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Research Article

PEAK End-Tidal NO as a Biomarker for Investigating the Effect of Different OLV Strategies on Lung Injury and Inflammation Response

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Abstract

One-Lung Ventilation (OLV) aggravates alveolar damage and inflammation response in the lung. The evaluation indicators of lung injury caused by OLV are not perfect. End-Tidal fraction of Nitric Oxide (ETNO) continuously collected during ventilation may be a new and non-invasive inflammatory marker of lung injury to investigate the effect of different OLV strategies. A total of 56 patients undergoing thoracic surgery were included and randomized into two groups. These patients had the same parameters during two-lung ventilation, but during OLV, the High-Volume group was set at a tidal Volume (VT)=8 ml/kg Predicted Body Weight (PBW) and a Positive End-Expiratory Pressure (PEEP)=5 cmH_2O, while the Low-Volume group was set at a VT=5 ml/kg PBW and a PEEP=5 cmH_2O with recruitment every 30 min. ETNO was acquired at the points of induction, OLV 0 min, OLV 15 min, OLV 30 min, OLV 1 h and immediately at two-lung re-ventilation. We also obtained traditional evaluation indicators at the same points. ETNO did not differ significantly between groups at baseline. When the patients suffered OLV, compared with the Low-Volume group, ETNO in the High-Volume group significantly decreased at all points (*P<0.001*), and the expression of endothelial NO synthase in plasma decreased but lagged for a quarter. There was almost no change in traditional inflammatory factor in plasma. Compared with traditional inflammatory factor, ETNO can be a new, rapid, convenient and accurate inflammatory marker for investigating the effects of different OLV strategies in early-phase lung injury and pro-inflammation response.

Keywords: OLV; ETNO; Biomarker; Pro-inflammatory

Introduction

One-Lung Ventilation (OLV) has sustained a number of thoracic procedures, such as lung, oesophageal or mediastinal surgery. Although OLV successfully improves the surgical field to facilitate the surgical procedure, hyperperfusion in the ventilated lung and transpulmonary shunt during OLV aggravate alveolar damage and inflammation response in the lung, which is associated with a high incidence of hypoxemia [1] and postoperative pneumonia [2].

Currently, lung-protective ventilation with low tidal Volume (VT), Positive End-Expiratory Pressure (PEEP) and Recruitment Manoeuvres (RMs) has been routinely used to reduce postoperative lung injury in two-lung ventilation [3,4]. However, the identification of a reasonable OLV strategy remains elusive owing to its ventilation/perfusion defection [5]. A high tidal Volume (VT) of 8–10 ml kg^{-1} and an end-expiratory pressure of zero was recommended to limit shunt and preserve arterial oxygenation during OLV [6], but other evidence from thoracic surgery studies indicated that compared with low VT, high VT during OLV may contribute to a significantly augmented inflammatory response that induces hypoxemia and postoperative pneumonia [7]. Randal S [5] suggests that without adequate PEEP, low VT does not prevent postoperative pneumonia. To date, there is no clear evidence of the additional benefit of these ventilation strategies of OLV, and the evaluation indicators of lung injury caused by OLV, are not perfect.

Nitric Oxide (NO) is an important mediator for physiological and pathological processes within human lungs induced by NO synthase (NOS) expressed in epithelial cells and inflammatory cells in lung tissues. Since Gustafsson et al [8] reported the measurable levels of exhaled NO (eNO) in humans, eNO has been successfully applied to clinical practice for respiratory system disease as a non-invasive biomarker of respiratory inflamma-

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tion, such as asthma [9]. The ventilated lung unbalances the production and consumption of NO by destroying the endothelium and inducing inflammatory and oxidative stress; the change in NO indicates lung injury. Currently, exhaled breath condensate nitrite and nitrate, the metabolism of NO in the lungs, has been measured frequently for assessing lung injury in ventilated patients [10-12]. As a more direct index, eNO collected during ventilation may be a new and convenient inflammatory marker of lung injury.

In this study, for the first time, we achieved continuous end-tidal fraction of NO (ETNO) combined with traditional evaluation indicators, such as intraoperative respiratory system parameters, inflammatory factors in plasma and postoperative observation to investigate the effects of different OLV strategies on lung injury and inflammation response.

Methods

The study was approved by the Ethics Committee of Harbin Medical University (No.201314), registered at clinical trials.gov (ChiCTR1800015993).

Screening

Patients who planned to undergo thoracic surgery under general anaesthesia were screened and randomized by the clinical anaesthesia service of our regional university hospital, the 1st Affiliated Hospital of Harbin Medical University, China, between October 2018 and April 2020.

Inclusion and Exclusion Criteria

Patients were enrolled if they met all of the following conditions: 1) they were scheduled to undergo lung resection, mediastinal tumour resection, or 3-incision oesophagectomy under general anaesthesia with double-lumen tube; 2) their one-lung ventilation time was expected to last more than 1 h; 3) ASA classification II or III. Patients were excluded if they met any of the following criteria: 1) their body mass index (BMI) was greater than 35 kg/m^2; 2) they smoked during the last 2 weeks; 3) they had asthma, Chronic Obstructive Pulmonary Disease (COPD) or other chronic lung disease and cannot suffer high mechanical stress during OLV; 4) vital capacity or forced expiratory volume in 1 s <50% of the predicted values in the lung function, 5) numbers of leukocytes less than 4.0 × 10^9/L or more than 10.0 × 10^9/L); 6) they had experienced acute lung injury or acute respiratory distress syndrome before surgery; 7) they had received mechanical ventilation within the last 30 days; 8) they were receiving systemic corticosteroid therapy, or intractable shock was considered; or 9) they failed to maintain oxygen saturation of pulse oximeter (SpO_2) greater than 95% during two-lung ventilation and greater than 85% during OLV.

Standard Procedures

The patients were pre-medicated with an intravenous injection of midazolam 0.05 mg/kg. Before the patients underwent general anaesthesia, a radial arterial tube was inserted, and restrictive fluid therapy with crystalloids was administered at 2ml·kg^{-1}·h^{-1}to maintain diuresis >0.5ml·kg^{-1}·h^{-1}. A fluid bolus of 250ml of crystalloids was administered when diuresis was <0.5ml·kg^{-1}·h^{-1} during surgery to stabilize haemodynamics [13]. All of the patients received routine anaesthesia according to protocol, including pre-oxygenated to attain FiO_2 100%, intravenous sufentanil (0.25-0.5 μg/kg) and propofol (1-2 mg/kg) at induction 4 minutes after administration of cisatracurium (0.03 mg/kg), a double-lumen tube (Mallinckrodt, 35–37Ch; COVIDIEN, USA) was inserted, and the position of the endobronchial tube was confirmed using a fibre-optic bronchoscope (Olympus Asian, Japan). Thereafter, anaesthesia was maintained with sevoflurane to maintain a Bispectral Index (BIS) of 40-60; analgesia was provided with a single intravenous injection of sufentanil 5 μg. Cisatracurium was administered every 30 min, and the last administration occurred at least 30 min before the end of surgical suturing and FiO_2 was maintained at approximately 0.5 during the whole anaesthesia procedure with tracheal intubation or increased to 100% when SpO_2 was less than 90%. Routine intraoperative monitoring included invasive blood pressure, electrocardiography, pulse oximetry, end-tidal fraction of carbon dioxide ($P_{ET}CO_2$), BIS and dynamic pressure-volume curve.

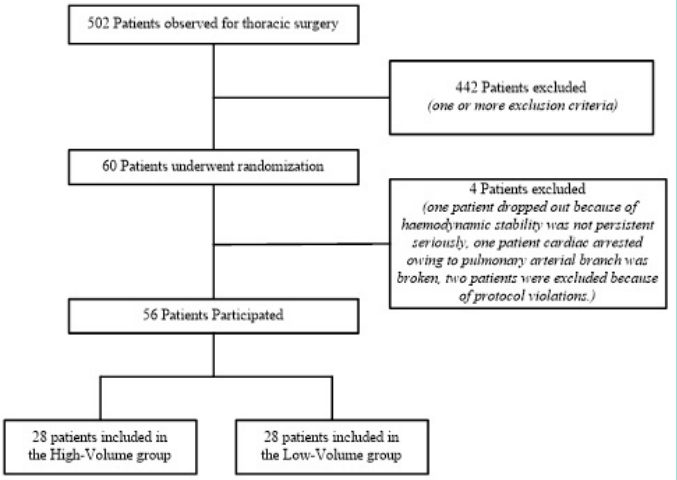

Figure 1: Flow diagram.

Ventilation Protocol

The subjects were randomly divided into two groups: High-Volume group and Low- Volume group. All of the parameters were set by the same type of anaesthesia machine (Drager Fabius GS, Lubeck, Germany). Patients in both groups were subjected to two-lung ventilation with the following parameters: a VT of 8 ml/kg Predicted Bodyv Weight (PBW), a PEEP of 5 cmH_2O, an inspiratory: expiratory (I:E) ratio of 1:2 and a fresh gas flow of 2 L/min. During OLV, the High-Volume group was maintained at a VT of 8 ml/kg PBW, a PEEP of 5 cmH_2O, an I:E of 1:2, and a fresh gas flow of 2 L/min; the Low-Volume group had a VT of 5 ml/kg PBW, a PEEP of 5 cmH_2O with recruitment [14] every 30 min, an I:E of 1:2, and a fresh gas flow of 2 L/min. We changed plates to maintain $P_{ET}CO_2$ between 27 and 40 mmHg.

Breath Sample and Measurement Methods

Breath sampling was performed at the following time points for ventilated lung: immediately following induction (T1), OLV 0 min (T2), OLV 15 min (T3), OLV 30 min (T4), OLV 1 h (T5) and immediately at re-ventilation (T6). Off-line sample of gas was sampled via a plastic sampling line placed just distal of the confluence of the ventilated limb of the double lumen tube into a hermetically sealed bag by Gas Sampler (Sunvou, SV-BSDM, Wuxi, China), which kept extracting the expiratory air at a flow rate of 300 ml min^{-1} when it detected a plateau. After nearly 5 min, the bag was filled and then immediately analysed using a Nano Coulomb Breath Analyzer (Sunvou, CA-2122, Wuxi, China). The analyser examined one gas sample 6 times to calculate an average value; after less than 1 min, ETNO was achieved.

Intraoperative Observation

Blood pressure, heart rates, SpO_2, FiO_2 and BIS were ob-

tained from a monitor (Datex-Ohmeda S/5, GE Healthcare, Finland, Europe) and were recorded at times entering into operating room (T0)-T6 and immediately at extubation (T7). When the FiO_2 increased to 100% but SpO_2 was still less than 90%, we defined the patients as hypoxemic. A D-lite sensor (GE Healthcare, Finland, Europe) was used to measure VT, respiratory rate (RR), $P_{ET}CO_2$, plateau pressure (PLAT), peak pressure (PEAK) and respiratory system dynamic compliance (COMPL) at T1-T6.

Blood Sample and Analysis

The blood sampling time points were the same as breath sampling (T1-T6). Blood samples of approximately 10 ml were taken from arterial indwelling catheters using a sterile centrifuge tube, which had been heparinized. The plasma was collected and stored at -80°C via centrifugation at 3000 rpm for 10 min. The levels of NOS and inflammatory factors were determined using enzyme-linked immunosorbent assay kits (USCN Life Science Inc., Houston, USA).

Postoperative Observation

The following observations were acquired postoperatively: duration of hospitalization, postoperative pneumonia, acute organ failure, primary postoperative intensive Care Unit (ICU) admission, and in-hospital death. All of the observations were diagnosed by the pneumology department with signs and exact auxiliary examination.

Statistical Analysis

The normality of the data distribution was tested with the Kolmogorov–Smirnov test. The homogeneity of variance was tested by Levene's test. The data are expressed as either the mean ± SD or median and interquartile range (25–75%), as appropriate. Comparisons of normally distributed variables were performed with two-tailed Student's t test, whereas a non-parametric test was used for non-normally distributed variables, and a chi-square test was used for categorical data. Statistical significance was indicated at *P<0.05*. All of the statistical analyses were performed with SPSS13.0 software.

Results

A total of 60 patients were included and randomized into two groups, but one patient dropped out because of haemodynamic stability was not persistent seriously, one patient cardiac arrested owing to pulmonary arterial branch was broken, two patients were excluded because of protocol violations. Ultimately, there were 28 patients in the High-Volume group and 28 patients in the Low-Volume group (Figure 1). The two groups had similar preoperative baseline and surgical characteristics (Table 1).

ETNO did not significantly differ between groups at baseline when the patients suffered OLV. Compared with the Low-Volume group, ETNO in the High-Volume group significantly decreased at all points (*P<0.001*; Table 2). Compared with T1, within-subject ETNO during OLV in the High-Volume group significantly decreased at each point (*P<0.01*). Nevertheless, compared with T3 and T4, ETNO in the Low-Volume group was higher at T5.

Table 3 shows the intraoperative data of the two groups. There were no significant differences in the vast majority of haemodynamic data points and baseline of ventilated parameters. During OLV, approximately 17 patients experienced hypoxemia at the beginning of T2 without differences between two groups.

Table 1: Baseline characteristics.

	High Volume group (n=28)	Low Volume group (n=28)	*P*
Age (year)	57.11±10.02	51.82±13.76	0.11
Sex (male/female)	16/12	16/12	1
Height (cm)	165.89±10.77	163.36±8.57	0.33
Weight (kg)			
Actual	67.21±17.19	60.57±10.92	0.09
Predicted	59.71±11.30	57.40±9.70	0.42
BMI kgm^{-2}	24.16±3.96	22.61±3.03	0.11
Collapsed lung (L/R)	21/7	18/10	0.38
FVC (% predicted)	96.52±15.32	93.13±22.18	0.34
FEV1 (% predicted)	89.70±14.30	84.90±18.49	0.43
Type of surgery (lung resection/ Mediastinal tumor resection or esophagectomy)	18/10	22/6	0.24
Duration of OLV (h)	1.84[1.17-2.39]	2.16[1.32-2.66]	0.26

Table 2: ETNO during operation.

	High Volume group (n=28)	Low Volume group (n=28)	*P*
T1	10.5[8-11.75]	11[9.25-13]	0.23
T2	8.5[8-10]*	10.5[9-12]	<0.001
T3	9[7.25-10]*	10[9-12]	<0.001
T4	8.5[7-9.75]*	10[9-12]	<0.001
T5	8[7-9]*	11[9.75-13]$^{+,\wedge}$	<0.001
T6	9[8-10]$^{*,\&}$	10.5[10-12]	0.008

*Compared with T1 within-subject, P<0.05; +Compared with T3 within-subject, P<0.05; ^Compared with T4 within-subject, P<0.05;

Otherwise, there were significant differences between the two groups in VT, RR, $P_{ET}CO_2$, PLAT, PEAK and COMPL.

The data for NOS and plasma inflammatory factor are shown in Table 4. Compared with the Low-Volume group at T3-T6, the concentration of eNOS was lower in the High-Volume group. Meanwhile, the expression of eNOS in the High-Volume group significantly decreased at T6 compared with T1 (0.11[0.10-0.12] vs 0.14[0.12-0.15]; *P=0.002*). To the contrary, the expression of eNOS in the Low-Volume group at T3 was significantly higher than T2 and T6 within group. iNOS in plasma did not significantly differ between the two groups. The expression of interleukin-8 (IL-8), IL-1β, Tumour Necrosis Factor-α (TNF-α), Prostaglandin F-2α (PGF-2α), and Prostaglandin E-2 (PGE-2) had no significant difference between the two groups, either. PGF-2α in the High-Volume group increased at T5 and T6 compared with T1. PGE in the Low-Volume group at T3 was decreased compared with T1 and T2 with group.

The results for the length of hospital stay showed no significant differences between the two groups, as shown in Table 5. There were no significant differences for the incidence rate of postoperative pneumonia. One patient in Low Volume Group went to primary postoperative Intensive Care Unit (ICU) admission. None of the patients had acute organ failure or in-hospital death.

Discussion

Our study examined the early changes of ETNO and other traditional evaluation indicators induced at 0 min, 15 min, 30 min and 1 h OLV with either 5 or 8 ml/kg PBW VT in surgical patients with healthy lungs. This is the first randomized controlled trial applying ETNO during ventilation in assessing the early biological impact of short-term OLV in patients undergoing thoracic surgery. In addition, we acquired NOS in plasma

Table 3: Intraoperative observation.

	High Volume group (n=28)	Low Volume group (n=28)	*P*
Systolic pressure (mmHg)			
T1	117.07±25.86	106.75±17.62	0.09
T2	123.14±24.58	113.42±25.64	0.15
T3	115.86±17.87	111.46±18.64	0.37
T4	110.00±18.79$^{\#}$	101.00±22.13$^{\#}$	0.14
T5	117.76±24.79	109.62±19.34	0.21
T6	115.11±18.03	115.25±15.12$^{\wedge}$	0.98
Diastolic pressure (mmHg)			
T1	62.04±13.37	58.04±12.06	0.25
T2	67.61±11.72	62.57±13.60	0.14
T3	64.68±11.30	62.11±10.89	0.39
T4	60.86±8.40$^{\#}$	57.00±7.41	0.07
T5	65.38±10.29	60.85±11.29	0.16
T6	65.00±9.86	64.00±11.01$^{*,\wedge}$	0.71
Heart rate (bpm)			
T1	62.96±12.37	60.36±10.44	0.40
T2	69.75±13.21	69.50±12.76	0.94
T3	67.43±10.08$^{*,\#}$	72.54±11.95$^{*,\#}$	0.09
T4	66.86±11.02*	68.15±11.04$^{*,\#}$	0.71
T5	62.41±11.23	66.54±11.75$^{*,\#}$	0.15
T6	60.64±12.19^{+}	60.32±10.04$^{*,\#,\wedge}$	0.32
SPO_2%			
T1	97.39±3.02	98.04±2.57	0.40
T2	94.57±2.84*	95.50±3.68	0.30
T3	94.93±2.39$^{*,\#}$	95.07±3.23$^{*,\#}$	0.85
T4	95.57±2.42$^{*,\#}$	97.31±2.28$^{*,\#}$	0.015
T5	99.26±1.20$^{*,\#}$	99.18±2.36$^{*,+,\wedge}$	0.83
T6	99.00±0.86$^{\#,+,\wedge,\&}$	98.89±1.23$^{\wedge,\&}$	0.71
VT (ml)			
Two-lung ventilation	476.79±93.73	459.64±77.63	0.46
OLV	476.79±93.73	286.79±48.31*	<0.001
RR (bpm)			
T1	12.25±1.48	12.86±1.58	0.14
T2	12.21±1.47	16.50±1.60*	<0.001
T3	12.04±1.90	17.25±1.97*	<0.001
T4	12.07±1.84	17.43±2.03*	<0.001
T5	11.90±1.84	17.54±2.14$^{*,\#}$	<0.001
T6	11.93±2.00	12.71±1.65$^{\#,+,\wedge,\&}$	0.11
$P_{ET}CO_2$ (mmHg)			
T1	35.18±4.08	35.93±3.21	0.45
T2	31.29±4.62*	32.82±3.19*	0.15
T3	32.89±2.64$^{*,\#}$	36.29±2.57$^{\#}$	<0.001
T4	32.04±2.69*	36.14±2.56$^{\#}$	<0.001
T5	31.67±2.33*	36.42±2.44$^{\#}$	<0.001
T6	30.67±3.32$^{*,+}$	34.82±2.86$^{\#,\&}$	<0.001
PLAT (cmH_2O)			
T1	16.32±2.94	15.93±2.88	0.62
T2	22.43±3.95*	17.14±3.46	<0.001
T3	22.25±4.12*	18.07±3.42*	<0.001
T4	22.75±4.11*	18.25±3.66*	<0.001
T5	21.86±2.74*	18.38±4.53*	0.002
T6	17.08±3.63$^{\#,+,\wedge,\&}$	17.25±3.50	0.86
PEAK (cmH_2O)			
T1	17.44±2.85	17.50±2.87	0.94
T2	25.50±5.20*	18.75±3.67	<0.001
T3	25.36±5.12*	19.93±3.93*	<0.001
T4	25.75±5.26*	20.25±3.82*	<0.001
T5	20.62±3.98*	20.23±5.10*	0.002
T6	18.96±3.76$^{\#,+,\wedge,\&}$	18.79±3.66	0.86
COMPL (cmH_2O)			
T1	41.61±8.93	41.29±10.51	0.90
T2	27.61±6.63*	24.93±7.06*	0.15
T3	27.61±6.06*	23.32±6.92*	0.02
T4	27.29±7.44*	22.46±6.21*	0.01
T5	27.57±6.33*	22.96±6.97*	0.02
T6	38.67±11.24$^{\#,+,\wedge,\&}$	36.11±10.00$^{*,\#,+,\wedge,\&}$	0.38

*Compared with T1 within-subject, P<0.05; $^{\#}$Compared with T2 within-subject, P<0.05; $^{+}$Compared with T3 within-subject, P<0.05; $^{\wedge}$Compared with T4 within-subject, P<0.05; $^{\&}$Compared with T5 within-subject, P<0.05

Table 4: The NOS and inflammatory factor of plasma in the Two Groups.

	High Volume group (n=28)	Low Volume group (n=28)	*P*
eNOS			
T1	0.13[0.11-0.14]	0.14[0.12-0.15]	0.21
T2	0.11[0.10-0.14]	0.14[0.12-0.15]	0.15
T3	0.11[0.10-0.12]	0.15[0.12-0.16]$^{\#}$	0.002
T4	0.11[0.10-0.13]	0.13[0.11-0.16]	0.04
T5	0.12[0.10-0.13]	0.14[0.12-0.15]	0.04
T6	0.11[0.10-0.12]*	0.14[0.12-0.15]$^{+}$	0.04
iNOS			
T1	5.49[3.97-11.53]	6.31[4.23-14.27]	0.95
T2	6.12[3.86-7.40]	7.13[4.62-12.53]	0.38
T3	5.84[4.27-7.29]	6.32[4.26-11.67]	0.45
T4	7.50[5.24-9.18]	7.89[4.32-12.73]	0.70
T5	6.48[4.47-7.09]	6.83[3.25-14.92]	0.64
T6	7.44[5.31-9.89]	7.00[2.52-11.02]	0.60
IL-8			
T1	9.73[9.13-11.05]	10.50[9.54-13.03]	0.40
T2	9.40[8.69-11.27]	10.17[9.09-11.62]	0.77
T3	9.29[8.64-10.17]	9.94[9.36-11.17]	0.10
T4	9.51[8.64-10.27]	9.94[8.96-12.34]	0.35
T5	10.17[9.17-12.79]$^{\wedge}$	9.92[9.35-11.11]	0.60
T6	9.84[8.45-12.07]	10.04[9.11-10.94]	0.95
IL-1β			
T1	5.48[4.34-6.62]	6.15[4.42-13.41]	0.33
T2	5.57[4.23-6.67]	5.57[3.41-9.80]*	0.98
T3	5.48[4.08-6.39]	6.70[3.41-10.60]	0.31
T4	4.39[3.73-7.08]	6.40[4.03-11.78]	0.27
T5	4.84[4.47-6.62]	5.61[4.22-13.45]	0.73
T6	5.39[3.83-6.39]	5.71[2.79-9.89]	0.84
TNF-α			
T1	9.49[5.36-34.36]	15.31[7.95-21.91]	0.51
T2	7.26[4.77-22.78]	10.84[8.55-14.90]	0.38
T3	12.64[5.17-20.57]	13.98[9.49-20.18]	0.67
T4	9.25[5.17-16.63]	12.24[8.70-15.00]	0.84
T5	10.44[6.16-14.06]	10.87[7.06-16.72]	0.57
T6	9.25[5.26-11.46]	12.78[9.55-23.07]$^{\wedge}$	0.06
PGF-2α			
T1	363.63[112.38-549.70]	482.39[123.36-544.40]	0.57
T2	470.32[164.34-545.70]	467.90[96.77-557.40]	0. 96
T3	469.86[149.53-559.77]	376.54[92.60-562.12]$^{*,\#}$	0.87
T4	429.55[167.24-560.06]	467.90[88.55-560.78]	0.96
T5	456.95[143.24-567.94]*	501.16[97.28-563.96]	0.85
T6	447.05[138.20-518.10]*	281.25[102.32-570.94]	0.85
PGE-2			
T1	262.52[82.40-511.89]	419.99[127.18-533.45]	0.29
T2	423.79[118.17-512.62]	408.15[98.68-549.15]	0.80
T3	422.70[125.89-525.65]	325.78[92.65-545.66]$^{*,\#}$	0.98
T4	411.24[141.16-520.57]	395.67[89.98-550.82]	0.91
T5	427.95[115.72-529.24]*	423.31[100.54-554.52]	1.00
T6	447.05[125.34-518.10]*	343.15[102.95-545.67]	0.87

*Compared with T1 within-subject, P<0.05; $^{\#}$Compared with T2 within-subject, P<0.05; $^{+}$Compared with T3 within-subject, P<0.05; $^{\wedge}$Compared with T4 within-subject, P<0.05;

at the same time points to probe the upstream inflammatory mechanism. Our data indicated that a high volume during OLV led to a decrease in ETNO at the first time of OLV. Compared with other indicators, ETNO was the most rapid and sensitive detection biomarker for the early lung injury of short-term OLV, which may indicate the potential of lung injury.

Table 5: Postoperative observation.

	High Volume group (n=28)	Low Volume group (n=28)	*P*
Duration of stay in hospital (days)	13.00±3.75	13.32±4.74	0.78
Pneumonia n (%)	11 (39.3)	7(25.0)	0.25
ICU n (%)	0 (0)	1 (3.57)	1.0
Acute organ failure	0 (0)	0 (0)	1.0
In-hospital death	0 (0)	0 (0)	1.0

NO production was generated by NOS, which uses L-arginine and molecular oxygen [15]. In human lungs, three isoforms of NOS have already been described: the neuronal (nNOS), inducible (iNOS), and endothelial (eNOS). Furthermore, nNOS can be found in neurons and endothelial cells; eNOS is found in bronchiolar epithelial cells and the endothelium [16]; and both forms maintain physiological processes. iNOS is expressed in human airway epithelium, lung endothelium, and alveolar macrophages [17] to maintain pathological processes. The activity of iNOS in the airway epithelium has been suggested to be the most important determining factor for the concentration of eNO in chronic respiratory disease, such as stable asthma [18] and COPD [19]. In our study, ETNO significantly decreased after OLV in the High-Volume group, while the expression of iNOS remained stable, and the expression of eNOS in plasma decreased but lagged for one quarter as ETNO decreased. The possible reason was that the production of NO had not been able to change, but the consumption of NO increased more in the High-Volume group at the beginning of OLV, as shown by the stable levels of PGE-2 and PGF-2a, the inhibitor of NO [20]. Animal experiment noted that regions with low ventilation and perfusion ratios (V/Q) in a High-Volume (VT=10 ml/kg) group increased in the ventilated lung after OLV, leading to the increasing of alveolar and interstitial oedema, haemorrhage, neutrophil infiltration, and microatelectasis [21]. Tidal volume delivered solely to the ventilated lung during OLV, hyperperfusion and hyperinflation of the high-volume ventilated lung, initiates diffuse damage in the alveolar compartment; NO may play an important role in this process as a free radical. However, as times lengthen, bronchiolar epithelial cells and the endothelium were destroyed, the expression of eNOS in the High-Volume group decreased indicating the seriousness of lung injury. Notably, after OLV, ETNO in the High-Volume group was recovered; it may be that the consumption of NO was weakened, but the expression of eNOS decline was owed to the irreversible damage of bronchiolar epithelial cells and the endothelium, which made ETNO still lower than the Low-Volume group at the same point. As there was a short ventilation time, the access of iNOS may not have been activated without any change during ventilation in both groups, which may be the reason why ETNO in the two groups did not increase.

Mechanical ventilation under general anaesthesia plays a large role in development of postoperative pulmonary complications. The benefits of lung-protective artificial ventilation involving consideration of tidal volume (VT), level of PEEP, and use of RMs in patients with ARDS are well established [7]. In humans, cytokines, such as TNF-α and IL in plasma and bronchoalveolar lavage were increased in ARDS patients ventilated with greater VT and lower positive end-expiratory pressure (PEEP) compared with those receiving smaller VT and greater PEEP [22]. The levels of TNF-α, IL-8 and IL-1β in bronchoalveolar lavage also increased in ICU patients without ARDS ventilated with VT 10 to 12 ml/kg PBW for 12 h compared with those ventilated with VT 5 to 7 ml/kg PBW and similar PEEP [23]. In our study, TNF-α, IL-8 and IL-1β were not elevated, this result was in accordance with Wrigge et al [24], who studied the effects of high tidal volume (12 ml/kg) without PEEP versus low tidal volume (6 ml/kg) with PEEP of 10 cm H2O on the mediators of systemic and pulmonary inflammation measured 3 h after surgery and did not find any difference in plasma or tracheal aspirate TNF-α, IL-8 and IL-1β levels. It seems that in the normal non-injured ventilated lung, the inflammatory reaction of these traditional inflammatory factors at early phase will most likely not have been activated. Although the lower occurrence of postoperative pneumonia in the Low-Volume group indicates reductions of tidal volumes in patients undergoing thoracic surgery, the subsequently decreased peak airway pressures had significant effects on alleviating epithelial damage, which has been verified in prior study [25]. Meanwhile, ETNO, as a biomarker of pro-inflammatory response in the ventilated lung, retained small airway injury via its successful decline at short period OLV.

Theoretically, ETNO was the definitive approach to eNO in pulmonary alveoli below 5 ppb. In another experiment, the investigator observed perioperative changes in eNO during oesophagectomy, the level of eNO was approximately 3 ppb [11]. However, the level in our study was approximately 10 ppb. The sample of gas in our study was collected in an endobronchial tube, so the data came from the lower respiratory tract, including pulmonary alveoli and bronchus. For the lower respiratory tract, 10 ppb could be assumed in the normal range. In addition, we obtained the sample at the moment of plateau stage, rather than the whole respiratory process, and analysed one sample 6 times; moreover, the RMs proceeded behind in the Low- Volume group, so the value could accurately describe the level of ETNO to assess the injury in the small airway.

Conclusion

ETNO can be a new, rapid, convenient and accurate inflammatory marker to investigate the effects of different OLV strategies on the early phase of lung injury and pro-inflammation response compared with traditional inflammatory factor. The decline of ETNO in the High-Volume group indicates the injury in the small airway.

Author Statements

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