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Rationale and Design of a Prospective Cohort Study to Assess Extravascular Lung Water as an Early Predictor and Marker of the Severity of Reperfusion Lung Injury in Pulmonary Endarterectomy

Vasileios Zochios,[1,2,*] Nicola Jones,[3] and Andrew A Klein[3]

[1]Department of Critical Care Medicine, University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Mindelsohn Way Edgbaston, UK
[2]College of Medical and Dental Sciences, Institute of Inflammation and Ageing, Perioperative Critical Care and Trauma (PACCT) Trials Group, University of Birmingham, Edgbaston, Birmingham, UK
[3]Department of Cardiothoracic Anesthesia and Intensive Care Medicine, Papworth Hospital NHS Foundation Trust, Papworth Everard, Cambridge, UK

[*]*Corresponding author*: Dr Vasileios Zochios MRCP, Academic Intensive Care Medicine (NIHR ACF) and StR in Intensive Care Medicine; University Hospitals Birmingham NHS Foundation Trust - Queen Elizabeth Hospital Birmingham, UK; College of Medical and Dental Sciences - University of Birmingham, Birmingham, UK; Senior Clinical Tutor University of Cambridge School of Clinical Medicine, E-mail: vasileioszochios@doctors.org.uk

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Abstract

Background: Reperfusion lung injury occurs in up to 40% of patients undergoing pulmonary endarterectomy and has been shown to represent a high permeability form of pulmonary edema. It is associated with prolonged mechanical ventilation and intensive care unit stay and in its severe form it may result in death. Extravascular lung water measured by transpulmonary thermodilution is identified as early indicator of lung injury in critically ill patients with established acute respiratory distress syndrome.
Methods: In this prospective cohort study we aim to evaluate extravascular lung water indexed to predicted body weight, using pulse-induced contour cardiac output monitor as a predictor of clinically significant peri-operative reperfusion injury in patients undergoing pulmonary endarterectomy. We hypothesize that pulmonary endarterectomy patients with high perioperative extravascular lung water indexed to predicted body weight values, are more likely to develop clinically significant reperfusion injury. A sample size of 51 patients is estimated to provide 80% (a = 0.05) power to detect correlations and differences.
Conclusions: As a unique in vivo example of high permeability edema, pulmonary endarterectomy patients constitute an ideal model for evaluating whether extravascular lung water correlates with clinical outcomes and assessing its applicability as diagnostic criterion in the definition of acute respiratory distress syndrome.

Keywords: Extravascular Lung Water, Reperfusion Injury, Pulmonary Endarterectomy

1. Background

Pulmonary endarterectomy is recognized as the definitive treatment of chronic thromboembolic pulmonary hypertension. High permeability edema after pulmonary endarterectomy constitutes a unique in vivo example of reperfusion lung injury (1).

Reperfusion lung injury is a localized form of high permeability edema seen in the areas of the lung that have been endarterectomized and reperfused. It occurs with varying severity in up to 40% of patients (1, 2). In its severe form, reperfusion lung injury can present as severe alveolar hemorrhage with profound hypoxemia and it is associated with significant increases in duration of mechanical ventilation, length of intensive care unit stay and mortality (3). 60% of cases occur immediately after surgery, 30% develop within the first 48 hours post-operatively and the minority (10%) later during hospitalisation (> 48 hours).

Reperfusion lung injury is defined as:

- $PaO_2/FiO_2 < 300$ mmHg (39.9 kPa),

- Opacity on chest radiograph in a region reperfused following pulmonary endarterectomy (one or more quadrants), and

- No other reason for the previous two criteria such as pneumonia and atelectasis

In clinically significant perioperative reperfusion lung injury ventilatory support (including non-invasive modes of mechanical ventilation or continuous positive airway pressure) is required (2, 4).

EVLW is a promising early marker of lung edema. It is the amount of water contained in the lungs outside the pulmonary vasculature that is the sum of interstitial, alveolar, intracellular and lymphatic fluid, except pleural effusions (5). EVLWi has been identified as an early indicator of lung injury in severe sepsis and marker of disease severity in patients with established acute respiratory distress syndrome (6, 7). It has been correlated with late markers of acute respiratory distress syndrome such as PaO_2/FiO_2, lung injury scores and pulmonary infiltrates on chest radiograph (8, 9). Recent studies have demonstrated that the maximum value of EVLW during episodes of high permeability pulmonary edema is an independent predictor of 28-day mortality (10). In critically ill patients with septic shock, EVLW measured early during the course of disease correlates with pulmonary function, and the combination of EVLW and diagnosis of lung injury increases the post-test odds of intensive care unit (ICU) mortality (11).

EVLW can be measured using transpulmonary thermodilution methods. Currently, the most common method of measuring EVLW is the single-indicator transpulmonary thermodilution (pulse-induced contour cardiac output; PiCCO; Pulsion Medical Systems, Munich, Germany) (12). This method has been validated by comparison with the "gold standard" gravimetric method in experimental animal studies (13). A fluid bolus of up to 20 mL of 0.9% iced normal saline (< 8°C) is injected into a central venous catheter. The change in temperature of this bolus is detected at the thermistor tip of a femoral arterial catheter and a thermodilution curve is generated. The thermodilution curve obtained is then analysed to calculate the cardiac output using the Stewart-Hamilton algorithm. Intrathoracic thermal volume and the pulmonary thermal volume are derived from the mean transit time and the exponential downslope time of the thermodilution curve and volumetric variables, including EVLW, may be estimated (12).

The validity of EVLW in predicting reperfusion pulmonary edema in pulmonary endarterectomy patients has not been studied before and the proposed study is highly novel in its concept. We aim to prospectively evaluate whether EVLWi can be utilized as an early marker of risk for progression to clinically significant reperfusion lung injury in the context of pulmonary endarterectomy. If confirmed, EVLWi would be a particularly attractive marker of reperfusion lung injury when studying time-sensitive therapeutic interventions and increase the opportunity of delivering early therapeutic interventions proven to improve outcomes.

The rationale of this study is to demonstrate that that pulmonary endarterectomy patients with high perioperative EVLWi are more likely to develop clinically significant reperfusion lung injury.

2. Methods

2.1. Study Participants, Measurements

The study design comprises a single-centre prospective cohort of patients undergoing pulmonary endarterectomy, at Papworth cardiothoracic hospital, UK.

Patients aged over 18 years, undergoing elective pulmonary endarterectomy and managed as part of an established pulmonary endarterectomy protocol at Papworth hospital NHS Foundation Trust will be prospectively included into the study. Patients requiring perioperative mechanical circulatory support (intra-aortic balloon pump, veno-arterial extracorporeal membrane oxygenation) will be excluded.

2.1.1. Anesthesia

The anesthetic technique and surgical procedure performed will not be affected by patients' participation in this study. Anesthesia will be induced with midazolam, fentanyl and propofol, neuromuscular blockade with pancuronium, and maintained with continuous infusions of both propofol, and/or inhalational anesthetic agent at the discretion of the attending anesthetist. All patients will be monitored according to standard pulmonary endarterectomy protocol including insertion of central venous catheter in the superior vena cava territory and a thermistor-tipped arterial catheter placed in the femoral artery (Pulsion Medical Systems; PiCCO). The femoral arterial catheter will be removed on the morning of day 2 after surgery which is 24 hours later than standard protocol and represents a small increased risk of infection and hematoma. All thermodilution measurements will be performed by injecting a 10-mL bolus of cold saline (< 8°C) through the central venous catheter. EVLW will be measured by the PiCCO device and the average result from three consecutive saline injections will be recorded for each patient. The PiCCO device will be operated within its normal use guidelines. The value of EVLWi considered as normal will be < 7 mL/kg of predicted body weight (14). A cutoff value of 10 mL/kg predicted body weight will be considered as the highest limit of the normal range (15, 16).

2.1.2. Surgical Strategy

According to our local protocol after median sternotomy, cardiopulmonary bypass (CPB) is instituted once activated clotted time is greater than 450 seconds. Systemic cooling (via pump oxygenator and head jacket) is instituted and continued until core temperature reaches 20°C on both nasopharyngeal and bladder temperature probes or until nasopharyngeal temperature has been at 20°C for over 20 minutes. A cooling jacket around the heart may be used to protect the right ventricle. Dissection of the pulmonary artery may commence before the first period of circulatory arrest. There are two methods for reducing pulmonary artery blood flow to allow a clear field for endarterectomy: either complete deep hypothermic circulatory arrest (DHCA) for a period up to 20 minutes, or selective anterograde cerebral perfusion (SACP) allowing continued blood flow to the head, but reduced flow to the lungs and rest of the body. With this technique, clamps are placed across the ascending aorta and aortic arch distal to the left carotid and approximately 1 L of perfusion continued to give a right radial pressure of approximately 40 mmHg.

When using DHCA, the aortic cross clamp is applied and 1 litre of cardioplegia administered. When DHCA has been instituted, and blood drained out to the CPB reservoir, the lungs are ventilated manually with air to drain out blood remaining in the pulmonary artery circulation.

Periods of circulatory arrest are strictly limited to 20 minutes, with a period of reperfusion after each arrest period of at least 10 minutes and once endarterectomies on both sides are completed, CPB is reinstituted and the patient is being rewarmed.

2.1.3. Data Collection

Measurements will be obtained at the following time points: first measurement after induction of anesthesia following insertion of the catheters (baseline). Second and third measurements will be obtained after separation from cardiopulmonary bypass (after protamine administration) and after sternal closure respectively (17). Additional measurements will be planned 2, 4, 6, 12, 24, 36, 40 hours after the third measurement.

The PaO_2/FiO_2 ratio will be calculated using arterial blood gas samples and ventilator data. Ventilator parameters recorded will include tidal volume, respiratory rate, minute ventilation, positive end expiratory pressure, mean airway pressure, peak pressure, plateau pressure, and static respiratory compliance. Murray lung injury scores will also be determined for each patient.

2.1.4. Chest Radiographs

Patients will also undergo daily chest radiographs as part of their standard care. These postoperative chest radiographs will be reviewed and reported by a blinded radiologist.

2.2. Endpoints

The primary goal of this investigation is to evaluate EVLW measured by transpulmonary thermodilution, as a predictor of clinically significant reperfusion lung injury in the context of pulmonary endarterectomy. The secondary end points of the trial are: correlation between EVLW and (a) worst post-operative PaO_2/FiO_2 (b) duration of mechanical ventilation (c) length of ICU stay (d) duration of hospital stay (e) in-hospital mortality.

2.3. Statistical Considerations

We undertook a preliminary analysis of 20 consecutive pulmonary endarterectomy patients at Papworth hospital between January and March 2015 and found that reperfusion lung injury occurred in 45% (9/20) of patients. Clinically significant reperfusion lung injury occurred in 25% (5/20) of patients. Neither the worst PaO_2/FiO_2 nor Murray lung injury scores were significantly associated with intensive care unit length of stay (R = 0.274, P = 0.242 and R = 0.283, P = 0.348, respectively). There was a moderate negative correlation between worst PaO_2/FiO_2 and duration of ventilatory support (R = -0.6499, P = 0.042) among patients with reperfusion lung injury. These results highlight the need for a robust early marker of clinically significant permeability oedema that confers predictive and diagnostic value in patients undergoing pulmonary endarterectomy. The clinical characteristics of the preliminary study population are outlined in Table 1.

Table 1. Characteristics of Preliminary Study Population[a]

Patient Characteristics	Data
Patients, No.	20
Gender, M/F	12/8
Age at time of inclusion, median (IQR)	63.5 (14)
Proportion with RLI, No. (%)	9/20 (45)
Worst PaO_2/FiO_2 ratio, mmHg, median (IQR)	117.76 (147)
Highest PEEP/CPAP level (cmH_2O), median (IQR)	7.5 (3)
LIS (Murray score), median (IQR)	1.25 (0.5)
ICU LOS, days, median (IQR)	2.04 (1.88)
Duration of respiratory support in clinically significant RLI, days, median (IQR)	4.17 (1.96)

Abbreviations: ICU LOS, Intensive Care Unit Length of Stay; IQR, Interquatrtile Range; LIS, Lung Injury Score (18); PaO_2/FiO_2, Partial Arterial Oxygen Tension/ Inspiratory Oxygen Fraction; PEEP, Positive-End Expiratory Pressure; RLI, Reperfusion Lung Injury.

[a]Respiratory support: invasive mechanical ventilation, non-invasive ventilation, continuous positive airway pressure or combination.

The primary goal of the proposed investigation is to assess the accuracy of EVLWi as a predictive marker of clinically significant reperfusion lung injury in patients undergoing pulmonary endarterectomy, using area under the receiver-operating characteristic curves.

The relationship between EVLW indices and respiratory parameters (presence of reperfusion injury, PaO_2/FiO_2, Murray lung injury score, positive end-expiratory pressure or continuous positive airway pressure values) to intensive care unit mortality will also be examined.

2.4. Power Analysis

In a prospective observational cohort of critically ill patients with shock, Martin et al, compared patients with and without acute respiratory distress syndrome (ARDS) (n = 15 and n = 14, respectively) and found a median EVLWi of 15 mg/kg and 7 mL/kg respectively (6). Perkins and colleagues compared salmeterol with placebo in ARDS patients (n = 19 and n = 21 respectively) and reported a baseline mean (SD) EVLWi 14 mL/kg (8 mL/kg). Using a t-test for difference between means and assuming the standard deviation of peak EVLWi is 8 mL/kg, a sample size of 52 patients is estimated to provide 80% power (two-tailed, alpha = 0.05) to detect a 6.5 mL/kg difference in EVLWi between patients with perioperative reperfusion lung injury and those without lung injury. We will therefore be recruiting 2 - 4 patients a week for up to 26 consecutive weeks and the total expected time devoted to the project will be 6 months to 1 year. We plan to conduct an interim analysis after 25 participants are recruited in order to check if the parameters used for the power calculation are correct.

3. Ethical Considerations

Full research ethics committee and local Research and Development approvals are in place. Patients will be informed about the study by post before attending hospital, where the study will be explained to them in detail by key study personnel and they will then be asked to provide written consent in accordance with the regulations of the regional ethics committee. Ethics approval has been granted from East Midlands Nottingham 2 research ethics committee (United Kingdom). We aim to publish our results in a high-impact peer-reviewed journal and present our data at major UK and international scientific meetings.

4. Discussion

ARDS is characterized by the acute development of hypoxemia and bilateral lung infiltrates due to increased pulmonary vascular permeability. It is associated with increased venous admixture, increased physiological dead space and reduced lung compliance (19).

ARDS is a leading cause of postoperative hypoxemic respiratory failure with reported prevalence of 3 to 9% and associated mortality rates between 27 and 45% (19, 20). As many as 20% of patients undergoing cardiac surgery will develop ARDS during the perioperative period, with a mortality as high as 80% (21). Beyond mortality, long-term health status can be compromised, with long term functional limitations after an ARDS episode. Postoperative respiratory failure also increases healthcare resource utilization and costs (19-22).

Early in the course of ARDS, intravascular fluid leakage into the interstitium and alveoli of the lung due to diffuse alveolar damage results in increased EVLW. It has been shown that increasing absolute EVLWi values in the early phase of ARDS are associated with poor clinical outcomes (23). Recent studies indicate that EVLWi values represent severity of lung injury in ARDS and that the maximum EVLWi value over the entire ARDS episode is an independent predictor of mortality (10).

Addition of EVLW to perioperative ARDS clinical risk prediction models could potentially increase the opportunity of delivering timely therapeutic interventions such as least damaging ventilatory strategies including optimal driving pressure, perioperative fluid management and blood product transfusion, and ultimately about prognostication.

However, the heterogeneous patient population included in most EVLW studies different cut-off values restrict its generalizability and validity as ARDS predictor in surgical patients (24).

Patients undergoing pulmonary endarterectomy constitute a unique patient population at risk of development of ARDS due to high permeability lung injury, and an ideal model for evaluating whether EVLW correlates with severity of lung injury, response to treatment and clinical outcomes, and assess its applicability as a diagnostic criterion of ARDS (1).

Footnotes

Conflicts of Interest: Nil.

Ethics Approval: East Midlands - Nottingham 2 Research Ethics Committee - REC reference: 15/EM/0486.

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