation of cardiopulmonary bypass), the optimal EVLWi cut-off for predicting severe RLI was 8.5 ml.kg^{-1}, but this was not significant, AUC 0.59 (CI 0.44–0.74). At 36 h, an EVLWi threshold of 10.4 ml.kg^{-1} diagnosed severe RLI with a sensitivity of 90.5% (95%CI 69.6–98.8%) and a specificity of 61.1% (95%CI 43.5–76.9%); AUC 0.90 (95%CI 0.80–1.00). AUC measures and cut-off values for severe RLI based on EVLWi levels at all time-points are shown in Table 3. There was no significant difference between pre-operative EVLWi and subsequent measurements.

The unadjusted association between potential predictors and the development of severe RLI showed duration of cardiopulmonary bypass, aortic cross-clamp, deep hypothermic circulatory arrest and EVLWi at 36 h to have p values < 0.2. These were selected for inclusion in the multivariate model together with PVR, which has shown good discriminative performance in other studies [5, 6]. The combination of these variables provided an AUC 0.91 (95% CI 0.82–1.00), which was not different from EVLWi on its own.

There was some correlation between the EVLWi measurements and worst PaO_2/F_IO_2 ratio, the Pearson correlation values (r) significantly different from 0 at a 5% level were at 24 h (r = −0.36) and 36 h (r = −0.37). A high EVLWi at sternal wound closure correlated significantly at a 5% level with mechanical lung ventilation time and ICU length of stay (r = 0.38 and 0.31 respectively), however, a high EVLWi at 40 h correlated more strongly with these outcome measures (r = 0.59 and 0.52, respectively). There were no significant correlations between EVLWi value and hospital length of stay or in-hospital mortality.

Ten out of 57 patients had pre-operative PVR values greater than, or equal to, 1000 dynes.s.cm^{-5}. These patients were more likely to have high pre-operative EVLWi values (r = 0.59, p < 0.001) and demonstrated a significantly higher

Table 2 Extravascular lung water index (EVLWi) values and outcome data in patients with and without severe reperfusion lung injury (RLI). Values are median (IQR [range]), number (proportion) or mean (SD).

	Severe RLI n = 21	Severe RLI not present n = 36	p value
EVLWi pre-surgery; ml.kg^{-1}	14.9 (10.2–21.8 [5.8–28.0])	12.2 (10.3–14.2 [8.0–40.0])	0.10
EVLWi after bypass; ml.kg^{-1}	11.5 (9.1–12.8 [6.9–26.0])	10.6 (7.8–12.3 [7.0-31.0])	0.27
EVLWi 2 h; ml.kg^{-1}	12.2 (9.7–14.7 [6.8–35.0])	11.2 (8.7–14.5 [8.0–21.0])	0.29
EVLWi 4 h; ml.kg^{-1}	10.7 (9.8–11.9 [4.2–25.0])	10.1 (8.3–13.1 [4.0 -15.0])	0.91
EVLWi 6 h; ml.kg^{-1}	9.8 (8.9–13.7 [5.7–18.0])	9.6 (7.7–13.4 [8.0 -19.0])	0.25
EVLWi 12 h; ml.kg^{-1}	11.2 (10.3–15.0 [4.7–23.0])	9.9 (8.2–15.1 [8.0–28.0])	0.29
EVLWi 24 h; ml.kg^{-1}	12.7 (11.0–16.6 [7.3-19.0])	10.6 [8.7–12.9 [10.0–23.0])	0.10
EVLWi 36 h; ml.kg^{-1}	12.9 (11.8–16.3 [7.0–15.0])	10.1 (9.1–10.5 [10.0–17.0])	<0.01
EVLWi 40 h; ml.kg^{-1}	12.8 (11.4–14.9 [7.3–29.0])	11.3 (9.0–13.9 [8.0–41.0])	0.16
CXR quadrants affected			<0.01
0	0	16 (44.4%)	
1	2 (9.5%)	7 (19.4%)	
2	12 (57.1%)	7 (19.4%)	
3	1 (4.8%)	1 (2.8%)	
4	6 (28.6%)	5 (13.9%)	
Worst compliance; ml.cmH_2O^{-1}	24.3 (12.8)	29.81 (9.8)	0.07
Worst Murray Score	2.6 (0.3)	1.9 (0.5)	<0.01
Mechanical lung ventilation; h	46 (20)	23 (18)	0.01
ICU length of stay; day	5 (2)	3 (2)	0.02
Hospital length of stay; day	16 (4)	11 (3)	0.07
Inpatient mortality	2 (9.5%)	0	0.26

CXR, chest radiograph; ICU, intensive care unit.

EVLWi at sternal wound closure and 2 h later (p = 0.016 and p = 0.009, respectively). Five of these 10 patients (50%) developed severe RLI (p = 0.60). This compared with a rate of severe RLI in patients with a PVR < 1000 dynes.s.cm^{-5} of 16 (34%). Higher PVR was associated with significantly prolonged mechanical lung ventilation (p = 0.010) and ICU length of stay (p = 0.004). There was poor correlation between the degree of right ventricular dysfunction and EVLWi values. Patients who developed severe RLI required longer mechanical lung ventilation times (p = 0.01); longer ICU length of stay, mean (SD) 5 (2) vs. 3 (2) days, p = 0.005; but showed no difference in hospital length of stay, mean (SD) 16 (4) vs. 11 (3) days, p = 0.07. Two patients died, both of whom manifested severe RLI (Table 2).

Discussion

We found that EVLWi measurements at sternal wound closure, after endarterectomy and cardiopulmonary bypass, did not predict the development of severe RLI after surgery, but that EVLWi measurements at 24 h, and especially at 36 h, were very effective at diagnosing severe RLI. The EVLWi measurement at sternal wound closure was only weakly correlated with duration of mechanical lung ventilation and ICU length of stay. The finding that EVLWi could not predict which patients would go on to develop severe RLI means it cannot be used clinically to identify that group of patients who have just undergone surgery who are most likely to suffer respiratory failure and increased morbidity. The finding that EVLWi measurements at 24 h and 36 h allows accurate diagnosis of severe RLI is clinically useful as this may allow clinicians to provide suitable respiratory support and treatment. Future research may be targeted to treatment of such patients in order to reduce morbidity and improve outcome.

In a recently published prospective observational cohort study, Stephan et al. evaluated the clinical significance of EVLWi in 31 haemodynamically stable patients undergoing pulmonary endarterectomy [28]. The authors reported higher EVLWi values in those developing RLI with an optimal threshold value of 8 ml.kg^{-1}. However, they used RLI of any severity as an outcome and did not differentiate patients into those who suffered the most severe form using current criteria. Therefore, they reported a rate of RLI of 84%. Our study reports the association

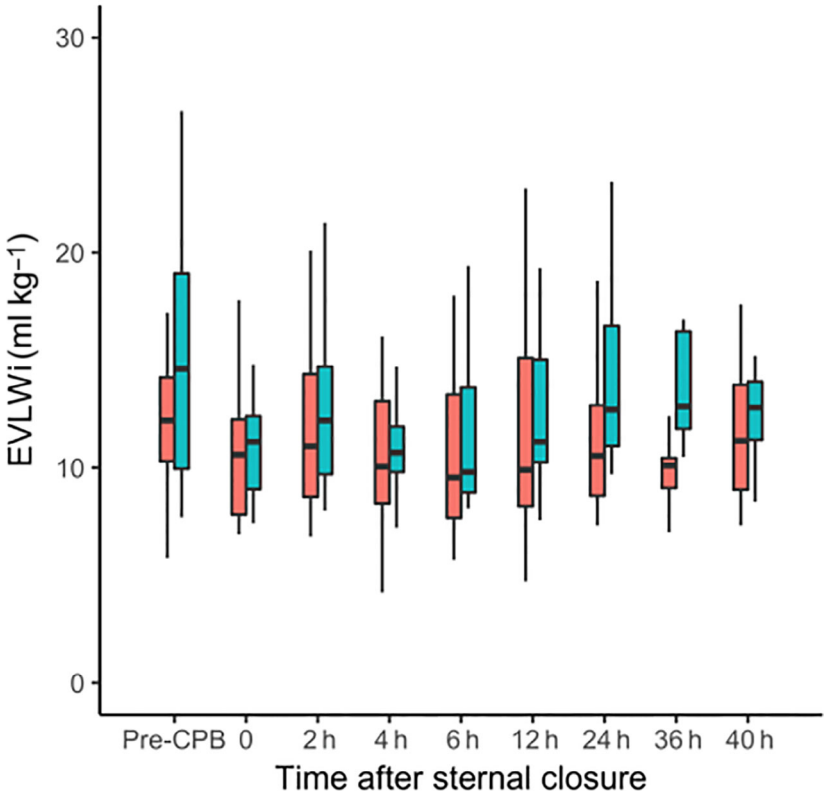

Figure 2 Extravascular lung water index course over time in patients in whom severe reperfusion lung injury was present (dark green) or not present (red). (Pre-cardiopulmonary bypass, the zero time-point corresponds to sternal wound closure).

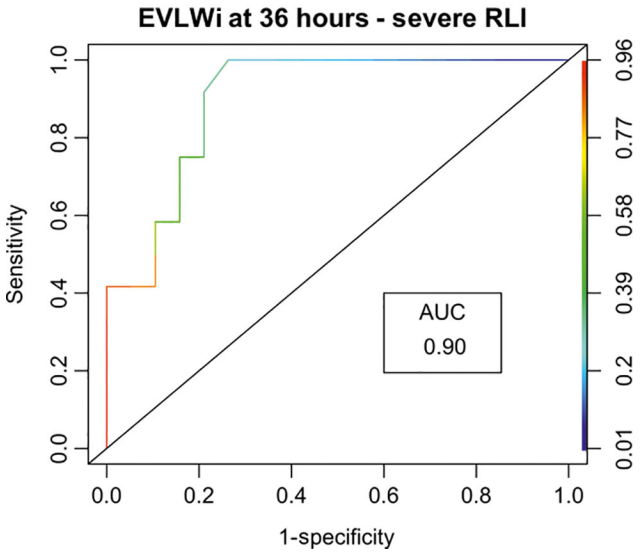

Figure 3 Receiver operator characteristic curve for extravascular lung water index 36 h after sternal wound closure.

between EVLWi and severe RLI, which we believe is more important and has the greatest impact on patient experience, morbidity and mortality [5, 6].

Although the incidence of RLI has reduced over time, it is recognised that 90% of RLI occurs within the first 48 h [4], and it is credible that EVLWi would mark cumulative

Table 3 The performance of extravascular lung water index (EVLWi) as a predictor of severe reperfusion lung injury (RLI) after pulmonary endarterectomy.

	AUC (95%CI)	Optimal EVLWi cut-off (logistic model); ml.kg^{-1}
EVLWi pre-CPB	0.63 (0.47–0.80)	14.3
EVLWi after CPB	0.59 (0.44–0.74)	8.5
EVLWi 2 h	0.59 (0.43–0.75)	9.3
EVLWi 4 h	0.49 (0.29–0.69)	14.7
EVLWi 6 h	0.61 (0.43–0.79)	8.1
EVLWi 12 h	0.59 (0.43–0.76)	9.3
EVLWi 24 h	0.74 (0.59–0.89)	9.7[a]
EVLWi 36 h	0.90 (0.80–1.00)	10.5[a]
EVLWi 40 h	0.64 (0.46–0.83)	11.3
Mean EVLWi	0.67 (0.53–0.81)	10.5[a]

AUC, area under the receiver operator characteristic curve; CPB, cardiopulmonary bypass.
[a]Indicates a significant result.

capillary leak which might be most evident at 24–36 h postoperatively. A higher EVLWi value would be expected to correlate with a greater degree of hypoxaemia. The 10.5 ml.kg^{-1} EVLWi threshold at 36 h in our study reliably confirms severe RLI, a higher value than the threshold for undifferentiated RLI in the study by Stephan et al. [28].

We chose pulmonary endarterectomy patients for this study as they represent a unique in-vivo example of ARDS. We speculate that the higher than anticipated EVLWi values may represent a greater degree of capillary permeability in patients with chronic thromboembolic pulmonary hypertension, with differences in hydrostatic pressure present pre-operatively and postoperative capillary leak from impaired function of injured pulmonary vascular endothelium. As patients undergoing pulmonary endarterectomy are known to suffer a relatively high incidence of RLI, we were able to undertake this study and recruit an adequate number of patients with this complication to demonstrate the usefulness of EVLWi measurement in this cohort of patients. Future research should seek to confirm whether this monitoring modality performs in the same way in other patient cohorts also likely to suffer acute lung injury, such as emergency laparotomy, lung resection, sepsis and chest trauma.

The present study has some limitations. First, there was a high rate of missing measurements at some time-points, particularly in the early overnight measurements. These missing data did not have a particular pattern, and stood up to statistical analysis, but would have reduced the power at specific time-points to detect a significant EVLWi difference, which may also explain why only 24 h and 36 h time-points were significant. Second, we were unable to quantify the degree of tricuspid regurgitation before EVLWi measurements. Third, the measured EVLWi was consistently higher, with a higher SD than that used for our power calculation. However, a greater number of patients than expected developed severe RLI which should have led to a relative improvement in our statistical power.

We conclude that EVLWi can be used for direct assessment of extravascular pulmonary fluid dynamics, and in particular fluid overload, and that it offers a useful measure to diagnose RLI 24–36 h after surgery. Future trials should focus on the role of EVLWi as part of a peri-operative goal-directed therapy including fluid balance and lung-protective ventilation strategies and might consider the utility of EVLWi as a therapeutic target.

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