

Effect of continuous administration of low-medium flow oxygen for non-ventilated lung during one lung ventilation surgery on blood gas analysis and oxidative stress response in lung tissue of tumor patient—A randomized controlled trial

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Research article

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Abstract

Background: One-lung ventilation (OLV) induces hypoxia during the operation and oxidative stress to the non-ventilated lung (NVL) which may cause acute lung injury (ALI). **Aims:** We sought to find out whether continuous administration of low-medium flow oxygen for NVL during OLV can mitigate the oxidative stress in lung tissue of patient.

Methods: After local Ethics Committee approval and informed consent, we randomly allocated fifty-seven patients scheduled for elective pulmonary tumor resection. The F14 tube was placed at 2-3cm beyond the carina of trachea in the NVL at the time of the beginning of the OLV in group O, administering continuously with oxygen. Blood samples were taken from radial artery and internal jugular vein simultaneously for blood gas analysis, immediately after induction of anesthesia (T 1), 30min (T 2), 1h (T 3) and 2h (T 4) after OLV. Lung tissue was taken 5cm distant from the tumor for determination of superoxide dismutase(SOD) and malondialdehyde(MDA), and expression of heme oxygenase-1(HO-1) .

Result: Compared with group C, the PaO₂ was significantly increased at T 2-4 and the PaCO₂ was significantly decreased at T 2,3 , the PvO₂ was significantly increased at T 2,3 and the PvCO₂ was significantly decreased at T 2-4 , the lung concentration of MDA was significantly lower and the local expression level of HO-1 in lung was significantly elevated in group O $\times P < 0.05$.

Conclusion: The administration of continuous low-medium flow oxygen for NVL during OLV has shown the effect of pulmonary protection. The possible mechanism is related with the inhibition of the oxidative stress response in lung tissue.

Background

One-lung ventilation (OLV) is usually performed to provide wide surgical area in thoracic surgeries[1]. Lots of studies implied that OLV can cause lung injury[2-4]. OLV is an important induced factor of acute lung injury (ALI), which is one of the major causes of death after thoracic surgery and the mortality is stable in 2-5%[5]. During OLV, alveolar collapse occurs in the NVL then causing hypoxia, and hypoxic pulmonary vasoconstriction caused hypoperfusion in the NVL tissue[6]. The reoxygenation and the ischemia-reperfusion injury also aggregate ALI.

Oxidative stress is an important factor of ALI during OLV, and it is found that oxidative stress plays an important role in the structure, function, and inflammatory response of the ALI model[7]. Misthos P et al stated that the degree of the amount of generated oxygen free radicals is associated with the duration of OLV, especially for patients with lung cancer[8]. After resuming two-lung ventilation (TLV), the reperfusion of the blood and reentry of oxygen to ischemic tissue cause sudden and significant increase in reactive oxygen species (ROS) production[9]. The total antioxidant status (TAS) of human body counteracts oxidative stress. Cheng YJ et al claimed that there is no significant decrease in the total antioxidant status after resuming TLV, which indicates adequate antioxidant capacity to counteract it, and they thought that severe oxidative injuries after OLV/TLV should be considered in patients without adequate

antioxidative capacity, such as those with cancer and trauma[9]. Therefore, the new question of how to reduce the oxidative stress injury for patient with lung cancer during the surgery needs to be answered.

Continuous administration of low-medium flow oxygen for NVL during OLV provides adequate oxygen supply in the NVL and avoid the interference of the operation view. We wish to investigate the effect of continuous administration of low-medium flow oxygen for NVL during OLV on oxidative stress in lung tissue of patient, and to seek a new protective strategy for ALI.

Methods

Study design and patient population

This randomized, prospective double-blind study enrolled 60 patients from Jan, 2, 2017 to Mar, 17, 2017. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Trial Registry number, 2016020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Criteria for inclusion and exclusion

The patients were classified as physical status I or II according to the American Society of Anesthesiologists, ranged in age between 18 and 64 years old and were scheduled to undergo video-assisted thoracoscopic surgery requiring OLV. Each of them was randomly divided into two groups by random number table method: experimental group (Group O, continued low-medium flow oxygen in NVL, n=28), control group (Group C, n=29). The exclusion criteria included patients with the following conditions: Surgery for more than 4 hours; Need to stop single lung ventilation during surgery to restore dual lung ventilation to maintain oxygen saturation > 90%; Patients have an immune disease; Upper respiratory tract infection; Preoperative pulmonary function tests measured values lower than the minimum required value of various lung resection preoperative pulmonary function test (FEV1 < 70% of predicted value); Adrenal dysfunction; After radiotherapy and chemotherapy; Pleural effusion; asthma; Oral hormonal therapy within three months before surgery.

Preoperative preparations and anesthesia protocol

The patients received no premedication. When the patients arrived in the operating room, they were monitored by pulse oximetry, electrocardiography (ECG), non-invasive blood pressure (NIBP). Using a catheter inserted into a peripheral vein, 6 ml/kg of crystalloid was injected into the patients. The patients were randomly assigned to groups O and C. After anesthesia was induced with sufentanil 0.2-0.3ug/kg, propofol 1-2mg/kg and rocuronium bromide 0.6-1.0mg/kg, the patients were intubated with a non-operation lateral double-lumen tube(DLT) (size F35 for women and size F37 for men) by experienced thoracic anesthesiologists involved in the study, and the correct position was confirmed using a fiberoptic bronchoscope (FOB). In the initial two-lung ventilation (TLV) and one-lung ventilation (OLV) period, the

tidal volume (V_t) was 4-5 ml/kg, the respiratory rate was 12-15 bpm, the I/E ratio was 1:2, and the positive endexpiratory pressure (PEEP) was 5cmH₂O. Anesthesia was maintained using propofol 4-10 mg·kg⁻¹·h⁻¹, remifentanyl 1.5-120 ug·kg⁻¹·h⁻¹, cisatracurium 0.05-0.1 mg·kg⁻¹·h⁻¹, dexmedetomidine 0.2-0.7 ug·kg⁻¹·h⁻¹, and auxiliary inhalation sevoflurane 0.5% -1%. The mean arterial blood pressures (MAP) and heart rates (HR) were 20% less than the baseline values. The patient was placed in a lateral decubitus position after right internal jugular central venous catheterization. Invasive blood pressure monitoring was achieved by cannulating the radial artery. The correct DLT position was confirmed again using a FOB. In group O, the F14 catheter was placed in the non-ventilated side lung of the patient for 2-3cm after the bifurcation of the trachea and continued to be given oxygen in the low-medium flow rate of 1-4L / min. In group C, no special treatment was given to the patient after the single lung ventilation. In both groups, anesthesia induction and OLV were initiated and maintained using 100% oxygen. At the end of the surgery, the lung recruitment maneuver was given to the patient. When the operation was completed, the patients were discharged to the PACU or ICU.

Measurements

Both groups were simultaneously collected radial artery and jugular vein blood samples for blood gas analysis at immediate induction of anesthesia (T_1), single lung ventilation 30min (T_2), 1h (T_3), 2h (T_4). Cut off about 5cm from the tumor size of about 3cmx3cmx3cm lung tissue. The contents of SOD and MDA in lung tissue were determined by chemical colorimetry(The kit was provided by Nanjing Jiancheng Bioengineering Institute). HO-1 expression was detected by Western-blot(Kit by Abcam Technology Co., Ltd. and KPL Beijing West Mei Jie Technology Co., Ltd).

The same surgeons who were blinded to the lung collapse technique performed all surgical procedures. All of the data were recorded by another anesthesiologist who was unfamiliar with the lung collapse technique.

Statistical analysis

The data are expressed as the mean \pm standard deviation (SD) or as the number of patients. The statistical analyses were performed using a paired Student's t-test. The categorical variables were performed using the χ^2 -test. We performed the statistical analyses using SPSS version 21.0 (SPSS Inc. Chicago, IL, USA). A P -value < 0.05 was considered statistically significant.

Results

A total of 60 patients were enrolled in this study, however, three patients were excluded from the data analysis. The final analyses included 28 patients in group O and 29 patients in group C (Fig. 1).

Patients' characteristics and surgical conditions, postoperative pulmonary complications were not different between two groups ($P > 0.05$) (Table 1).

Table 1 Patient characteristics

Variable	Group O (n=28)	Group C (n=29)
Sex (M/F)	13/16	13/15
Age (years)	63.42±5.34	65.88±4.80
Height (cm)	162.16±6.90	163.125±7.08
Weight (kg)	63.48±7.47	64.34±5.46
ASA class I/II	13/15	12/17
Preoperative pulmonary function (normal / abnormal)	21/10	16/16
Anesthesia time (min)	254.03±58.69	260.69±55.48
Operation time (min)	202.10±50.63	210.01±48.56
OLV time (min)	172.71±51.15	170.21±47.44
Hospitalization time (d)	16.45±3.42	18.65±3.22
Postoperative hospital stay (d)	9.03±2.11	9.21±2.06
Second intubation	0	0
Chest tube indwelling time (d)	6.26±1.75	6.34±1.73

The data are expressed as the mean ± SD values or the number of patients. ASA, American Society of Anesthesiologists

The levels of arterial and venous blood gas analysis are given in table 2. The results of statistical analysis are presented in Fig. 2, from which we can see at T₂₋₄, the PaO₂ levels were significantly higher in group O than in group C (127±4.2 vs 90±2.2, 180±8 vs 92±2.1, 196±7.7 vs 91±2.2). At T₂₋₃, the PaCO₂ levels were significantly lower in group O than in group C (41.7±4.4 vs 45.9±3.4, 40.5±5.7 vs 44.2±3.2). At T₂₋₃, the PvO₂ levels were significantly higher in group O than in group C (61±1.7 vs 42±1.3, 58±1.7 vs 46±2.4). At T₂₋₄, the PvCO₂ levels were significantly lower in group O than in group C. (50±0.5 vs 57±0.6, 50±0.6 vs 62±0.9, 46±0.8 vs 59±0.7).

Table 2 Blood gas analysis

Variable	Group	T1	T2	T3	T4
PaO ₂ (mmHg)	O(n=28)	337±10.4	127±4.2*	180±8*	196±7.7*
	C(n=29)	318±4.9	90±2.2	92±2.1	91±2.2
PaCO ₂ (mmHg)	O(n=28)	40.9±5.6	41.7±4.4*	40.5±5.7*	43.3±5.5
	C(n=29)	35.6±1.4	45.9±3.4	44.2±3.2	43.0±3.4
PvO ₂ (mmHg)	O(n=28)	54±3.1	61±1.7*	58±1.7*	58±1.6
	C(n=29)	53±2.7	42±1.3	46±2.4	48±2.6
PvCO ₂ (mmHg)	O(n=28)	47±1.1	50±0.5*	50±0.6*	46±0.8*
	C(n=29)	51±0.9	57±0.6	62±0.9	59±0.7

The data are expressed as the mean ± SD values. **P* < 0.05 compared with group C

The levels of SOD, MDA and the expression levels of HO-1 in the lung tissue are given in table 3. The results of statistical analysis and the image of western-blotting are presented in Fig. 3, from which we can see that the levels of MDA were lower in group O than in group C (8.09±3.30 vs 17.39±8.40); however, the HO-1 expression levels were higher in group O than in group C (0.76±0.49 vs 0.21±0.15) (table3)

Table 3 MDA, SOD levels and expression of HO-1

Variable	Group O (n=28)	Group C (n=29)
SOD (U/mgprot)	13.46±2.97	17.69±1.65
MDA (nmol/mgprot)	8.09±1.30*	17.39±2.40
HO-1 expression	0.76±0.09*	0.21±0.05

The data are expressed as the mean ± SD values. **P* < 0.05 compared with group C

Discussion

Temporary, one lung ventilation (OLV) is an anesthetic procedure performed to facilitate thoracic surgeries. While this procedure is medically necessary, there is ample evidence to suggest that OLV procedures can lead to lung injury through various mechanisms. These include hypoxia, ischemia/reperfusion, mechanical injury in the collapsed lung, hyperperfusion of the ventilated lung (due in part to its gravitationally dependent positioning during surgery and in part to pulmonary shunting and over distension of alveoli), and oxidative injury from high FiO₂[1,10], which are causes of ALI after surgery. Protective ventilation is essential to reduce lung injury. Therefore, protective ventilation (including tidal volume, respiratory frequency and PEEP) was applied before OLV and for the ventilated lung during OLV to reduce the influence of non-research factors on the observed factors.

As for collapsed lung, protective OLV results in reduced ALI, critical care admissions, and hospital length of stay[11]. Continuous Positive Airway Pressure(CPAP) should be considered as one of the protective ventilation during OLV for collapsed lung to avoid dense atelectasis and minimize the shunt fraction. The incomplete lung collapse associated with CPAP is compatible with many chest wall and peripheral lung procedures. Even during thoracoscopic procedures, low-level CPAP of 2 cm H₂O has been shown to be feasible without impairing surgical exposure[5]. This approach has been shown to reduce hypoxic pulmonary vasoconstriction(HPV) and attenuate inflammatory cytokine release during clinical esophagectomy[12]. The impact of recruitment maneuvers on the alveolar-capillary membrane may be minimized by the use of slow airway pressure increases[13] and cycling maneuvers[14]. The use of lower FiO₂ during recruitment maneuvers may reduce the creation of reactive oxygen species, but this has not been studied in the OLV setting[15]. Therefore, we applied the continuous administration of low-medium flow oxygen (1-4L/min) and maintain the pressure between 1-2 cmH₂O for NVL to simulate CPAP in our study. Our result showed that compared with group C, the PaO₂ levels increased at T₂₋₄ in group O, the PaCO₂ levels decreased at T_{2,3}, the PvO₂ levels increased at T_{2,3}, the PvCO₂ levels decreased at T₂₋₄, implying that the continuous administration of low-medium flow oxygen for NVL during OLV may improve partial pressure of oxygen (PO₂) and lower partial pressure of carbon dioxide (PCO₂) to improve abnormal ventilation / blood flow ratio in NVL and thus play a role in lung protection.

Chow CW et al reported that lung parenchyma is one of the largest accumulations of neutrophils, monocytes and macrophages, and is also an important organ for oxidative stress reaction[16]. (After ipsilateral lung recover ventilation and, but a large number of oxygen molecules into the tissues release large amounts of oxygen free radicals and cause tissue damage). Once ipsilateral lung ventilation recovers and low blood perfusion lung/hypoxia improves, excessive oxygen molecules in the tissues will release large amounts of oxygen free radicals and cause tissue damage. SOD is an oxygen free radical scavenger, widely presenting in the lung and having a protective effect on lung injury[17]. MDA is the final product of lipid peroxidation, directly reflecting the level of free radicals. The MDA content level is an important sign of tissue damage[18]. HO-1, the heme-degrading enzyme, has shown anti-inflammatory effects in several models of pulmonary diseases. HO-1 attenuates lung edema by inhibiting the oxidation of lipid membranes and scavenging free radicals, the expression level of which increases when hypoxia, ischemia or other noxious stimulations occurs[19]. Almolki A et al confirmed that upregulation of the HO pathway has a significant protective effect against oxidative stress response[20]. The result showed that The MDA levels in the lung tissue were lower in group O than in group C; however, the HO-1 expression levels were higher in group O than in group C, which implied that the administration of continuous low-medium flow oxygen for NVL during OLV may inhibit lung tissue oxidative stress response, resulting in the role of lung protection. The possible mechanism is as follows: 1. Improvement of hypoxia can directly affect the SOD content: Studies have shown that hypoxia can directly inhibit the generation of endogenous SOD. Improving the hypoxia can increase the content of SOD, accelerate the elimination of oxygen free radicals to inhibit oxidative stress[21-22]. The results of this study showed no significant difference in lung tissue SOD content between the two groups of patients. It may be related to the smaller sample size, also related to the decrease of antioxidant ability in patients with cancer. Misthos P et al

founded that patients with cancer have a higher oxidative burden and may have less antioxidant capacity[8]. 2. Improvement of changes in the pulmonary circulation (HPV) caused by hypoxia in NVL can reduce the formation of oxygen free radicals: The existing research has shown that HPV is directly related to the generation of oxygen free radicals and oxidative stress response[23]. As HPV causes relatively insufficient perfusion in lung tissue, it directly causes the generation of oxygen free radicals and the destruction of vascular structure, and indirectly causes the release of various vasoactive factors and inflammatory factors, resulting in the occurrence of oxidative stress response. Cheng YD et al founded that during OLV in NVL, acute HPV is produced with increased systemic MDA, suggesting an increased oxidative stress response[6]. Therefore, the administration of continuous low-medium flow oxygen for NVL during OLV can improve the acute HPV occurrence in NVL in order to inhibit oxidative stress. 3. Ischemia-reperfusion injury: Acute HPV during OLV causes increased pressure on the pulmonary circulation, decreased blood flow and oxygen supply in NVL tissue, abnormalities in the production or inactivation of vasoactive substances in the tissue, which may cause or exacerbate pulmonary vascular endothelial cell damage such as cell swelling, interstitial edema or vascular wall permeability changes. Liu R et al have confirmed such pathophysiological process on rat-OLV model[24]. After reoxygenation, while hypoperfusion and hypoxia improve in NVL, a large number of oxygen molecules influx into the tissue, releasing a large number of oxygen free radicals, thus causing oxidative stress response, and then lung tissue damage. After clinically relevant durations of lung collapse in rat models[25] and patients, as reventilation after a period of clinical OLV substantially increased exhaled hydrogen peroxide concentrations in breath condensate, myeloperoxidase levels in bronchoalveolar lavage samples, and systemic markers of oxidative stress[8-9,26]. So the administration of continuous low-medium flow oxygen for NVL during OLV may inhibit the occurrence of ischemia-reperfusion injury to a certain extent. 4. Upregulation of HO-1 gene expression: Studies have shown that HO-1, one of the most important endogenous protective protein in the body, has a variety of physiological regulatory functions, such as anti-oxidation, anti-inflammatory response, anti-necrosis and cell protection[27]. HO-1 and its metabolites have strong antioxidant effects[28]. Our results showed that the expression of HO-1 was up-regulated in the lung tissues of the patients with continuous low-medium flow oxygen supply for the NVL during OLV compared with that in the control group, indicating that HO-1 could play a role in lung protection.

Conclusion

The administration of continuous low-medium flow oxygen for NVL during OLV has shown the effect of pulmonary protection. The possible mechanism is related with the inhibition of the oxidative stress response in lung tissue.

Abbreviations

ALI: Acute lung injury; CPAP: Continuous Positive Airway Pressure; DLT: Double-lumen tube; ECG: Electrocardiography; FEV1: forced expiratory volume in one second; FOB: Fiberoptic bronchoscopy; HO-1: Heme oxygenase-1; HPV: Hypoxic pulmonary vasoconstriction; HR: Heart rates; ICU: Intensive care unit;

MAP: Mean arterial blood pressures; MDA: Malondialdehyde; NIBP: Non-invasive blood pressure; NVL: Non-ventilated lung; OLV: One-lung ventilation; PaCO₂: Arterial carbon dioxide partial pressure; PACU: Post-anesthetic care unit; PaO₂: Arterial oxygen partial pressure; PEEP: Positive end expiratory pressure; PvCO₂: Venous carbon dioxide partial pressure; PvO₂: Venous oxygen partial pressure; ROS: Reactive oxygen species; SOD: Superoxide dismutase; TAS: Total antioxidant status; Vt: Tidal volume.

Declarations

- Ethics approval and consent to participate

This study was approved by the the ethical standards of the Medical Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Trial Registry number, 2016020), and the patients provided written informed consent.

-Consent for publication

Not applicable.

-Availability of data and materials

The datasets generated during the current study are not publicly available due to the authors do not wish to share their data, because the patients who participated in this study did not agree to share their individual data.

-Competing interests

The authors declare that they have no competing conflicts of interest.

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Authors' contributions

TJ Wu carried out the experiments and prepared the manuscript. J Zhan, JJ Ke and ZZ Zhang participated in the design of the experiments and carried out the experiments. YL Wang designed the study and prepared the manuscript. All authors have read and approved the manuscript.

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Figures

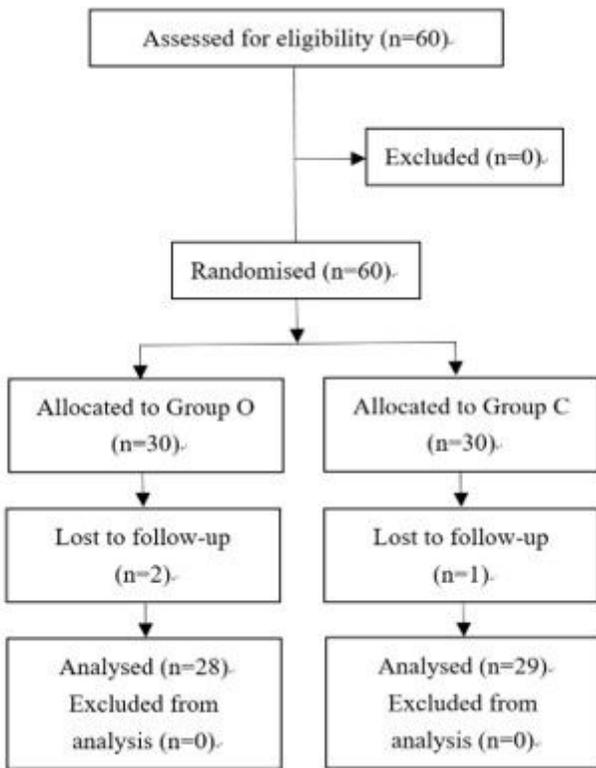


Figure 1

CONSORT flow diagram

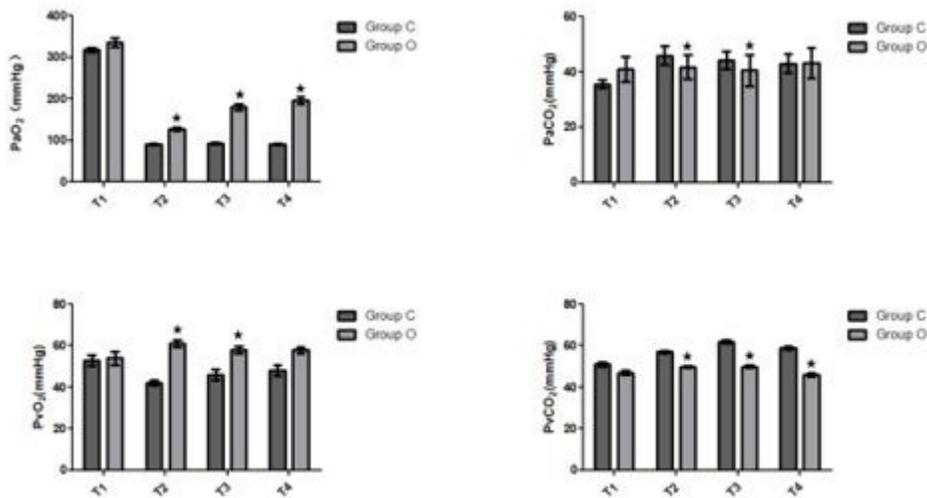


Figure 2

Levels of arterial and venous blood gas analysis in each group at different times: T1, T2, T3 and T4. *P < 0.05 compared with group C.

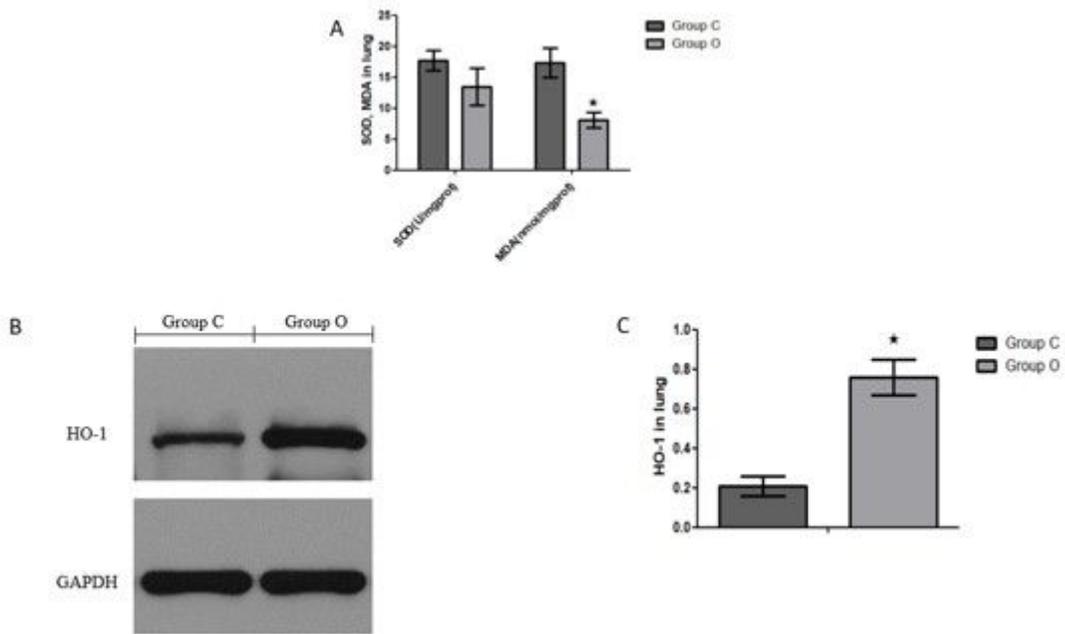


Figure 3

Histograms of SOD, MDA and HO-1 in lung tissues of two groups. *P < 0.05 compared with group C.