

Effects of inverse ratio ventilation combined with lung protective ventilation on pulmonary function in patients with severe burns for surgery

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ABSTRACT

Objective: To investigate the effects of inverse ratio ventilation combined with lung-protective ventilation on pulmonary function and inflammatory factors in severe burn patients undergoing surgery. **Populations and Methods:** Eighty patients with severe burns undergoing elective surgery were divided randomly into two groups: control (CG, $n = 40$) and experiment (EG, $n = 40$). The CG had conventional ventilation, whereas the EG were ventilated with tidal volume (TV) of 6–8 ml/kg, I (inspiration): E (expiration) of 2:1, and positive end-expiratory pressure (PEEP) 5 cm H₂O. The following variables were evaluated before (T0), 1 h after start of surgery (T1) and after surgery (T2): oxygenation index (OI), partial pressure of carbon dioxide (PaCO₂), TV, peak airway pressure (Ppeak), mean airway pressure (Pmean), PEEP, pulmonary dynamic compliance (C_{dyn}), alveolar–arterial difference of oxygen partial pressure D(A-a)O₂, lactic acid (Lac), interleukin (IL)-6 and IL-10, and lung complications. **Results:** At T1 and T2 time points, the OI, Pmean and C_{dyn} were significantly greater in the EG than in the CG while the TV, Ppeak, D(A-a)O₂, IL-6 and IL-10 were significantly smaller in the EG than in the CG. At the end of the surgery, the Lac was significantly smaller in the EG than in the CG (1.28 ± 0.19 vs. 1.40 ± 0.23 mmol/L). Twenty-four hours after the surgery, significantly more patients had hypoxemia (27.5 vs. 10.0%), increased expectoration (45.0 vs. 22.5%), increased lung texture or exudation (37.5 vs. 17.5%) in the CG than in the EG. **Conclusions:** Inverse ratio ventilation combined with lung-protective ventilation can reduce Ppeak, increase Pmean and C_{dyn}, improve the pulmonary oxygenation function, and decrease ILs in severe burn surgery patients.

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1. Introduction

Patients with severe burns are often complicated with multiple organ dysfunction, and lung dysfunction usually occurs very early with a higher incidence in severe burns [1,2]. The greatest challenges in initial burn management are associated with mechanical and physiologic alterations caused by severe thermal injury [3,4]. Inflammation response may result in pulmonary edema, and influx of plasma within the pulmonary parenchyma causes progressing exaggeration of ventilation–perfusion mismatch, leading to intrapulmonary shunt, alveoli collapse, worsening arterial oxygenation, impaired gas exchange, and ultimately, hypoxemia and rising arterial carbon dioxide (CO₂) [5]. Elective surgery for burn wound excision and skin grafting may further cause a series of pathophysiological changes and exaggerate pulmonary injury [6]. Mechanical ventilation is a crucial supportive approach for critically ill patients or for patients undergoing major surgical procedures. However, mechanical ventilation with a high tidal volume (TV) may subject the lung to a variety of potentially

injurious stimuli and cause a significantly higher mortality in patients with severe pulmonary injury or acute respiratory distress syndrome [7,8].

Thus, the concept of protective ventilation strategies has been put forward by application of smaller physiological TVs to minimize alveolar overdistension or repetitive alveolar collapse and also by application of a higher positive end-expiratory pressure (PEEP) to improve oxygenation [7,9]. Some studies in the general surgery of patients with a high risk of postoperative pulmonary complications had reported improved clinical outcomes in patients with preoperatively healthy lungs using this protective ventilation strategy [10,11]. Blank et al [7], have proven that a low TV does not prevent postoperative respiratory complications without adequate PEEP even though a low TV is an important component of the lung-protective ventilation strategy. Pressure-controlled inverse ratio ventilation has been reported to have successfully recruited collapsed alveoli and improved oxygenation at lower peak airway pressure (Ppeak) [9,12–14].

Since the use of increased inspiratory time with the inspiratory to expiratory ratio (I:E) of over 3:1 may

affect cardiac output, the optimal I:E is set at 2:1 by some authors [9,15]. It was hypothesized that the volume-controlled inverse ratio ventilation combined with a protective ventilation strategy with a lower TV and a higher PEEP would benefit burn patients with severe pulmonary injury than a conventional ventilation strategy. This study was consequently performed to investigate this hypothesis in a cohort of patients with severe burn injury who underwent elective surgery for burn wound excision and skin grafting under general anesthesia.

2. Populations and methods

This study was approved by the ethics committee of the hospital with all patients given their written informed consent. All methods were performed in accordance with the relevant guidelines and regulations. Patients with severe burn injury who were undergo elective surgery for burn wound excision and skin grafting under general anesthesia were enrolled in this study. The inclusion criteria were patients aged 26–63 years old, of severe burn American Society of Anesthesiologists (ASA) [16] grade II–IV, with a total burned area of over 30%, with a third-degree burned area of over 10% or with inhalation injury. Patients with cardiopulmonary diseases were not included. All enrolled patients were randomly divided into two groups: the experiment group (EG, $n = 40$) and the control group (CG, $n = 40$) using a computer generated randomization list.

Midazolam 0.04 mg/kg, cisatracurium 0.2 mg/kg, etomidate 0.3 mg/kg and fentanyl 4 μ g/kg were injected intravenously for induction of anesthesia. After the patient fell asleep, visual laryngoscope was placed through the mouth, and subsequently the endotracheal tube was inserted. Anesthesia was maintained with propofol 3–5 mg/kg/h, and remifentanyl hydrochloride was continuously pumped in the dose of 0.1–0.2 μ g/kg/min, and sevoflurane was inhaled in. All patients were successfully intubated once, and then mechanical ventilation was started. Ventilation parameters were different in the two groups. Patients in the CG were ventilated with a TV of 7 ml/kg, a respiratory rate of 13 breaths/min, I:E of 1:2, whereas patients in the EG had the same ventilation parameters before operation but the inverse ratio ventilation of 2:1 in I:E and the PEEP of 5 cm H₂O, which was applied after start of the operation with all the other parameters maintained the same. No PEEP was applied in the CG, however, the mechanical ventilator may produce endogenous PEEP by itself.

Arterial blood was obtained before (T0), 1 h after (T1) and at the end (T2) of surgery for blood gas analysis of the oxygenation index (OI), partial pressure of oxygen (PaO₂), partial pressure of carbon dioxide (PaCO₂), alveolar–arterial difference of oxygen partial

pressure (D(A-a)O₂) and lactic acid value (Lac). The OI was calculated with the formula of $OI = PaO_2/FiO_2$ (forced inspiratory oxygen concentration) [17]. The following respiratory parameters were also recorded: TV, Ppeak, mean airway pressure (Pmean), PEEP, and pulmonary dynamic compliance (Cdyn, equals TV/(Ppeak-PEEP)). Venous blood of 4 ml was obtained at the above time points, stood for 30 min, and was centrifuged for 5 min at 3000 revolutions per minute. The supernatant was extracted and restored at –80 refrigerator for test. The enzyme-linked immunosorbent assay (ELISA) was used to test the level of the interleukins (IL-6 and IL-10). Pulmonary complications were recorded within 48 h including hypoxemia, increased expectoration, and ventilator-assisted breathing, and chest radiography was performed for evaluation of the lung complications like exudation before and after surgery.

3. Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM, Chicago, IL, USA). Measurement data were presented as mean \pm SD (standard deviation) if the data were in normal distribution. Two-tailed Student's *t*-test was used for comparison between the two groups. If the measurement data were not in normal distribution, median and range were used for description of the data and tested with the χ^2 test. For categorical variables, the χ^2 test was applied. $p < 0.05$ was set as statistically significant. The size of sample was decided according to the following conditions. The primary variable was PaO₂ which had a standard deviation of 37 from our previous pilot study in 20 patients. Analysis of the priori power with the two-sided analysis using the α error of 5% and the power at 95% demonstrated that at least 46 patients were needed in a two-arm study [18]. Thus, 80 patients could well meet the requirements to reach a statistically significant difference.

4. Results

No significant difference existed in the ASA grades, age, sex, operation duration, and amount of bleeding in the surgery between the two groups (Table 1).

When patients in the two groups had the same ventilation parameters before T0, no significant difference existed in the blood gas indexes (Table 2). At T1 and at T2, the OI was significantly greater in the EG than in the CG while the D(A-a)O₂ was significantly smaller in the EG than in the CG (Table 2). At T2, the Lac was significantly smaller in the EG than in the CG.

At T0 when the two groups had the same ventilation parameters, no significant difference existed in the respiratory parameters (Table 3). At T1 and at T2, the TV and the Ppeak were significantly smaller but

Table 1. General conditions between the two groups.

Groups	n	ASA grade	Age (y)	Sex (M/F)	Operation duration (min)	Amount of bleeding (ml)
Control	40	28/12	49.73 ± 6.15	32/8	176.32 ± 47.58	1018.34 ± 76.33
Experiment	40	30/10	46.87 ± 7.24	31/9	184.07 ± 39.61	987.25 ± 81.54

ASA, American Society of Anesthesiologists; M, male; F, female; y, year; min, minutes; ml, milliliter. No significant ($p > 0.05$) difference existed between the two groups.

the Pmean was significantly greater in the EG than in the CG (Table 3).

At T0, no significant difference existed in the Cdyn parameter. At T1 and T2, the Cdyn was significantly greater in the EG than in the CG.

At T0, no significant difference existed in the inflammatory factors between the two groups (Table 4). At T1 and T2 time points, the IL-6 and IL-10 were significantly smaller in the EG than in the CG (Table 4).

For pulmonary complications, 24 h after the surgery, there were five patients in the CG and three patients in the EG who needed ventilator-assisted breathing ($p > 0.05$) (Table 5). Hypoxemia occurred in 11 and 4 patients, respectively, in the CG and in the EG ($p < 0.05$). Increased expectoration took place in 18 and 9 patients, respectively, in the CG and in the EG ($p < 0.05$). Chest radiograph demonstrated

increased lung texture or exudation in 15 and 7 patients, respectively, in the CG and in the EG ($p < 0.05$).

5. Discussion

In this study, an investigation was performed on the effect of volume-controlled inverse ratio ventilation with an I:E of 2:1 combined with lung-protective ventilation on pulmonary function and inflammatory factors in severe burn patients undergoing elective surgery for burn wound excision and skin grafting. It was found that the volume-controlled inverse ratio ventilation combined with lung-protective ventilation can significantly reduce Ppeak, Pmean and Cdyn, improve the pulmonary oxygenation function and decrease IIs in severe burn surgery patients.

Table 2. Blood gas indexes in two groups (mean ± standard deviation).

Variables	Group	T0	T1	T2
OI (mmHg)	Control	304.17 ± 43.51	254.53 ± 61.42	228.17 ± 58.21
	Experiment	308.60 ± 48.29	306.18 ± 59.07*	294.10 ± 54.18*
PaCO ₂ (mmHg)	Control	39.04 ± 10.03	40.26 ± 9.23	42.17 ± 9.61
	Experiment	37.15 ± 9.42	39.80 ± 9.74	41.53 ± 10.16
D(A-a)O ₂ (mmHg)	Control	151.34 ± 15.21	164.39 ± 54.41	182.37 ± 36.48
	Experiment	149.27 ± 13.54	132.71 ± 37.69*	124.90 ± 41.73*
Lac (mmol/L)	Control	1.34 ± 0.21	1.38 ± 0.25	1.40 ± 0.23
	Experiment	1.32 ± 0.26	1.31 ± 0.32	1.28 ± 0.19*

OI, oxygen index; PaCO₂, partial pressure of carbon dioxide; PaO₂, partial pressure of oxygen; D(A-a)O₂, alveolar-arterial difference of oxygen partial pressure; Lac, lactic acid; T0, before operation; T1, 1 h after start of the operation; T2, at the end of the operation. * $p < 0.05$ compared with the control group.

Table 3. Respiratory parameters in two groups (mean ± standard deviation).

Variables	Group	T0	T1	T2
TV (ml)	Control	534.28 ± 26.70	532.47 ± 25.98	533.34 ± 26.47
	Experiment	530.51 ± 28.07	434.14 ± 27.15*	435.37 ± 26.38*
Ppeak (cmH ₂ O)	Control	20.35 ± 1.32	21.58 ± 1.74	21.61 ± 1.57
	Experiment	20.05 ± 1.27	18.16 ± 1.39*	18.24 ± 1.48*
Pmean (cmH ₂ O)	Control	11.47 ± 1.20	8.27 ± 1.45	8.43 ± 1.40
	Experiment	11.14 ± 1.03	11.85 ± 1.31*	11.76 ± 1.18*
PEEP (cmH ₂ O)	Control	2.03 ± 0.14	2.05 ± 0.11	2.06 ± 0.13
	Experiment	2.10 ± 0.12	6.35 ± 0.18*	6.28 ± 0.21*
Cdyn(ml/cmH ₂ O)	Control	31.36 ± 2.54	28.23 ± 2.61	29.31 ± 3.07
	Experiment	30.27 ± 3.18	35.17 ± 2.94*	36.25 ± 2.14*

TV, tidal volume; Ppeak, peak airway pressure; Pmean, mean airway pressure; PEEP, positive end-expiratory pressure; Cdyn, pulmonary dynamic compliance; T0, before operation; T1, 1 h after start of the operation; T2, at the end of the operation. * $p < 0.05$ compared with the control group. Here, the PEEP in the control group was produced by the mechanical ventilator itself.

Table 4. Inflammatory factors in two groups (mean ± standard deviation).

Variables	Group	T0	T1	T2
IL-6 (pg/ml)	Control	43.24 ± 21.32	61.13 ± 18.41	73.40 ± 20.25
	Experiment	49.75 ± 26.43	36.54 ± 17.53*	34.26 ± 16.47*
IL-10 (pg/ml)	Control	28.13 ± 11.25	34.62 ± 9.56	39.24 ± 8.47
	Experiment	29.46 ± 10.37	26.47 ± 10.24*	25.64 ± 9.36*

IL, interleukin; T0, before operation; T1, 1 h after start of the operation; and T2, at the end of the operation. * $p < 0.05$ compared with the control group.

Table 5. Complications in the lungs after surgery (case no., %).

Group	Ventilator-assisted breathing	Hypoxemia	Increased expectoration	Increased lung texture or exudation
Control	5 (12.50)	11 (27.50)	18 (45.00)	15 (37.50)
Experiment	3 (7.50)*	4 (10.00)*	9 (22.50)*	7 (17.50)*

* $p < 0.05$ compared with the control group.

The inverse ratio ventilation is well known to improve arterial oxygenation in acute respiratory distress syndrome, reduce intrapulmonary shunt, recruit atelectatic alveoli, improve ventilation, and decrease dead space ventilation [9]. Increase of the inspiratory time permits sufficient time to gas exchange. At the same time, short expiratory time in inverse ratio ventilation allows air trapped in the lungs for generation of intrinsic PEEP or auto-PEEP. Moreover, the PEEP generated in inverse ratio ventilation can improve oxygenation, contributing to advantageous effects on pulmonary mechanics [19,20]. The inverse ratio ventilation with increased inspiratory time can also increase the mean distribution time to facilitate distribution and mixture of inhaled gas within the lungs and to enhance CO₂ elimination. Increasing the inspiratory time does not affect elimination of CO₂ which is probably associated with blood absorption of CO₂. This is why there was a significant increase in OI, a significant decrease in D(A-a)O₂ but no significant difference in the PaCO₂ between the EG with inverse ratio ventilation and CG in this study. In this study, the I:E ratio of 2:1 used is considered as the optimal ratio. Sari et al. [15] studied the effects of alteration of the I:E and found that stepwise prolongation of the I:E ratio from 1:1.9 to 2:1 had significantly decreased the intrapulmonary shunting, whereas increase of the I:E from 2.1 to 2.6 or at 4:1 had not further decreased the intrapulmonary shunting. Therefore, the I:E ratio at 2:1 was used in this study and had proved its effects in improving oxygenation and protecting the lung.

Atelectasis may contribute to an increased risk of morbidity in surgical patients who were ventilated with both a low TV and low PEEP, and studies have shown that application of significant PEEP can promote lung protection, improve lung function, and decrease the risk of postoperative complications during ventilation with one or two lungs [7,11,21]. Application of either high PEEP or a low TV as a sole parameter between groups has not been proven to be protective, and TVs and PEEP are interdependent for synergistic interaction which has been demonstrated in some experimental models [22,23]. Combination of low TV and zero end-expiratory pressure led to a much greater mortality compared to groups receiving either higher TVs or PEEP [24]. Mechanical ventilation has a potential to adversely affect results in surgical patients, and protective ventilation with low TVs and PEEP has been suggested by some experts [25,26]. However, no standardized guidelines are available. Although the ideal

amount of PEEP and the ideal approach to titrating PEEP in surgical patients have not yet been clearly proved, 5 cm H₂O PEEP and 6–8 ml/kg for TVs were used in this study, and it had proved the lung-protective effect in combination with low TV and inverse ratio ventilation, resulting in decreased lung complications in the inverse ratio ventilation group with decreased incidences of ventilator-assisted breathing, hypoxemia, expectoration, and lung texture or exudation. Moreover, the OI and pulmonary compliance were significantly increased while the D(A-a)O₂ and Lac were significantly decreased in the inverse ratio ventilation group, indicating the beneficial effects of the inverse ratio ventilation combined with lung-protective ventilation.

In the current study, the IL-6 and IL-10 were significantly decreased at 1 h after start of the operation and at the end of surgery in the EG with the inverse ratio ventilation and lung-protective ventilation than in the CG. Acute lung injury is associated with acute inflammatory responses with production of cytokines, and mechanical ventilation and operative wound may provoke release of inflammatory factors like IL-6, IL-8, and tumor necrosis factor- α (TNF- α) which play an important role in stress responses [9]. IL-6 is one of the most important inflammatory factors, with the degree of lung injury positively correlated with the concentration of IL-6 [27]. IL-10 is an anti-inflammatory immunosuppressive cytokine and can perform immune regulation relevant to both inflammatory and infectious disease [28]. IL-10 inhibits synthesis of proinflammatory cytokines and release of reactive oxygen and nitrogen intermediates if mononuclear phagocytes or dendritic cells are exposed to IL-10. Moreover, IL-10 protects mice against endotoxin shock by preventing over-production of proinflammatory cytokines [29]. IL-10 can consequently turn off the signaling cascade of inflammatory cytokines and inhibit development of multiple organ injury such as acute respiratory distress syndrome. Mechanical ventilation is an external force and may cause or aggravate lung injury by interfering with the natural respiration process [30]. Studies have demonstrated that patients receiving mechanical ventilation may be subjected to over-dilation of the alveoli by mechanical traction that may induce inflammation and acute lung injury or ventilator-induced lung injury [31,32]. An important characteristic of acute lung injury is over-expression of inflammatory mediators like TNF- α

and IL-8. TNF- α , IL-6, and IL-8 have been proved to be increased in the bronchoalveolar lavage with conventional ventilation without inverse ratio ventilation in obese patients undergoing gynecological laparoscopy [9]. The current study showed that the IL-6 and IL-10 concentrations were both decreased during and at the end of the surgery. Because the inverse ratio ventilation plus lung-protective ventilation has benefited and protected the lung from further injury with decreased complications (decreased incidences of hypoxemia, expectoration, and lung texture or exudation) in the EG compared with the CG, the inflammatory factor IL-6 was decreased (other inflammatory factors may have also decreased), and because of decreased inflammatory factors, the anti-inflammatory factor IL-10 was also decreased.

Some limitations may exist in this study including a small cohort of patients, Chinese ethnicity only and one single-center study nature, which may potentially affect the bias of the study. Future studies will have to solve these issues for a better outcome.

In conclusion, the use of volume-controlled inverse ratio ventilation combined with lung-protective ventilation with low TVs and high PEEP can reduce Ppeak, increase Pmean, and Cdyn, improve pulmonary oxygenation function and decrease ILs in severe burn patients receiving surgery.

Disclosure statement

No potential conflict of interest was reported by the authors.

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