Extravascular Lung Water and Pulmonary Vascular Permeability Index as Markers Predictive of Postoperative Acute Respiratory Distress Syndrome: A Prospective Cohort Investigation*

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Objective: Robust markers of subclinical perioperative lung injury are lacking. Extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index are two promising early markers of lung edema. We aimed to evaluate whether extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index would identify patients at risk for clinically significant postoperative pulmonary edema, particularly resulting from the acute respiratory distress syndrome.

Design: Prospective cohort study.

Setting: Tertiary care academic medical center.

Patients: Adults undergoing high-risk cardiac or aortic vascular surgery (or both) with risk of acute respiratory distress syndrome.

Interventions: None.

Measurements and Main Results: Extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index measurements were obtained intraoperatively and in the early postoperative period. We assessed the accuracy of peak extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index as predictive markers of clinically significant pulmonary edema (defined as acute respiratory distress syndrome or cardiogenic pulmonary edema) using area under the receiver-operating characteristic curves. Associations between extravascular lung water indexed to predicted body weight and pulmonary vascular permeability patient-important outcomes were assessed. Of 150 eligible patients, 132 patients (88%) had extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index measurements. Of these, 13 patients (9.8%) had postoperative acute respiratory distress syndrome and 15 patients (11.4%) had cardiogenic pulmonary edema. Extravascular lung water indexed to predicted body weight effectively predicted development of clinically significant pulmonary edema (area under the receiver-operating characteristic curve, 0.79; 95% CI, 0.70–0.89). Pulmonary vascular permeability index discriminated acute respiratory...
distress syndrome from cardiogenic pulmonary edema alone or no edema (area under the receiver-operating characteristic curve, 0.77; 95% CI, 0.62–0.93). Extravascular lung water indexed to predicted body weight was associated with the worst postoperative \( \text{Pa}_2/\text{Fi}_2 \), duration of mechanical ventilation, ICU stay, and hospital stay. Peak values for extravascular lung water indexed to predicted body weight and pulmonary vascular permeability index were obtained within 2 hours of the primary intraoperative insult for the majority of patients (> 80%).

**Conclusions:** Perioperative extravascular lung water indexed to predicted body weight is an early marker that predicts risk of clinically significant postoperative pulmonary edema in at-risk surgical patients. Pulmonary vascular permeability index effectively discriminated postoperative acute respiratory distress syndrome from cardiogenic pulmonary edema. These measures will aid in the early detection of subclinical lung injury in at-risk surgical populations. *(Crit Care Med 2015; 43:665–673)*

**Key Words:** acute respiratory distress syndrome; biologic markers; critical care; outcomes; perioperative care; prevention; pulmonary edema; technology

**Materials and Methods**

The Mayo Clinic Institutional Review Board approved this study, and written informed consent was obtained from all study participants.

**Study Design**

This was a prospective cohort investigation. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in the design and reporting of this observational study.

**Study Participants**

Study participants included adult patients (≥ 18 yr old) undergoing nonemergent cardiac or aortic vascular surgery with a predicted risk of early postoperative ARDS more than or equal to 10%, as estimated using the previously described secondary surgical lung injury prediction model. The exclusion criteria for this study protocol and justification for each are noted in Table 1.

**Outcome Variables**

The primary outcome was development of clinically significant pulmonary edema resulting from ARDS or CPE. Clinically significant pulmonary edema was defined as pulmonary edema

**Table 1. Study Participant Exclusion Criteria With Justification for Their Inclusion**

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate or severe cardiac valve regurgitation</td>
<td>Unreliable extravascular lung water and pulmonary vascular permeability index measurements</td>
</tr>
<tr>
<td>Preexisting ARDS</td>
<td>Inability to assess outcome</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>Unable to obtain consent</td>
</tr>
<tr>
<td>Anesthetic plan does not include the placement of arterial and central venous catheters</td>
<td>Risk of catheter placement</td>
</tr>
<tr>
<td>Presence of preoperative polytrauma, sepsis, aspiration, shock, acute congestive heart failure, or respiratory failure</td>
<td>Potential confounding from major ARDS risk factors</td>
</tr>
<tr>
<td>Recent high-risk surgery (within 30 d before the current surgical procedure)</td>
<td>Potential confounding from a major ARDS risk factor</td>
</tr>
</tbody>
</table>

ARDS = acute respiratory distress syndrome.
manifesting with acute bilateral infiltrates on chest radiography (not fully explained by effusions, lobar or lung collapse, or nodules) with associated hypoxemia (Pao/Fio \(_2\) \(\leq\) 300) and the need for ventilatory support (including noninvasive modes of mechanical ventilation).

The more specific diagnosis of ARDS was defined according to the recently endorsed Berlin criteria (14). As recommended by this new definition of ARDS (14), the assessment for evidence of hydrostatic pulmonary edema was not restricted to pulmonary artery catheter measurements. Rather, all available clinical data were considered, including the following measures (when available): 1) evidence of left atrial hypertension as determined by pulmonary artery catheterization (pulmonary artery capillary wedge pressure > 18 cm H\(_2\)O), echocardiography (left ventricular ejection fraction < 45%), or the ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity more than 15; 2) clinical context (e.g., presence of myocardial ischemia, valvular pathology, and absence of nonsurgical major risk factors for ARDS); 3) volume status; and 4) clinical course (e.g., rapid resolution with volume reduction is considered suggestive of hydrostatic pulmonary edema). In the current study, the presence of hydrostatic pulmonary edema resulted in a diagnosis of either CPE alone or CPE plus ARDS when ARDS was judged to coexist.

ARDS and CPE ascertainment proceeded in three steps. First, screening was performed by a member of the study team. Patients with a Pao/Fio \(_2\) value less than or equal to 300 and a chest radiograph with any findings suggestive of bilateral infiltrates, edema, or congestion were considered screen positive and were sent to two experts in ARDS and CPE adjudication (D.J.K., O.G.) who independently reviewed each case and assigned one of four conditions: ARDS, CPE, both, or neither. Disagreements in the outcome of ARDS were resolved by a third expert (R.D.H.). Interobserver agreement for ARDS adjudication was determined with \(\kappa\) values. Secondary outcome variables included the worst postoperative Pao/Fio \(_2\), duration of mechanical ventilation, ICU stay, and hospital stay. All study personnel involved in outcome adjudication remained blinded to the EVLW and PVPI measurement results until all outcome determinations were complete.

**Predictor Variables**

EVLW and PVPI were measured with the PiCCO system (Pulsion Medical Systems, Munich, Germany). Procedural details for obtaining these measurements have been previously described (7) and are briefly summarized here. EVLW and PVPI measurements were obtained by triplicate central venous injections of 20 mL of iced (< 8°C) 0.9% NaCl (saline) and recorded as the mean of the three measurements. Volumetric variables were derived as previously described (7). EVLW was calculated as the difference between the thermal indicator distribution in the chest and the blood volume of the chest: EVLW = intrathoracic thermal volume – intrathoracic blood volume (ITBV) (measured in mL) (7, 16, 17). EVLW is expressed in mL and as mL/kg when indexed to predicted body weight (EVLWi), which more accurately characterizes lung edema (9, 18). PVPI has been variably described as the ratio of absolute (unindexed) EVLW to ITBV or pulmonary blood volume (7, 10, 19–21). In the present investigation, PVPI is calculated as the ratio of EVLWi:ITBV. All EVLW and PVPI measurements were obtained by certified monitoring technicians or licensed respiratory therapists who were specifically trained to use the PiCCO device. Standard operating procedures were developed before study onset, and multiple focused training sessions were completed before initiating patient enrollment.

Measurements were obtained at the following time points. The first measurement followed the induction of anesthesia after insertion of the catheters (baseline). The timing of the second and third measurements depended on the surgical procedure. For cardiac surgery patients, the second and third measurements were obtained immediately before initiation of cardiopulmonary bypass (CPB) and within 30 minutes of separation from CPB, respectively. For aortic vascular surgery patients, the second measurement was obtained just before aortic cross-clamp placement and the third was obtained within 30 minutes after aortic cross-clamp removal. Thus, for all patients, the third measurement was timed to immediately follow a defined major surgical event. Additional measurements were planned 2, 4, 6, 12, and 24 hours after the third measurement.

**Statistical Analyses**

**Sample Size Determination.** Measurements of EVLWi and PVPI were planned for 150 eligible patients with a calculated risk of early postoperative ARDS more than or equal to 10%. Therefore, we estimated 15 study participants would have ARDS. In a previous study comparing patients with and without ARDS \(n = 15\) and \(n = 14\), respectively, the median EVLWi was 15 and 7 mL/kg, respectively (7). Similarly, in a trial comparing salmeterol with placebo in patients with ARDS \(n = 19\) and \(n = 21\), respectively, the median EVLWi at baseline was 14 mL/kg (8 mL/kg) (22). Using the method of Hsieh et al (23), 15 patients with events and 135 patients without events were estimated to provide 80% power (two-tailed, \(\alpha = 0.05\)) to detect a between-group difference of 0.8 mL units. Assuming the SD of peak EVLWi is 8 mL/kg, a sample size of 150 was estimated to provide 80% power to detect a 6.5 mL/kg difference in EVLWi between groups.

**Analysis Plan.** Dichotomous variables are presented as number (%); continuous data are presented as median (interquartile range [IQR]). Preliminary analyses compared patients with and without ARDS by using Pearson chi-square tests, Fisher exact tests, or Wilcoxon rank-sum test (Mann-Whitney U statistic), as appropriate.

The primary goal of this investigation was to evaluate EVLWi as a predictor of clinically significant postoperative pulmonary edema (ARDS or CPE) and PVPI as a discriminator of ARDS. Peak EVLWi and PVPI values among all available measurements were determined for each patient. These values were compared among subjects who had development of ARDS or CPE (alone or in combination) or no postoperative pulmonary edema. The validity of peak EVLWi and PVPI as predictive markers of
clinically significant pulmonary edema and ARDS were assessed by calculating the area under the receiver-operating characteristics curve (AUC). The threshold score that maximized the Youden index (24) was determined. The corresponding positive and negative likelihood ratios at this optimal threshold were calculated. To improve the functionality of the prediction models, sensitivity analyses were performed to determine model performance at two additional thresholds.

The association of these peak measurements with secondary outcome measures (worst postoperative PaO₂/FIO₂, duration of mechanical ventilation, ICU stay, and hospitalization) was assessed by evaluating Spearman rank correlation coefficients for the associations of interest. Two-sided tests were used, with p values less than or equal to 0.05 being statistically significant. All statistical analyses were conducted using SAS software v9.3 (SAS Institute, Cary, NC).

RESULTS

From October 2010 to March 2013, 150 study subjects were enrolled (Fig. 1). Of these, 132 subjects (88%) had at least one EVLWı and PVPI measurement. The primary reason for absent measurements was difficult catheter placement (n = 12). Of the 132 patients with EVLWı and PVPI measurements, seven patients (5.3%) had postoperative ARDS without CPE, nine patients (6.8%) had postoperative CPE without ARDS, and six patients (4.5%) had combined ARDS and CPE. Thus, 22 patients (16.7%) had clinically significant postoperative pulmonary edema and 13 patients (9.8%) had ARDS. The κ value (95% CI) for the adjudication of ARDS was 0.66 (0.47–0.86).

Baseline information for the 132 study participants are shown in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/B147). Compared with those who did not have postoperative ARDS, patients with ARDS appeared to have more extensive surgical procedures, as evidenced by longer operative duration, greater time on CPB, and a greater volume of fluid and blood product administration. Those who ultimately had development of postoperative ARDS received lower tidal volume ventilation in the operating room environment.

For all patients, peak EVLWı and PVPI values ranged from 6.97 to 38.78 and from 0.27 to 3.05, respectively. Peak EVLWı was higher in patients who subsequently had pulmonary edema (median [IQR], 15.06 mL/kg [13.74–19.01 mL/kg]) than in patients who did not (10.82 mL/kg [9.36–13.51 mL/kg]) (p < 0.001). Peak PVPI was greater in those who subsequently had ARDS (median [IQR], 0.64 [0.49–0.84]) than in those who did not (0.44 [0.39–0.52]) (p = 0.001). EVLWı and PVPI measurements from the four groups evaluated are presented in Table 2.

The measurement time points at which peak values were noted for both EVLWı and the PVPI are shown in Figure 2. Peak EVLWı and PVPI values occurred within 2 hours of separating from either CPB (cardiac surgery) or removal of the aortic cross clamp (aortic vascular surgery) in more than 80% of patients and within 6 hours in more than 90% of patients. Peak EVLWı and PVPI measurements were noted at the baseline measurements for 19.7% and 23.5% of the cohort, respectively. In comparison, the median (IQR) time from the end of CPB (cardiac surgery) or removal of the aortic cross clamp (aortic vascular surgery) to ARDS onset using the Berlin criteria was 20.4 hours (10.6–40.8 hr). In 10 of 13 ARDS cases, the chest imaging study was the final variable met to fulfill all ARDS criteria. In the remaining three cases, PaO₂/FIO₂ was the final criteria used to determine ARDS onset time. Median (IQR) time to CPE using the qualifying chest radiograph as the onset time was 13.0 hours (4.9–32.9 hr). Although the worst PaO₂/FIO₂ most often occurred on the first postoperative day (n = 91/131 [69.5%]), the worst ratio was observed on the second postoperative day in approximately one quarter of the patients (n = 33/131 [25.2%]), with the remaining worst values being spread over the last 3 days of the 5-day evaluation interval.

Results from the AUC analyses are presented in Figure 3. Peak EVLWı effectively discriminated between those with and without clinically significant pulmonary edema (Fig. 3A) (AUC [95% CI], 0.79 [0.70–0.89]). EVLWı was also an effective discriminator of both ARDS versus no ARDS (Fig. 3B) (AUC [95% CI], 0.76 [0.63–0.89]) and CPE versus no CPE (Fig. 3C) (0.75 [0.63–0.87]).
IQR = interquartile range, PVPI = pulmonary vascular permeability index.

In contrast, PVPI effectively discriminated ARDS from CPE alone or no edema (Fig. 3B) (AUC [95% CI], 0.77 [0.62–0.93]), but as expected, it did not perform well for the more general diagnosis of clinically significant pulmonary edema versus no edema (Fig. 3A) (0.69 [0.56–0.82]) or the specific diagnosis of CPE versus no CPE (Fig. 3C) (0.60 [0.43–0.76]).

For peak EVLW\textsubscript{i} as a predictor of clinically significant postoperative pulmonary edema, receiver-operating characteristic (ROC) curve analysis determined that the optimal threshold value was 14.25 mL/kg. This value yielded a sensitivity of 69.2% (95% CI, 42.4–87.3%) and a specificity of 81.8% (95% CI, 73.6–87.9%). The corresponding positive and negative likelihood ratios for the diagnosis of clinically significant pulmonary edema were 4.00 and 0.33, respectively. The negative likelihood ratios for the diagnosis of clinically significant pulmonary edema versus no pulmonary edema were 3.17 and 0.39, respectively. The results of the sensitivity analyses evaluating alternative thresholds for both EVLW\textsubscript{i} as a predictor of clinically significant pulmonary edema (ARDS or CPE vs no pulmonary edema) and PVPI as a discriminator of ARDS (vs either CPE alone or no pulmonary edema) can be seen in Table 3.

For the secondary outcomes, EVLW\textsubscript{i} correlated with the worst postoperative Pao\textsubscript{2}/FiO\textsubscript{2} (ρ = –0.314; p < 0.001), duration of mechanical ventilation (ρ = 0.357; p < 0.001), ICU stay (ρ = 0.438; p < 0.001), and hospitalization (ρ = 0.186; p < 0.01). However, although peak PVPI did correlate with the worst postoperative Pao\textsubscript{2}/FiO\textsubscript{2} (ρ = –0.183; p = 0.04), it did not correlate well with the more clinically relevant secondary outcomes. The results of these analyses are provided in Table 4.

### DISCUSSION

In this investigation, we aimed to evaluate EVLW\textsubscript{i} and PVPI as early predictive markers of clinically significant postoperative pulmonary edema and ARDS in at-risk surgical patients. We confirmed that peak EVLW\textsubscript{i} effectively discriminated between patients with and without development of clinically significant pulmonary edema in the early postoperative period. This discriminatory capacity remained for hydrostatic (CPE) and nonhydrostatic (ARDS) edema. PVPI was an effective prognostic marker for outcomes of postoperative ARDS. EVLW\textsubscript{i} also correlated with the worst postoperative Pao\textsubscript{2}/FiO\textsubscript{2}, duration of mechanical ventilation, ICU stay, and hospital stay. However, peak PVPI did not correlate as well with these secondary outcomes.

ARDS remains a life-threatening concern in surgical populations undergoing high-risk procedures (1, 2, 4, 5). This concern is magnified by the lack of effective therapeutic options, which likely is partly attributable to delayed implementation of therapeutic interventions evaluated in clinical trials (25–29). Although early identification of subclinical lung injury may afford new opportunities for testing the efficacy of novel interventions, no effective markers currently exist that can be used in this context. This absence of early markers of lung injury is a major barrier to progress in the prevention and management of ARDS (6, 7).

### TABLE 2. Peak EVLW\textsubscript{i} and PVPI Measurements

<table>
<thead>
<tr>
<th>Postoperative Clinical Classification</th>
<th>Peak EVLW\textsubscript{i} Median (IQR), mL/kg</th>
<th>Peak PVPI Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary edema (n = 22)</td>
<td>15.06 (13.47–19.01)</td>
<td>0.57 (0.42–0.70)</td>
</tr>
<tr>
<td>ARDS, with or without CPE (n = 13)</td>
<td>15.09 (12.93–19.16)</td>
<td>0.64 (0.49–0.84)</td>
</tr>
<tr>
<td>CPE, with or without ARDS (n = 15)</td>
<td>15.03 (12.68–20.50)</td>
<td>0.48 (0.41–0.64)</td>
</tr>
<tr>
<td>ARDS only (n = 7)</td>
<td>15.22 (14.54–17.72)</td>
<td>0.65 (0.50–0.74)</td>
</tr>
<tr>
<td>CPE only (n = 9)</td>
<td>15.03 (13.21–19.51)</td>
<td>0.46 (0.41–0.62)</td>
</tr>
<tr>
<td>ARDS and CPE (n = 6)</td>
<td>14.85 (10.07–21.14)</td>
<td>0.60 (0.39–1.94)</td>
</tr>
</tbody>
</table>

No pulmonary edema (n = 110) 10.82 (9.36–13.51) 0.44 (0.39–0.52)

ARDS = acute respiratory distress syndrome, CPE = cardiogenic pulmonary edema, EVLW\textsubscript{i} = extravascular lung water indexed to predicted body weight, IQR = interquartile range, PVPI = pulmonary vascular permeability index.
In light of the barriers identified above, interest has focused on identifying biologic markers of subclinical lung injury that predict risk of ARDS (30–38). Although numerous markers have been associated with ARDS development and subsequent outcome, the robustness of these relationships has often been limited by inconsistent findings (39). In part, this may be due to the syndromic nature of ARDS, as the clinical events that portend risk for this syndrome can be quite heterogeneous (31). Indeed, investigations suggest that biomarker profiles associated with ARDS may differ, depending on the clinical context (40). Additionally, the lack of point-of-care testing for most of these assays significantly limits their use in clinical medicine and the study of ARDS prevention or early treatment.

In contrast to risk factors and specific mechanisms underlying ARDS, the primary pathophysiologic events of alveolar flooding and hypoxemia remain consistent, regardless of the clinical context. Therefore, readily available intermediate physiologic markers may prove more robust in identifying heterogeneous populations at risk for ARDS. Recent

![Figure 3. Receiver-operating characteristics curves for predicting postoperative pulmonary edema. A, Pulmonary edema (acute respiratory distress syndrome [ARDS] with or without cardiogenic pulmonary edema [CPE]) versus no edema. B, ARDS (with or without CPE) versus no ARDS (CPE alone or no edema). C, CPE (with or without ARDS) versus no CPE (ARDS alone or no edema). AUC = area under the receiver-operating characteristic curve, EVLW = extravascular lung water indexed to predicted body weight, PVPI = pulmonary vascular permeability index.](image)

### TABLE 3. Sensitivity Analyses Evaluating the Diagnostic Performance of EVLW for the Prediction of Clinically Significant Pulmonary Edema and PVPI for the Prediction of Acute Respiratory Distress Syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>EVLW, mL/kg</th>
<th>PVPI</th>
<th>PVPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 12.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>81.8 (61.5–92.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>64.5 (55.3–72.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>2.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 14.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>72.7 (51.8–86.8)</td>
<td>84.6 (57.8–95.7)</td>
<td>53.8 (29.1–76.8)</td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>81.8 (73.6–879)</td>
<td>85.5 (77.7–90.8)</td>
<td></td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>4.00</td>
<td>62.2 (63.2–70.4)</td>
<td>84.0 (76.4–89.5)</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.33</td>
<td>2.81</td>
<td>3.17</td>
</tr>
<tr>
<td></td>
<td>≥ 15.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity, % (95% CI)</td>
<td>40.9 (23.3–61.3)</td>
<td>69.2 (42.4–87.3)</td>
<td></td>
</tr>
<tr>
<td>Specificity, % (95% CI)</td>
<td>85.5 (77.7–90.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>2.81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.69</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EVLW = extravascular lung water indexed to predicted body weight, PVPI = pulmonary vascular permeability index.

### TABLE 4. Correlation of EVLW and PVPI With Secondary Patient Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Peak EVLW</th>
<th>Peak PVPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ρ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>p</td>
</tr>
<tr>
<td>Worst postoperative ratio of $\text{PaO}_2$ to $\text{FiO}_2$</td>
<td>−0.314</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>0.357</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of ICU stay</td>
<td>0.438</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td>0.186</td>
<td>0.01</td>
</tr>
</tbody>
</table>

EVLW = extravascular lung water indexed to predicted body weight, PVPI = pulmonary vascular permeability index.

<sup>a</sup>Spearman rank correlation coefficients.
investigations evaluating patients requiring acute care services (e.g., emergency department and ICU) note the potential utility of $FIO_2$, $SpO_2$, respiratory rate, serum lactate, and lung ultrasonography in estimating risk of ARDS. However, the standards of care in the setting of high-risk cardiac and aortic vascular surgery (e.g., high $FIO_2$ and pharmacologic paralysis with controlled respiratory rates) minimize the utility of these physiologic markers. Additionally, intraoperative lung ultrasonography can be technically challenging in patients with highest risk of postoperative ARDS (e.g., cardiac, thoracic, and aortic vascular surgery). Similarly, point-of-care laboratory tests for serum lactate are frequently not available in the operating room environment. Therefore, the need persists for an accurate and reliable marker of subclinical lung injury that can be feasibly implemented in the operating room environment.

EVLW, is proposed as an early marker of subclinical ARDS (7, 15, 44–46). As with the protein biologic markers, it has primarily been evaluated as a marker predicting outcome in patients with established ARDS (45). However, recent evidence suggests that EVLW may also be useful in predicting risk of ARDS development (7, 15, 46). Martin et al (7) identified EVLW as a useful marker of subclinical lung injury in patients with severe sepsis, correlating higher EVLW measurements with more severe hypoxemia and reduced survival. Similarly, LeTourneau et al (46) identified EVLW on day 1 of ICU admission to be predictive of subsequent development of ARDS in a population of at-risk patients; specifically, mean (SD) EVLW on day 1 was 15.5 mL/kg (7.4 mL/kg) and 8.7 mL/kg (2.3 mL/kg) for those who did and did not have ARDS development, respectively ($p = 0.04$). In contrast, no other physiologic markers tested in that study (physiologic dead space, $PaO_2/FIO_2$, or static lung compliance) predicted progression to ARDS.

PVPI has been proposed as a useful early marker of ARDS (15, 45, 47). Jozwiak et al (45) identified PVPI as an independent risk factor for 28-day mortality in patients with ARDS. Similarly, Kushimoto et al (15) noted the utility of PVPI as a diagnostic tool for ARDS in patients with hypoxemic respiratory insufficiency. However, other investigations have not confirmed these findings (19, 46). Perhaps, the greatest value of PVPI is its ability to differentiate hydrostatic from nonhydrostatic lung edema. Indeed, numerous investigations have suggested the utility of PVPI in this regard (10, 15). Preliminary data suggest that PVPI may be particularly useful when assessing patients with concomitant increases in EVLW (17).

Notably, greater than 90% of the current study population had their peak EVLW and PVPI measurements within 6 hours of separation from CPB (cardiac surgery) or removal of the aortic cross clamp (aortic vascular surgery). Although the early rise in EVLW and PVPI was unexpected, particularly for those with baseline elevations, we believe this may simply confirm the ability of EVLW and PVPI to detect subclinical lung edema in a cohort of patients with clear baseline risk. Indeed, these findings suggest that EVLW and PVPI may be very early markers of risk for progression to clinically significant pulmonary edema and lung injury. If confirmed, EVLW and PVPI would be particularly attractive markers of subclinical lung injury when studying time-sensitive therapeutic interventions. Interestingly, in the study by LeTourneau et al (46), EVLW measurements were similar for those with prevalent ARDS and those who later progressed to ARDS, perhaps corroborating our findings that increased EVLW is a very early change in the progression from healthy lungs to the full ARDS phenotype.

Although the prospective design, rigorous training of the investigative team, and specific focus on at-risk surgical populations are notable strengths of this investigation, important limitations must be discussed. First is the single-center nature of the study. Second, we had a limited sample size and small number of ARDS outcomes ($n = 13$), which prevents us from drawing firm conclusions regarding the validity of the study findings. Nonetheless, our findings are consistent with those reported in the multicenter study of ICU patients with risk of ARDS (46), as well as with the study by Martin et al (7) in patients with sepsis. A third concern relates to the reproducibility of the diagnosis of ARDS and differentiating this outcome from CPE. Although these challenges affect all clinical ARDS studies, they are particularly relevant in the study of postoperative ARDS, in which atelectasis and ventilatory support are common after surgery. To address this concern, we had two independent evaluations of the outcomes of interest, and when disagreements arose, a third consulting expert made the final determination. Nonetheless, we acknowledge the remaining potential for misclassification of ARDS and CPE. Finally, the requirement for both central venous and arterial catheterization may limit the use of the PiCCO device in patients with low risk of ARDS. However, we emphasize that surgical patients with high risk of postoperative ARDS (e.g., those undergoing cardiac, aortic vascular, and high-risk thoracic surgery) often have both of these procedures performed as a routine part of their anesthetic care.

CONCLUSIONS

Perioperative EVLW is an effective early marker that predicts risk of clinically significant postoperative pulmonary edema in at-risk surgical patients. PVPI will aid in discriminating postoperative ARDS from CPE. If validated in a larger cohort, these measures may prove useful in the early detection of subclinical lung injury in at-risk surgical populations.

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