Recruitment maneuver application following pulmonary endarterectomy; does it have any impact on reperfusion lung injury and outcome?

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Abstract
Aim: The only curative treatment of chronic thromboembolic pulmonary hypertension is Pulmonary Endarterectomy. This surgery, may result in ischemia-reperfusion lung injury, which may be related with higher mortality. The aim of the study was to assess the effect of intraoperative recruitment maneuver on ischemia-reperfusion lung injury following Pulmonary Endarterectomy.

Material and Methods: The study was designed as a randomized prospective study with the approval of the Clinical Trials Ethics Committee of our hospital. Between January 2019 and December 2019, 60 patients were included in the study. Randomization was performed using a computer program. The patients were divided into two groups: the study group, in which the recruitment maneuvers were performed and the control group. The primary outcome of this study was to compare the biochemical markers of ischemia-reperfusion injury and oxygenation in patients with and without recruitment maneuvers.

Results: In the recruitment group, arterial pO2 value was 312±82 mmHg, while it was 268±85 mmHg in the control group (p: 0.044). Malondialdehyde, a biomarker of ischemia-reperfusion injury in Broncho Alveolar Lavage fluid were 5±1 and 4±0 (p:0.008) in the control and recruitment groups, and Superoxide Dismutase were 10±2 and 11±1 (p: 0.011) in the control and recruitment groups, respectively.

Discussion: During pulmonary endarterectomy operations, the application of recruitment maneuvers at high inflation pressures after cardiopulmonary bypass, where reperfusion injury may occur, results in a decrease in ischemia-reperfusion injury markers especially in broncho alveolar lavage fluid, and an increase in antioxidant molecules.

Keywords
Chronic Thromboembolic Pulmonary Hypertension; Pulmonary Endarterectomy; Recruitment Maneuver; Reperfusion Lung Injury; Antioxidant Molecule
Introduction

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a rare disease characterized by the progression of thromboembolism as an organized tissue in the pulmonary arteries[1]. Pulmonary Endarterectomy (PEA) is the only curative treatment option for CTEPH. Following operation, reperfusion of the occluded pulmonary artery may result in ischemia-reperfusion lung injury and right ventricular failure [2]. Reperfusion lung injury is characterized by arterial hypoxia caused by focal pulmonary infiltrates in the regions distal to the endarterectomy[3].

Understanding the process is extremely important to develop a new treatment strategy or procedure that can reduce tissue injury[4]. The mechanisms that cause ischemia-reperfusion injury are very complex and mainly involve a number of events, such as the production of molecular oxygen due to the improvement of blood flow within the ischemic tissue, and consequently the release of reactive oxygen derivatives, prominent inflammatory response and endothelial dysfunction [5].

To prevent reperfusion lung damage that may develop after operation, pre- and post-operative fluid restriction[6], avoidance of high-dose catecholamine and vasodilator therapy, low tidal volume (TV) and inspiratory peak pressures, and recruitment maneuvers (RM) with high PEEP in the postoperative period have been proposed [7].

High PEEP and RM have resulted in better survival and are associated with decreased inflammatory mediator levels in plasma and Broncho Alveolar Lavage (BAL) fluids [8,9], increased oxygenation and decreased Pulmonary Vascular Resistance (PVR)[10-12].

The aim of this study was to investigate the effect of intraoperative lung protection with RM maneuver in patients undergoing PEA for ischemic reperfusion lung injury. The primary outcome of this study was to compare the biochemical markers of ischemia-reperfusion injury and oxygenation in patients with and without RM. The secondary outcome was a comparison of hemodynamics, lung damage, intensive care and hospital stay in patients with and without RM.

Material and Methods

Patient Selection:
The study was designed as a randomized prospective study and approved by the Institutional Review Board (IRB) of Kartal Koşuyolu High Speciality Educational and Research Hospital (IRB#: 2018.6.62). Written informed consent was obtained from all patients participating in the trial, a legal surrogate, parents or legal guardians for minor subjects. Between January 2019 and December 2019, 60 patients were included in the study.

Randomization was performed through a computer program. The patients were divided into two groups: the study group, in which RM was performed (RM, n=30), and the control group (C, n=30). Patients with chronic inflammatory disease, chronic liver and kidney failure, patients who had postoperative complications requiring Extracorporeal Membrane Oxygenation (ECMO), and patients who died after surgery were excluded from the study.

Anesthetic and Surgical Procedure:
Central venous and pulmonary artery catheterization were performed with an 8F catheter from the internal jugular vein, and cardiac output was measured with the Thermol dilution (Arrow®Thermol dilution Catheters) method in all patients. Anesthesia maintenance was achieved with 2% sevoflurane in 60% oxygen-air mixture. Pulmonary endarterectomy was performed during Total Circulatory Arrest (TCA) at 18°C. The recruitment maneuver was performed in patients in the study group for 45 seconds at 35 cmH2O PEEP, FiO2:%100 PCV mode after cardiopulmonary bypass (CPB) with open chest. Throughout the RM, mean arterial pressure, central venous pressure (CVP) and transesophageal echo (TEE), right ventricular function and septum position, and signs of RM-related right ventricular overload were monitored. Following the RM, we decreased PEEP to 6-8 cm H2O in one step and returned mechanical ventilation to baseline values. Patients in the control group were ventilated in the PCV mode at 6-8 ml/kg tidal volume, 6-8 cmH2O PEEP, FiO2 %60 (pO2>100 mmHg) and 12-15/min respiratory rate. All patients received 20-30 ppm inhaled nitric oxide therapy throughout the surgery. Patients were transferred to the intensive care unit after the operation. The patients were kept anaesthetized and sedated postoperatively in the intensive care unit. Extensive ventilatory and circulatory monitoring were continuously performed, including online measurement of pulmonary artery pressure with an oxymetric Swan-Ganz catheter, cardiac output, mixed venous oxygen saturation, and arterial blood gases. Pressure-controlled mechanical ventilation with PEEP of 6-8 cmH2O, FiO2: %60 (pO2>90-100 mmHg) and tidal volume of 6-8 ml/kg was applied to all patients. Depending on blood gas values (pH>7.30, pO2>90-100 mmHg), high PEEP values were reduced to 3 cmH2O before extubation by PEEP titration. Inhaled nitric oxide, which started in the intraoperative period was reduced for the first 4-6 hours postoperatively and weaned. PaO2/FiO2 ≥150 or SpO2 ≥92% (FiO2 ≤ 40%) and positive end expiratory pressure (PEEP) ≤3 cmH2O, pH > 7.25, hemodynamic stability (no vasopressor drugs or low dose), can initiate inspiratory effort and neurologically awake patients were extubated. Postoperative fluid treatment of all patients was planned to have a negative fluid balance and chest radiographs were taken daily. Postoperative chest radiographs of all patients at 24 hours were evaluated by a single radiologist. According, both lungs were divided into three parts: the lower, middle and upper zones. Parenchyma infiltration images were scored 1 point and airspace images were scored 3 points. The total reperfusion score was accepted as a total of 18 points for both lungs [13].

Measurement of Biochemical Parameters:
Blood and BAL fluid samples were collected from all patients 4 hours following the operation. Inlood and BAL samples were centrifuged, and their plasmas were separated, and this plasma was stored in the deep-freeze at -200C until biochemical measurements were performed in Eppendorfs. Biochemical measurements were performed at the end of the study by dissolving all plasmas at once.

Measurement of malondialdehde (MDA) levels:
The rate of lipid peroxidation was measured using the Buege and Aust procedure. MDA and its products formed a colored product by reacting with thiobarbituric acid. 250 µL of plasma and BAL were boiled at 95°C for 15 minutes by adding 1 mL.
of thiobarbituric acid, 1.5 mL of trichloroacetic acid and 200 µL of hydrochloric acid. Following the centrifugation process, the absorbances of the supernatants were read at 532 nm wavelength.

**Measurement of superoxide dismutase (SOD) activity:**

Superoxide dismutase (SOD) activity was measured with modification using the method of Sun et al. This method has been used in the inhibition of nitroblue tetrazolium reduction. Xanthine oxidase was used as a superoxide stimulant. SOD reagent (100 µL) and 20 µL xanthine oxidase were pipetted onto the 20 µL sample. After twenty minutes of incubation, 20 µL of copper 2 chloride was added to stop the reaction. Absorbances were read against the reagent blind at 560 nm wavelength. The activity of 1 unit Cu, Zn-SOD was defined as the inhibition of 50% xanthine oxidase activity.

**Determination of advanced oxidation protein products (AOPP) concentration:**

Advanced oxidation protein products (AOPP) were made according to Hanasand’s method. Citric acid (200 µL) was added to 20 µL of the sample pipetted into UV plates. One minute later, 10 µL of potassium iodide was pipetted, and the reading was performed at a wavelength of 340 nm. In order to make concentration calculations, Chloramine-T equivalents were used as a standard in the 0-100 µmol/L concentration range.

**Measurement of the level of thiol groups:**

Plasma and BAL total thiol (T-SH) and non-protein thiol (NPSH) concentrations were analyzed using 5.5 dithiobis (2-nitrobenzoic acid) (DTNB) with the method developed by Sedlak and Lindsay. Plasma aliquots of 20 µL were treated with 400 µL of 0.2 M tris buffer, pH 8.2 and 20 µL of 0.01 M DTNB to determine the T-SH groups. NPSH samples were measured in the following way: 20 µL plasma was mixed with 400 µL 50% TCA. The tubes were centrifuged at 3000g for 15 minutes. Supernatant fractions were studied as the T-SH method mentioned above. The absorbance values of the samples were read at 412 nm wavelength against the reactive blind. The molar extinction coefficient of thiol (SH) groups at 412 nm wavelength was considered to be approximately $\nu=13,100$ m$^{-1}$/cm$^{-1}$. P-SH groups were calculated by subtracting NP-SH from T-SH.

**Statistical Analysis:**

Results were expressed as either mean (SD) or frequencies. The Chi-square test was used for the comparison of the categorical variable. Continuous random variables were tested for normality of the data distribution using a histogram or Shapiro-Wilk test. The primary outcomes, which were continuous random variables, were compared between the groups using the Unpaired t-test. For the secondary outcomes, which were also continuous random variables; Paired t-tests were used in each group, then a new variable which was named as “percent of change” was calculated in order to determine the amount of change between pre and post measurements. Therefore, an Unpaired t-test was used to compare the mean percentage of change between the groups. To test the differences in hemodynamic parameters between groups (RM-Control group), we carried out ANCOVA analysis using baseline variables. Analyses were performed using SPSS Statistics version 15.0 software (SPSS Inc., Chicago, IL, USA). A P-value of 0.05 was considered statistically significant.

**Results**

The demographic characteristics of the patients are shown in Table 1. The mean age of the patients was 49±16 years, and 52.5% (n: 31) were female. There were no differences between the two groups in terms of demographic characteristics (Table 1).

The mean cardiopulmonary bypass duration, aortic cross-clamp and total circulatory arrest duration were 191±3, 40±2 and 21±1 min, respectively, and there were no differences between the two groups. The comparison of two groups in terms of the postoperative 4th-hour arterial blood gas values and the postoperative 24th-hour ischemia-reperfusion injury score in the chest X-ray are given postoperative arterial pO2 value was significantly higher in the recruitment group compared to the control group (312±82 vs 268±85 mmHg; p: 0.044) (Table 1). Preoperative and postoperative hemodynamic data are summarized in Table 3. When pre-postoperative changes of hemodynamic values were compared within each group (RM ve control) mAP, mPAP, CO, CI and PVR, which were hemodynamic parameters, significantly decreased. However, after the adjustment of absolute change, % change, and pre-postoperative changes according to baseline values with ANCOVA, changes in these hemodynamic parameters were detected to be non-significant (Table 2, Figure 1). The comparison of biochemical markers due to ischemia-reperfusion injury in BAL and blood sample is shown in Table 3. MDA, the most important marker of ischemia-reperfusion injury, especially in BAL, was found to be significantly higher in the control group than in the recruitment group (5±1 and 4, respectively) (p: 0.008), and SOD, which reduces ischemia-reperfusion injury, was found to be low in the control group, and the difference between the two groups was significant (10±2 and 11±1, respectively) (p: 0.011) (Table 3).

Clinically, there were no differences between the RM and Control groups, in terms of duration of mechanical ventilation (19±18 hours vs 18±7 hours; p: 0.868, respectively), intensive care unit (2±1 days vs 3±1 days; p: 0.863, respectively) and hospital stay (8±2 days vs 10±5 days; p: 0.146, respectively).

| Table 1. Demographic characteristics and per-postoperative data |
|----------|---------|----------|---------|-------|
|          | Total   | RM       | C       | P      |
|----------|---------|----------|---------|-------|
| Age (year) | 49±2    | 51±15    | 47±16   | 0.386 |
| Gender (female) | 31 (51.7%) | 17 (56.7%) | 14 (46.7%) | 0.438 |
| BSA (m2) | 1.86±0.22 | 1.87±0.18 | 1.85±0.16 | 0.762 |
| CPB duration (min) | 191±3 | 190±21 | 193±35 | 0.758 |
| AoXCl duration (min) | 40±2 | 36±13 | 43±20 | 0.133 |
| TCA duration (min) | 21±1 | 20±7 | 22±10 | 0.332 |
| pH | 7.34±0.01 | 7.34±0.03 | 7.34±0.08 | 0.845 |
| Arterial pO2 (mmHg) | 290±11 | 312±82 | 268±85 | 0.044 |
| Arterial pCO2 (mmHg) | 40±1 | 40±5 | 40±5 | 0.749 |
| Lactate (mEq/L) | 3.9±0.2 | 3.8±1.9 | 3.9±1.4 | 0.811 |
| Hemoglobin (g/L) | 28±0 | 28±3 | 27±3 | 0.797 |
| Chest X-ray score | 5.1±0.3 | 4.7±2 | 5.7±2.8 | 0.196 |

RM: recruitment maneuver group, C: control group, BSA: body surface area, CPB: cardiopulmonary bypass, AoXCl: aortic cross-clamp, TCA: total circulatory arrest.
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Discussion

In this study, the biochemical and clinical effects of two different ventilator strategies applied to patients after PEA on ischemia-reperfusion lung injury were investigated. The most important and primary findings of the study were that the RM, applied in the early period of reperfusion reduced MDA in BAL samples of the patients and increased SOD, an antioxidant molecule, and oxygenation in arterial blood gas samples. No significant difference was observed in the findings of ischemia-reperfusion injury on the chest X-ray, intensive care unit, and hospital stay of the patients.

Ischemia-reperfusion lung injury following PEA is an important risk factor for early mortality. Pulmonary artery pressure increases more significantly in the RM group compared to the C group. This finding is in line with previous studies indicating a possible protective effect of RM on pulmonary vascular resistance.

Table 2. Pre-postoperative comparison of hemodynamic parameters

|                | Total (n:60) | RM (n:30) | C (n:30) | P     |
|----------------|--------------|-----------|----------|-------|
| mAP (mmHg)    | 79±14        | 75±13     | 0.01     | 71±10 | 69±10 | 0.0.1 | 0.09 |
| mAP (% change)  | 0.06±0.17 | 0.02±0.19 | 0.46     | 0.06±0.17 | 0.02±0.19 | 0.46 |
| mPAP (mmHg)   | 42±2         | 30±7      | <0.001   | 43±15 | 33.7±10 | <0.001 | 0.14 |
| mPAP (% change) | -11.9±13.4 | -10±11.9  | 0.56     | -11.9±13.4 | -10±11.9 | 0.56 |
| mPAP (% change) | -0.23±0.23 | -0.18±0.23 | 0.41     | -0.23±0.23 | -0.18±0.23 | 0.41 |
| C (L/min)     | 4±1          | 6±1       | <0.001   | 4±1   | 6±2    | <0.001 | 0.56 |
| C (% change)   | 0.44±0.46   | 0.46±0.69 | 0.85     | 0.44±0.46 | 0.46±0.69 | 0.85 |
| CI (L/min/m2)  | 2±0.6        | 3±0.9     | <0.001   | 2±0.8 | 3±1.1  | <0.001 | 0.46 |
| CI (% change)  | 0.9±1        | 0.9±1     | 0.95     | 0.9±1 | 0.9±1  | 0.95 |
| PVR (dyn/cm-5) | 614±378     | 194±128   | <0.001   | 668±437| 235±184| <0.001 | 0.40 |
| PVR (% change) | -419±337    | -433±355  | 0.87     | -419±337 | -433±355 | 0.87 |

Table 3. Ischemia-reperfusion injury biochemical biomarkers

| Biomarker                        | Total (n:60) | RM (n:30) | C (n:30) | P     |
|----------------------------------|--------------|-----------|----------|-------|
| Blood AOPP (μmol/L chloramine T equivalent) | 101±5       | 100±40   | 103±42 | 0.724 |
| Blood t-SH (nmol/mg protein)     | 22±1         | 22±9     | 22±7 | 0.961 |
| Blood MDA (μmol/mg protein)      | 6±0          | 6±1      | 7±1 | 0.405 |
| Blood SOD (U/mg protein)         | 6±0          | 6±1      | 6±1 | 0.697 |
| BALF AOPP (μmol/L chloramine T equivalent) | 80±4       | 81±40   | 79±36 | 0.863 |
| BALF t-SH (nmol/mg protein)      | 13±0         | 12±6     | 14±7 | 0.201 |
| BALF MDA (μmol/mg protein)       | 5±0          | 4±0      | 5±1 | 0.008 |
| BALF SOD (U/mg protein)          | 10±0         | 11±1     | 10±2 | 0.011 |

Discussion

In this study, the biochemical and clinical effects of two different ventilator strategies applied to patients after PEA on ischemia-reperfusion lung injury were investigated. The most important and primary findings of the study were that the RM, applied in the early period of reperfusion reduced MDA in BAL samples of the patients and increased SOD, an antioxidant molecule, and oxygenation in arterial blood gas samples. No significant difference was observed in the findings of ischemia-reperfusion injury on the chest X-ray, intensive care unit, and hospital stay of the patients.

Ischemia-reperfusion lung injury following PEA is an important risk factor for early mortality. Pulmonary artery pressure
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In the pre-postoperative period, it has been suggested to avoid excessive fluids, especially to prevent the development of pulmonary edema [6]. Different ventilator strategies are also applied, since they decrease mortality and morbidity by reducing reperfusion injury in the lung tissue. Although the optimum ventilation strategy is not fully known, these strategies have been developing based on the experience gained from both lung transplantation and PEA operations. It has been reported that performing RM before reperfusion of ischemic lungs protects the lungs from reperfusion lung injury [20], and early administration of optimal PEEP reduces extravascular lung water in oleic acid lung injury [21]. In PEA operations, avoiding vasoactive and vasodilator treatments following CPB, the use of low TV and low peak inspiratory pressures reduce reperfusion lung injury and the development of right ventricular failure [3]. After PEA operation, the application of RM and high PEEP in the intensive care unit reduce pulmonary edema caused by reperfusion injury or lung injury due to atelectasis [7]. The results obtained from this study indicated that RM, performed in the early period of reperfusion injury, significantly increased SOD and reduced the reperfusion lung injury at the cellular level by decreasing MDA caused by ischemia-reperfusion.

Application of RM with PEEP and subsequent maintenance of high PEEP levels prevent alveolar micro atelectasis and repair the oxygenation [22]. In patients with mechanical ventilation support, PEEP may increase hyperinflation in the non-dependent lungs, while clearing off closed alveoli in the dependent lungs. Thus, high PEEP has positive effects in reversible ARDS patients [23]. In particular, it reduces hospital and intensive care mortality rates [24], and significantly increases oxygenation in patients after CPB [25]. In hypoxemic patients with pulmonary hypertension who underwent PEA operation due to chronic pulmonary thromboembolism, there is an increase in oxygenation with the RM application and subsequent application of high PEEP [8]. In this study, it was found that the application of recruitment maneuver at high inflation pressures in PEA operations in the early period immediately after weaning from CPB caused a significant increase in oxygenation compared to the control group.

Patients in both groups were extubated on average on the first operative day. It was determined that the intensive care and a hospital stay of the patients and reperfusion injury findings in chest X-ray were less in the recruitment group, who were applied high PEEP, although there was no statistically significant difference between the two groups.

The limitations of our study are the low number of patients and the role of the surgical procedure itself as a primary driver of the observed physiological changes. While the study demonstrated an increase in superoxide dismutase and a decrease in malondialdehyde, both of which indicate a decrease in reperfusion injury, we did not find any significant difference between measurable clinical outcomes, such as chest X-ray score findings, ICU and hospital length of stay. The RM itself potentially "washes" out or dilutes the alveolar content, and this may be the reason why SOD activity and MDA were marginally reduced in BAL of the RM group. The measurement of BAL total protein concentration could help determine whether such a washout effect might have happened. In this study we used sample sizes of 30 in each group by holding to the Central Limit Theorem and Law of Large Numbers because the incidence of CTEPH patients in the society is limited.

In conclusion, during PEA operations, the application of RM at high inflation pressures after CPB, where reperfusion injury begins, resulted in a decrease in ischemia-reperfusion injury markers, especially in BAL fluid, and an increase in antioxidant molecules. While application of RM provided a significant increase in oxygenation without causing hemodynamic instability, no clinical important differences were detected.

Scientific Responsibility Statement
The authors declare that they are responsible for the article’s scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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