# Effect of Therapeutic Hypercapnia on Inflammatory Responses to One-lung Ventilation in Lobectomy Patients

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## ABSTRACT

**Background:** One-lung ventilation (OLV) can result in local and systemic inflammation. This prospective, randomized trial was to evaluate the effect of therapeutic hypercapnia on lung injury after OLV.

**Method:** Fifty patients aged 20 to 60 yr undergoing lobectomy were randomly provided with air or carbon dioxide (partial pressure of carbon dioxide: 35 to 45 mmHg or 60 to 70 mmHg). Peak pressure, plateau pressure, and lung compliance were recorded. Bronchoalveolar lavage fluid (BALF) and blood samples were collected. Adverse events were monitored. The primary outcome was the concentration of BALF tumor necrosis factor, and the secondary outcomes were serum cytokine concentrations.

**Results:** The BALF tumor necrosis factor was lower in the carbon dioxide group than in the air group (median [range], 51.1 [42.8 to 76.6] *vs.* 71.2 [44.8 to 92.7]; $P = 0.034$). Patients in the carbon dioxide group had lower concentrations of serum and BALF interleukin (IL)-1, IL-6, and IL-8, but higher serum concentrations of IL-10, accompanied by reduced numbers of cells and neutrophils as well as lower concentrations of protein in the BALF. Also, patients in the carbon dioxide group had lower peak (mean ± SD, 22.2 ± 2.9 *vs.* 29.8 ± 4.6) and plateau pressures (20.5 ± 2.4 *vs.* 27.1 ± 2.9), but higher dynamic compliance (46.6 ± 5.8 *vs.* 38.9 ± 6.5). Furthermore, patients in the carbon dioxide group had higher postoperation oxygenation index values. Ten patients experienced slightly increased blood pressure and heart rate during OLV in the carbon dioxide group.

**Conclusion:** Under intravenous anesthesia, therapeutic hypercapnia inhibits local and systematic inflammation and improves respiratory function after OLV in lobectomy patients without severe complications. **(Anesthesiology 2015; 122:1235-52)**



DURING one-lung ventilation (OLV), inflammation and acute lung injury (ALI) can be induced by many factors.[1–3] The incidence of OLV-related ALI varies in different situations.[4] Inflammation and ALI can be attributed to an imbalance in levels of cytokines, such as proinflammatory tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, and IL-8 and antiinflammatory IL-10. Therefore, prevention and mitigation of OLV-related inflammation will be of great significance in the management of patients undergoing thoracic surgery.

Hypercapnia is one of the lung-protective strategies for intervention in patients with acute respiratory distress syndrome and currently can be divided into permissive and therapeutic hypercapnia. Whereas permissive hypercapnia is considered to be undesirable but tolerable to low ventilation, which may provide the potential beneficial effects of hypercapnic acidosis,[5] therapeutic hypercapnia is described as desirable hypercapnic acidosis for treatment purpose established by intentional inhalation of carbon dioxide or lowering ventilation.[6] Therapeutic hypercapnia can reduce injury resulting from mechanical ventilation,[7] ischemia–reperfusion,[8] endotoxins,[9] sepsis,[10] and acute respiratory distress syndrome.[10] Although hypoventilation may lead to atelectasis, hypoxemia, impairment in gas exchange, increased intrapulmonary shunt, and lung injury,[11,12] continual inhalation of carbon dioxide can improve ventilation–perfusion matching.[13] Previous clinical studies have demonstrated the safety of hypercapnia in adults and children.[14,15] However, there has been no study on the effect of therapeutic hypercapnia on inflammatory responses to OLV. In this study, we tested the hypothesis that a combination of therapeutic hypercapnia and intravenous anesthesia may have a superior effect in inhibiting local and systemic inflammation and improving lung function compared with intravenous anesthesia alone in patients undergoing a lobectomy.

### What We Already Know about This Topic

- One-lung ventilation has been associated with local and systemic inflammation

### What This Article Tells Us That Is New

- Fifty patients undergoing lobectomy under intravenous anesthesia randomly received carbon dioxide at partial pressures of 35 to 45 mmHg or 60 to 70 mmHg for approximately 210 min
- The bronchoalveolar lavage fluid from the patients in the higher carbon dioxide group had decreased the total number of cells, total protein, and some cytokines after surgery

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## Materials and Methods

This prospective, single-center, randomized, parallel-group, single-blinded trial (Chinese Clinical Trial Registry: ChiCTR-TRC-12002468) was approved by the Ethics Committee of Harbin Medical University (Harbin, Heilongjiang Province, China). Informed written consent was obtained from all patients.

This study was conducted in the Department of Thoracic Surgery and Anesthesia at the Second Affiliated Hospital of Harbin Medical University from September 2012 to April 2013. All patients were continually recruited through a centrally located clinical service of our hospital without advertisement. A total of 50 patients (male: 26 and female: 24, aged 20 to 60 yr) with class II or III according to the American Society of Anesthesiologists' classification were enrolled in the current study. These patients required a lobectomy after thoracotomy but not a video-assisted thoracoscopic surgery or robotic surgery under propofol general anesthesia. Exclusion criteria were individuals with smoking cessation less than 2 weeks, body mass index greater than 35 $kg/m^2$, abnormal lung function (vital capacity or forced expiratory volume in 1 s <50% of the predicted values), abnormal numbers of leukocytes ($<4.0 \times 10^9$ or $>10.0 \times 10^9$/l), symptoms of intracerebral hypertension (headache, giddiness, papilledema, nausea, and vomiting), previous cranial hemorrhage, cardiac arrhythmia classified as Lown IIb, emotional disturbance, or a history of or current nonlung cancer, chronic lung disease (chronic pneumonia, bronchitis, pneumoconiosis, silicosis, or asthma), pleural effusion, or pulmonary hypertension (>30 mmHg). Patients with chronic obstructive pulmonary disease (diagnosed according to the criteria established by the Global Initiative for Chronic Obstructive Lung Disease) were excluded because they were more likely to require a lower tidal volume to reduce the mechanical stress during OLV and were prone to endogenous hypercapnia. In addition, patients with severe obstructive lung disease and potentially chronic hypercapnia were excluded to avoid the potential interference of endogenous hypercapnia. Moreover, an individual was excluded if she/he required a lobectomy of more than two lobes or pneumonectomy. Moreover, a patient was excluded from this study if she/he failed to maintain oxygen saturation of pulse oximeter ($Spo_2$) greater than 95% during two-lung ventilation and greater than 90% during OLV, required an alternative surgical procedure, or suffered a surgical failure due to any reason.

All recruited patients were randomized into either the air group or carbon dioxide group by sequentially blocking based on a random number table. In brief, we set up five blocks, and each block contained 10 subjects. We randomly selected 10 numbers from the random number table, and if a number had been used already, we selected another number. The randomly selected 10 numbers for the first recruited 10 patients were sorted according to the order. The five patients corresponding to the first five numbers were allocated into the air group, and the other five patients corresponding to the remaining five numbers were allocated into the carbon dioxide group. This process was repeated five times to randomize all 50 patients to these two groups at a 1:1 ratio. The patients in the air and carbon dioxide groups received oxygen with air or a combination of oxygen, air, and carbon dioxide during OLV, respectively.

To ensure blinding, two anesthesiologists were involved in the study. The first anesthesiologist, who did not administer anesthesia in this study, had access to the randomization code and prepared the gas with the same outer cover for ventilation during OLV in this study. Then, this anesthesiologist monitored arterial blood gas levels using a blood gas analyzer (ABL 505; Radiometer, Denmark). The inspiratory gas (mixed gas of oxygen, air, and carbon dioxide) was also monitored using a Datex/Ohmeda S/5 (Datex Instrumentation, Finland), and the concentrations of oxygen and carbon dioxide were adjusted according to the partial pressure of oxygen ($Pa_{O_2}$) and partial pressure of carbon dioxide ($Pa_{CO_2}$) by the first anesthesiologist. All monitored data were kept in a secure place until analyses. The second anesthesiologist who did not have knowledge of the gas monitor and arterial blood analysis data performed intravenous anesthesia and bronchoalveolar lavage (BAL) and collected BAL fluid (BALF) and blood samples. During operation, a baffle board was set up between the first and second anesthetists to further ensure blinding.

The patients not given any premedication were transferred to the operating room and subjected to percutaneous radial artery cannulation to monitor mean arterial pressure and to analyze blood gas levels. Subsequently, all patients were infused with 5 ml/kg of a colloidal solution and then continually with a mixture (2:1) of colloidal and crystal solution at 8 $ml \cdot kg^{-1} \cdot h^{-1}$.

These patients were given injections of lidocaine (1 mg/kg), fentanyl (4 μg/kg), rocuronium (0.6 mg/kg), and propofol (1.5 mg/kg). After induction, a left or right double-lumen endobronchial tube was inserted (Broncho-Cath, 35–37 Ch; Mallinckrodt Medical Ltd, Ireland), and the position of the endobronchial tube was confirmed using a fiber-optic bronchoscope (Olympus Europe, Switzerland). The patients were treated with propofol (3 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanyl (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for the maintenance of anesthesia. Patients in both groups were subjected to either two-lung ventilation (8 ml/kg) or OLV (6 ml/kg) according to the actual body weight (with a mixture of oxygen and air for the air group and a mixture of oxygen, air, and carbon dioxide for the carbon dioxide group) using a ventilator (Fabius Tiro; Dräger, Germany). To maintain the $Spo_2$ at greater than 95% for two-lung ventilation and greater than 90% for OLV and to exclude the effect of low fraction of inspired oxygen ($Fio_2$) on lung injury induced by OLV, $Fio_2$ was adjusted within the range of 0.5 to 0.8 for two-lung ventilation and maintained at greater than 0.8 for OLV, at a respiratory rate of 12 to 15 $min^{-1}$ for patients in the air group. During OLV, the $Pa_{CO_2}$ was maintained at 35 to 45

mmHg for the air group and 60 to 70 mmHg for the carbon dioxide group.[16] The patients inhaled carbon dioxide from separate gas tanks, which were connected with the nitrous oxide gas supply interface of the ventilator. The inhaled carbon dioxide was adjusted with the nitrous oxide flow meter. The carbon dioxide absorber was used in the circuit to ensure no rebreathing of carbon dioxide. After return to two-lung ventilation, the patients in the carbon dioxide group stopped inhaling carbon dioxide to increase their respiratory rate (16 to 18 $min^{-1}$) and to decrease the $Paco_2$ to within the normal range. During OLV, some patients received treatment to improve $Pao_2$ if they displayed hypoxemia. These strategies included ensuring the ventilator was functioning normally, adjusting the location of the double-lumen endobronchial tube or ensuring the tube was unobstructed and increasing the $Fio_2$. If these treatments were ineffective, carbon dioxide or air inhalation was stopped, and the patient's tidal volume or respiratory rate was adjusted. Such patients were excluded from this trial. Before and after OLV, the collapsed and ventilated lungs were recruited 10 s each for four times with an airway pressure of 30 cm $H_2O$. During OLV, the positive end-expiratory pressure was set at 5 cm $H_2O$. During operation, the mean arterial pressure and heart rates of individual patients were maintained at 20% of baseline values. Before OLV and 30 min after reexpansion, individual patients were subjected to BAL with 60 ml saline per lung using a flexible fiber-optic bronchoscope to avoid iatrogenic edema and atelectasis. In brief, the two bronchial segments of the collapsed and ventilated lungs were selected under a fiber-optic bronchoscope, injected with 60 ml saline, and gently aspirated with −50 cm $H_2O$ pressure. The recovery of BALF was approximately 50 to 60%. The collected BALF samples were centrifuged at 1,000*g* at 4°C for 15 min and stored at −80°C.

After OLV, the patients were subjected to a positive airway pressure of 30 cm $H_2O$ twice for 5 s each to dilate the lungs. When the patients returned to spontaneous respiration and opened their eyes following commands, the patients were extubated and taken to a postanesthesia care unit. After the absence of respiratory dysfunction or hemorrhage was confirmed, the patients were transferred to the regular ward. The patients in both groups were subjected to postoperative analgesia with self-controlled sufentanil infusion (0.05 $\mu g \cdot kg^{-1} \cdot h^{-1}$). They were tested using the visual analog scale from 0 to 10 to evaluate potential pain.

The primary outcome of this trial was the concentration of BALF TNF-α in the collapsed lung and ventilated lung. The secondary outcomes of this study were the serum cytokine concentrations during the 3-day postoperative observation period. All data were recorded, and the samples were collected before OLV (T1), at 30 min after reexpansion (T2), and 24 (T3), 48 (T4), and 72 h (T5) postoperation. The duration of surgery, mechanical ventilation, OLV, and volumes of hemorrhage and infusion were recorded. During the OLV, the arterial blood gas levels, mean arterial pressure, and heart rate were monitored every 30 min. The peak pressure, plateau pressure, and dynamic compliance of individual patients were monitored and recorded at T1 and T2. The arterial blood analyses and peripheral blood samples were collected from T1 to T5. The peripheral blood samples were centrifuged at 2,000*g* at 4°C for 20 min, and the collected serum samples were immediately stored at −80°C.

The surgery-related adverse events, including pulmonary infection, pneumothorax, pneumonia, pulmonary edema, atelectasis, effusion, fistula, reintubation, systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome, and hyperglycemia, were monitored. The therapeutic hypercapnia-related complications, including postoperative emotional dysfunction, flushed skin, muscle twitching, disorientation, hand flaps, panic, hypertension, convulsions, unconsciousness, intracranial hypertension (headache, giddiness, and blurred vision), tachycardia, arrhythmias, and delayed recovery, were monitored and recorded.

The cell pellets of BALF samples were resuspended in phosphate-buffered saline, and the numbers of total cells were counted using a hemocytometer. The cells were subjected to cytospins and Wright–Giemsa staining to determine the numbers of neutrophils and macrophages. The concentrations of total protein in the BALF were measured using the Micro BCA Protein Assay Kit (Pierce, USA). The concentrations of BALF and serum cytokines (TNF-α, IL-1β, IL-6, IL-8, and IL-10), complement (C) 3a, and C-reactive protein (CRP) were examined by enzyme-linked immunosorbent assay using specific kits (Wuhan Boster Bio-Engineering, China) and calculated according to standard curves. The limits of detection were 3.8 pg/ml for TNF-α, 1.56 pg/ml for IL-1β, 2.5 pg/ml for IL-6, 7.8 pg/ml for IL-8, 3.4 pg/ml for IL-10, and 7 μg/ml for C3a.

### Statistical Analysis

The normally distributed data are presented as the mean ± SD, and skewed data are presented as medians (range). The normally distributed data were analyzed using two-way repeated ANOVA and *post hoc* Bonferroni correction. The skewed data were logarithmically transformed to achieve a normal distribution and analyzed with two-tailed Student *t* tests. If these data remained heteroscedastic after transformation, the data between groups were analyzed using a nonparametric Friedman test and subsequently a Kruskal–Wallis H test. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS, Inc., USA). A two-tailed *P* value less than 0.05 was considered statistically significant.

The sample size for measuring the primary outcome (the concentration of BALF TNF-α in the ventilated lung) was estimated using the Kruskal–Wallis H test with a type 1 error of 0.05, and a minimum sample size of 16 patients allowed an 80% power to detect a size effect difference of 40% in the concentrations of BALF TNF-α.[16] The actual sample size of 25 per group allowed us to attain a statistically significant difference after the potential loss of disqualified participants.

## Results

Fifty patients undergoing lobectomy with general propofol anesthesia were recruited and randomized into the air and carbon dioxide groups (fig. 1). There were no missing data for any of the analyses in this study. There were no statistically significant differences in the demographic and surgical characteristics of the patients in the two groups (table 1). During the study, no patient was excluded according to the intraoperative exclusion criteria (change in procedure, desaturation, technical problems, and others). No patients required a blood transfusion or developed adverse surgical events throughout the observation period. Ten patients experienced slightly increased blood pressure and a faster heart rate during OLV in the carbon dioxide group, but no other adverse events related to therapeutic hypercapnia occurred in this population. No patient reported a postoperative visual analog score of greater than 4 and needed additional analgesia. There were no statistically significant differences in the VAS scores between these two groups of patients.

There were no statistically significant differences in the values of peak pressure, plateau pressure, and dynamic compliance at T1 between the air and carbon dioxide groups. However, the values of peak airway pressure and plateau pressure in the carbon dioxide group at T2 were lower than those in the air group. In contrast, the values of dynamic compliance in the carbon dioxide group at T2 were greater than that in the air group (table 2).

There were no statistically significant differences in the values of $Pa_{CO_2}$, pH, and $Sp_{O_2}$ between the two groups of patients at T1 to T5 (fig. 2 and table 3). In comparison with that at T1, the values of $Pa_{O_2}/F_{IO_2}$ during OLV in both groups were reduced at later time points; the values of the $Pa_{O_2}/F_{IO_2}$ in the carbon dioxide group were greater than those in the air group at T3 to T5 (fig. 2 and table 3).

During OLV, there was no significant difference in $F_{IO_2}$ between the two groups. The values of $Pa_{CO_2}$ in the carbon dioxide group were higher than those in the air group, whereas the values of pH in the carbon dioxide group were lower than those in the air group (fig. 3 and table 4). In addition, the values of mean arterial pressure and heart rate in the carbon dioxide group were slightly higher than those in the air group, but the differences were not statistically significant (fig. 3 and table 4). There was no statistically significant difference in the expired volume between the two groups of patients during OLV (fig. 3 and table 4).

There also were no statistically significant differences in the numbers of total cells, neutrophils, and macrophages or the total protein concentrations between the two groups at T1. Compared with the air group, the numbers of total cells and neutrophils, but not macrophages, in BALF were less in the carbon dioxide group than in the air group at T2 (fig. 4). The concentrations of BALF proteins in the carbon dioxide group were lower than those in the air group after OLV (fig. 4 and table 5).

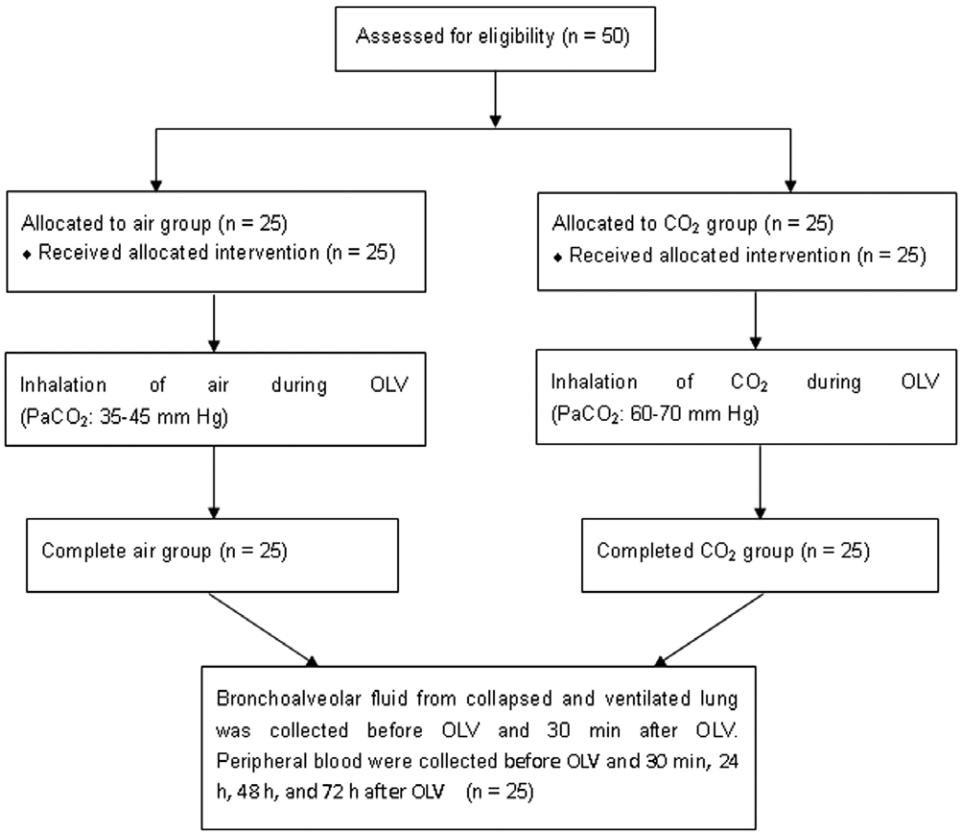


**Fig. 1.** Flow diagram of enrolled patients. OLV = one-lung ventilation; $Pa_{CO_2}$ = arterial partial pressure of carbon dioxide.

**Table 1.** The Demographic and Surgical Characteristics of Patients Who Underwent Intravenous Anesthesia and Lobectomy and Received Oxygen with Air (Air Group) or Combination of Oxygen, Air, and Carbon Dioxide (Carbon Dioxide Group)

| Characteristics | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | 95% CI* | *P* Value† |
|---|---|---|---|---|
| Age (yr) | 47.6 ± 10.2 | 48.7 ± 9.9 | −2.57 to 4.81 | 0.69 |
| Height (cm) | 169.7 ± 6.9 | 170.3 ± 7.2 | −3.04 to 4.64 | 0.58 |
| Weight (kg) | 63.9 ± 10.6 | 64.6 ± 11.1 | −6.53 to 6.05 | 0.81 |
| Men | 12 (48%) | 14 (56%) | 0.24 to 2.21 | 0.77 |
| Collapsed lung (left lung) | 10 (40%) | 12 (48%) | 0.23 to 2.21 | 0.56 |
| FVC (% predicted) | 82% (58 to 118) | 80% (59 to 116) | | 0.98 |
| $FEV_1$ (% predicted) | 70% (57 to 125) | 68% (55 to 123) | | 0.83 |
| $Pa_{O_2}$ (mmHg) | 73.6 (56.7 to 104.5) | 75.8 (57.9 to 107.8) | | 0.31 |
| $Pa_{CO_2}$ (mmHg) | 37.5 (28.7 to 48.6) | 35.7 (29.4 to 50.9) | | 0.53 |
| Duration of one-lung ventilation (min) | 174 ± 37 | 189 ± 41 | −37.31 to 7.46 | 0.18 |
| Total volume of fluids infused (ml) | 1,745 ± 163 | 1,783 ± 146 | −127.45 to 47.45 | 0.38 |
| Blood loss (ml) | 478 ± 67 | 512 ± 71 | −74.34 to 4.75 | 0.08 |
| Duration of mechanical ventilation (min) | 247 ± 42 | 268 ± 55 | −50.71 to 4.63 | 0.14 |

Data are presented as mean ± SD, number (%), or median (range) where appropriate.

* 95% CI of the difference between means of the two groups. † Bonferroni adjusted.

$FEV_1$ = forced expiratory volume in 1 s; FVC = forced vital capacity; $Pa_{CO_2}$ = arterial partial pressure of carbon dioxide; $Pa_{O_2}$ = arterial partial pressure of oxygen.

**Table 2.** The Ventilatory Parameters in the Two Groups at T1 and T2

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | Mean Difference | 95% CI* | *P* Value† |
|---|---|---|---|---|---|
| Peak pressure (cm $H_2O$) | | | | | |
| T1 | 16.9 ± 2.5 | 17.5 ± 2.2 | −0.6 | −1.41 to 0.54 | 0.37 |
| T2 | 29.8 ± 4.3 | 22.2 ± 3.6 | 7.6 | 5.15 to 9.73 | <0.001 |
| Plateau pressure (cm $H_2O$) | | | | | |
| T1 | 14.8 ± 2.1 | 15.3 ± 1.9 | −0.5 | −1.45 to 0.33 | 0.25 |
| T2 | 27.1 ± 2.9 | 20.6 ± 2.4 | 6.5 | 5.02 to 8.09 | <0.001 |
| Dynamic compliance (ml/cm $H_2O$) | | | | | |
| T1 | 55.7 ± 5.9 | 54.3 ± 6.5 | 1.4 | −4.01 to 6.81 | 0.38 |
| T2 | 38.9 ± 6.5 | 46.6 ± 5.8 | −9.4 | −12.92 to -6.05 | <0.001 |

Data are presented as mean ± SD.

* 95% CI of the difference between means of the two groups. † Bonferroni adjusted.

$H_2O$ = dihydrogen monoxide; T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

There was a significant interaction in the BALF TNF-α concentrations between group and time ($P = 0.009$). Compared with T1, the BALF TNF-α concentrations were significantly increased at T2 in both the carbon dioxide group (51.1 [42.8 to 76.6]; $P = 0.024$) and air group (71.2 [44.8 to 92.7]; $P < 0.001$). At T1, there was no difference in the BALF TNF-α concentrations between the carbon dioxide and air groups (29.3 [19.8 to 63.6] *vs.* 32.9 [15.2 to 65.6]; $P = 0.639$). However, the BALF TNF-α concentrations at T2 were lower in the carbon dioxide group than in air group ($P = 0.034$). There were no statistically significant differences in BALF concentrations of IL-1β, IL-6, IL-8, and IL-10 between the two groups at T1. Also, the levels of IL-1β, IL-6, and IL-8 from two lungs in the carbon dioxide group at T2 were lower, but the IL-10 levels in the carbon dioxide group at T2 were higher than those in the air group (fig. 5 and table 5). Further stratification indicated that in BALF from either collapsed or ventilated lungs at T2, the concentrations of TNF-α, IL-1β, IL-6, and IL-8 were lower, whereas the concentrations of IL-10 were higher in the carbon dioxide group of patients than in the air group.

There were no statistically significant differences in the serum concentrations of TNF-α, IL-1β, IL-6, IL-8, and IL-10 between the carbon dioxide and air groups at T2. The concentrations of serum TNF-α, IL-1β, IL-6, IL-8, and IL-10 increased from T3 to T5 in the air group. As a result, the concentrations of serum TNF-α, IL-1β, IL-6, and IL-8 in the air group were higher than those in the carbon dioxide group, whereas the levels of serum IL-10 were lower than those in the carbon dioxide group from T3 to T5 (fig. 6 and table 5).

There were no statistically significant differences in the levels of BALF and serum C3a and CRP between the two groups at T1 and T2 (fig. 7 and tables 3 and 5). However, the levels of serum C3a and CRP in the carbon dioxide group from T3 to T5 were lower than those in the air group.

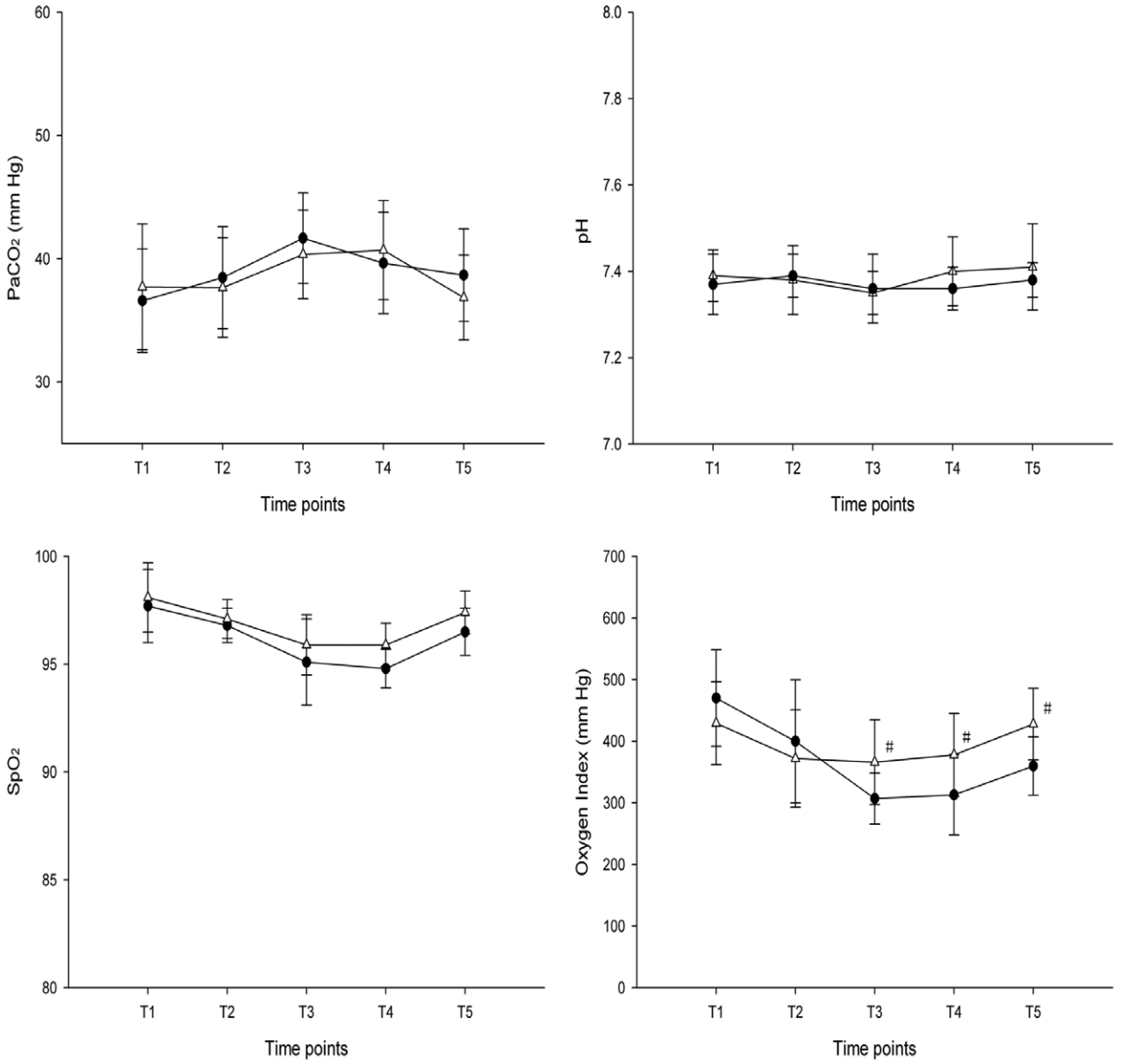


**Fig. 2.** Analysis of arterial blood samples. The levels of arterial blood $Paco_2$, pH, and $Spo_2$ as well as the $Pao_2/Fio_2$ in individual patients at the indicated time points during one-lung ventilation were measured and are expressed as the mean ± SD for each group of patients (n = 25 per group). *Filled circle* and *triangle* represent the air and carbon dioxide groups, respectively. #$P < 0.05$ compared with air group. $Paco_2$ = arterial partial pressure of carbon dioxide; pH = potential of hydrogen; $Spo_2$ = oxygen saturation of pulse oximeter; T1 = before one-lung ventilation; T2 = 30 min after reexpansion; T3 = 24 h postoperation; T4 = 48 h postoperation; T5 = 72 h postoperation.

Further stratification indicated that there were no statistically significant differences in the results for BALF cytokines and cell distribution between the ventilated and nonventilated lungs in the two groups after OLV (table 6).

## Discussion

In this study, we found that therapeutic hypercapnia lowered airway pressure but increased the compliance and $Pao_2/Fio_2$ after surgery. Furthermore, therapeutic hypercapnia decreased the numbers of total cells and neutrophils as well as the total protein concentrations in BALF at 30 min postsurgery. More importantly, therapeutic hypercapnia inhibited the local inflammation and especially reduced the levels of BALF TNF-α. In addition, hypercapnia decreased the concentration of BALF and serum proinflammatory IL-1β, IL-6, and IL-8 as well as serum C3a and CRP, but increased the concentrations of serum and BALF antiinflammatory IL-10 in the carbon dioxide group of patients after surgery. To the best of our knowledge, our data for the first time indicate that therapeutic hypercapnia during OLV not only improves respiratory function but also mitigates the OLV-related local and systemic inflammation in patients undergoing a lobectomy.

**Table 3.** The Arterial Blood Analysis and Inflammatory Responses in the Two Groups from T1 to T5

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | Mean Difference | 95% CI* | *P* Value† |
|---|---|---|---|---|---|
| Arterial blood analysis | | | | | |
| $Paco_2$ | | | | | |
| T1 | 36.52 ± 1.32 | 37.12 ± 1.69 | −0.60 | −1.46 to 0.26 | 0.16 |
| T2 | 37.84 ± 2.15 | 38.6 ± 2.31 | −0.76 | −2.03 to 0.51 | 0.23 |
| T3 | 40.40 ± 1.81 | 39.32 ± 2.04 | 1.08 | −0.13 to 2.17 | 0.06 |
| T4 | 38.82 ± 1.99 | 38.56 ± 2.29 | 0.26 | −0.94 to 1.51 | 0.66 |
| T5 | 38.20 ± 1.69 | 38.96 ± 2.42 | −0.68 | −1.94 to 0.58 | 0.28 |
| pH | | | | | |
| T1 | 7.39 ± 0.02 | 7.38 ± 0.01 | 0.01 | −0.002 to 0.020 | 0.12 |
| T2 | 7.39 ± 0.02 | 7.38 ± 0.03 | 0.01 | −0.002 to 0.020 | 0.10 |
| T3 | 7.39 ± 0.05 | 7.39 ± 0.03 | −0.01 | −0.030 to 0.010 | 0.59 |
| T4 | 7.41 ± 0.03 | 7.40 ± 0.01 | 0.01 | −0.010 to 0.020 | 0.71 |
| T5 | 7.39 ± 0.03 | 7.41 ± 0.02 | −0.02 | −0.030 to 0.002 | 0.07 |
| $Spo_2$ | | | | | |
| T1 | 99.0 ± 0.9 | 99.3 ± 0.8 | −0.3 | −0.75 to 0.19 | 0.23 |
| T2 | 96.9 ± 1.1 | 96.8 ± 1.4 | 0.1 | −0.57 to 0.81 | 0.73 |
| T3 | 94.9 ± 1.2 | 95.3 ± 1.5 | −0.4 | −1.10 to 0.30 | 0.27 |
| T4 | 94.3 ± 1.4 | 94.9 ± 1.2 | −0.6 | −1.10 to 0.30 | 0.09 |
| T5 | 97.4 ± 2.4 | 96.9 ± 2.6 | 0.4 | −1.00 to 1.80 | 0.57 |
| $Pao_2/Fio_2$ | | | | | |
| T1 | 457.8 ± 83.7 | 430.7 ± 101 | 27.1 | −15.07 to 69.21 | 0.22 |
| T2 | 402.1 ± 101.3 | 389.4 ± 76.9 | 12.7 | −38.53 to 63.86 | 0.62 |
| T3 | 306.7 ± 42.1 | 370.1 ± 75.4 | −66.3 | −101.67 to −31.54 | <0.001 |
| T4 | 310.9 ± 65.5 | 372.1 ± 62.1 | −61.1 | −97.38 to −24.79 | 0.001 |
| T5 | 357.8 ± 47.4 | 417.2 ± 58.7 | −59.4 | −89.80 to −29.10 | <0.001 |
| Inflammatory responses | | | | | |
| TNF-α | | | | | |
| T1 | 45.5 ± 22.1 | 44.4 ± 11.8 | 1.1 | −8.94 to 11.17 | 0.82 |
| T2 | 60.1 ± 20.5 | 54.4 ± 9.1 | 5.7 | −3.75 to 15.04 | 0.23 |
| T3 | 85.1 ± 30.9 | 70.5 ± 14.3 | 14.6 | 0.95 to 28.30 | 0.04 |
| T4 | 71.8 ± 25.7 | 54.6 ± 15.6 | 17.2 | 5.19 to 29.38 | 0.006 |
| T5 | 61.8 ± 17.6 | 48.4 ± 15.5 | 13.4 | 3.96 to 22.82 | 0.006 |
| IL-1β | | | | | |
| T1 | 6.43 ± 2.08 | 5.55 ± 2.35 | 0.88 | −0.38 to 2.13 | 0.16 |
| T2 | 8.59 ± 2.71 | 7.79 ± 3.26 | 0.80 | −0.90 to 2.5 | 0.35 |
| T3 | 21.49 ± 6.05 | 6.59 ± 1.86 | 14.9 | 12.35 to 17.44 | <0.001 |
| T4 | 11.14 ± 3.96 | 5.16 ± 1.65 | 5.98 | 4.20 to 7.70 | <0.001 |
| T5 | 9.99 ± 3.58 | 4.63 ± 1.72 | 5.36 | 3.70 to 6.90 | <0.001 |
| IL-6 | | | | | |
| T1 | 10.76 ± 3.46 | 11.56 ± 7.09 | −0.80 | −3.98 to 2.37 | 0.61 |
| T2 | 11.64 ± 4.34 | 11.15 ± 6.12 | 0.52 | −2.49 to 3.53 | 0.73 |
| T3 | 25.47 ± 10.79 | 18.88 ± 8.81 | 6.59 | 0.99 to 12.19 | 0.02 |
| T4 | 23.11 ± 8.33 | 15.89 ± 3.98 | 7.22 | 3.50 to 10.90 | <0.001 |
| T5 | 18.43 ± 7.72 | 11.99 ± 4.76 | 6.44 | 2.79 to 10.08 | <0.001 |
| IL-8 | | | | | |
| T1 | 46.77 ± 14.03 | 46.59 ± 14.12 | 0.18 | −7.83 to 8.18 | 0.96 |
| T2 | 58.73 ± 15.32 | 58.47 ± 8.89 | 0.26 | −6.87 to 7.38 | 0.94 |
| T3 | 92.98 ± 23 | 72.36 ± 18.76 | 20.62 | 8.67 to 32.55 | <0.001 |
| T4 | 93.89 ± 26.46 | 65.49 ± 16.63 | 28.40 | 5.83 to 40.97 | <0.001 |
| T5 | 70.28 ± 21.27 | 51.03 ± 13.05 | 19.25 | 9.21 to 29.28 | <0.001 |
| IL-10 | | | | | |
| T1 | 24.14 ± 5.62 | 23.65 ± 8.79 | 0.49 | −3.70 to 4.70 | 0.81 |
| T2 | 30.11 ± 8.21 | 32.24 ± 12.28 | −2.13 | −8.14 to 3.84 | 0.47 |
| T3 | 28.45 ± 11.08 | 52.29 ± 14.36 | −23.84 | −31.12 to −16.57 | <0.001 |
| T4 | 36.92 ± 12.05 | 48.19 ± 17.78 | −11.27 | −19.92 to −2.68 | <0.001 |
| T5 | 20.63 ± 6.93 | 29.96 ± 7.56 | −9.33 | −13.44 to −5.28 | <0.001 |

(*Continued*)

**Table 3.** *Continued*

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | Mean Difference | 95% CI* | *P* Value† |
|---|---|---|---|---|---|
| C3a | | | | | |
| T1 | 67.18 ± 10.68 | 66.13 ± 7.63 | 1.05 | −4.23 to 6.34 | 0.69 |
| T2 | 70.08 ± 16.65 | 67.27 ± 8.41 | 2.81 | −4.61 to 10.32 | 0.45 |
| T3 | 106.75 ± 12.65 | 82.51 ± 8.08 | 24.24 | 18.22 to 30.25 | <0.001 |
| T4 | 91.02 ± 12.86 | 71.22 ± 9.18 | 19.80 | 13.42 to 26.17 | <0.001 |
| T5 | 86.62 ± 7.82 | 71.14 ± 9.06 | 15.48 | 10.63 to 20.25 | <0.001 |
| CRP | | | | | |
| T1 | 7.67 ± 2.85 | 8.07 ± 2.18 | −0.40 | −1.80 to 1.05 | 0.57 |
| T2 | 13.18 ± 2.61 | 10.99 ± 1.84 | 2.19 | −0.46 to 4.89 | 0.09 |
| T3 | 59.23 ± 7.78 | 34.86 ± 5.83 | 24.37 | 20.42 to 28.24 | <0.001 |
| T4 | 87.24 ± 12.23 | 61.38 ± 9.31 | 25.86 | 19.66 to 32.12 | <0.001 |
| T5 | 104.66 ± 12.26 | 74.6 ± 15.04 | 30.06 | 22.27 to 37.85 | <0.001 |

Data are presented as mean ± SD.

* 95% CI of the difference between means of the two groups. † Bonferroni adjusted.

CRP = C-reactive protein; C3a = complement 3a; $FIO_2$ = fraction of inspired oxygen; IL = interleukin; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PaO_2$ = arterial partial pressure of oxygen; $SpO_2$ = oxygen saturation of pulse oximeter; TNF-α = tumor necrosis factor-α; T1 = before one-lung ventilation; T2 = 30 min after reexpansion; T3 = 24 h postoperation; T4 = 48 h postoperation; T5 = 72 h postoperation.

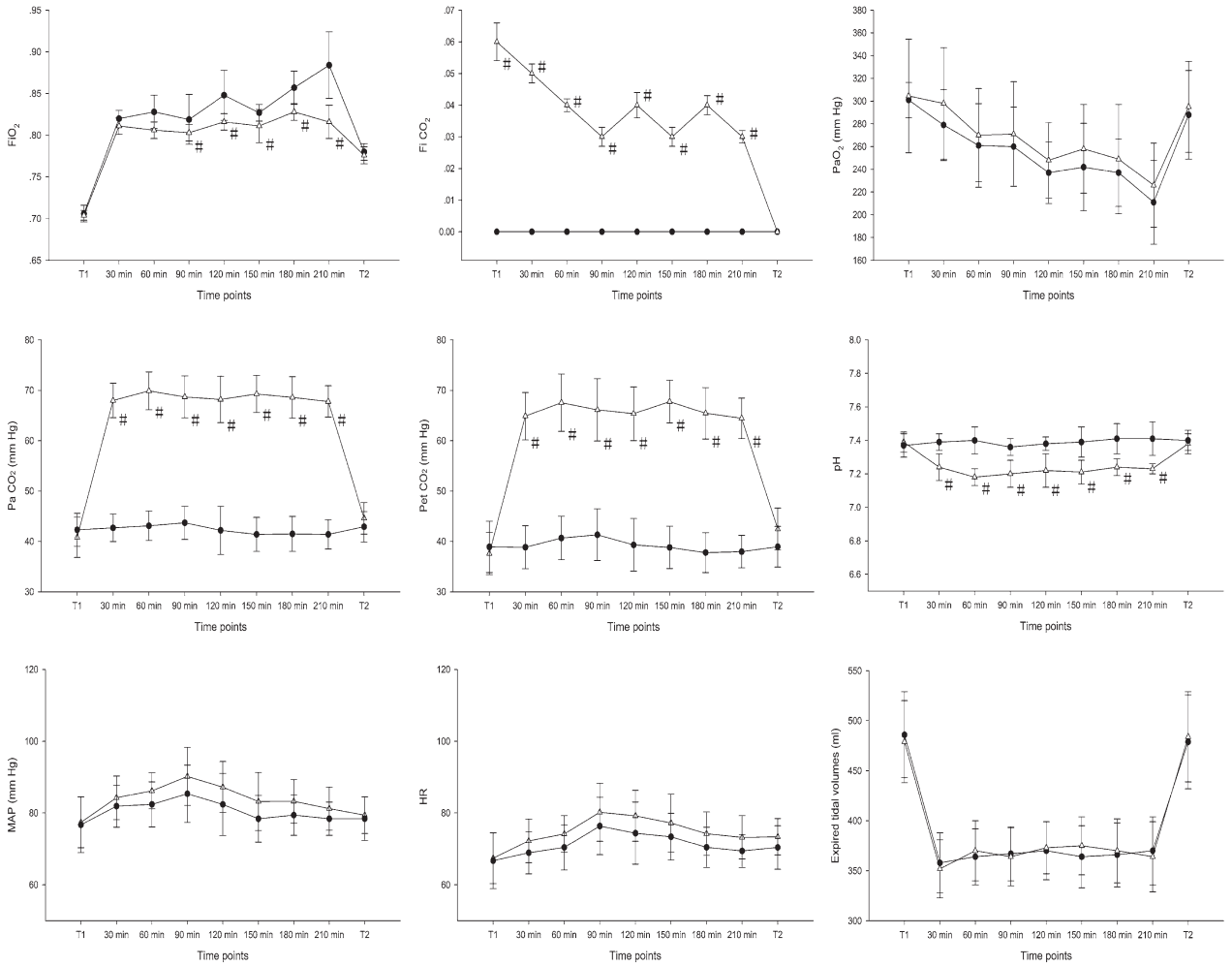


**Fig. 3.** Dynamic changes in the arterial blood and hemodynamic measures. Dynamic changes in the arterial blood gas and hemodynamic measures in individual patients during one-lung ventilation were monitored every 30 min between T1 and T2. Data are expressed as the mean ± SD of each group (n = 25). *Filled circle* and *triangle* represent the air and carbon dioxide groups, respectively. #$P < 0.05$ compared with air group. $FICO_2$ = fraction of inspired carbon dioxide; $FIO_2$ = fraction of inspired oxygen; HR = heart rate; MAP = mean arterial pressure; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PaO_2$ = arterial partial pressure of oxygen; $PETCO_2$ = pressure of end-tidal carbon dioxide; pH = potential of hydrogen; T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

**Table 4.** The Ventilatory Parameters, Arterial Blood Analysis, and Hemodynamic Measures in the Two Groups from T1 to T2

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | Mean Difference | 95% CI* | *P* Value† |
|---|---|---|---|---|---|
| Arterial analysis | | | | | |
| $F_{IO_2}$ | | | | | |
| T1 | 0.706 ± 0.01 | 0.704 ± 0.01 | 0.002 | −0.007 to 0.011 | 0.620 |
| 30 min | 0.82 ± 0.01 | 0.81 ± 0.01 | 0.009 | 0.000 to 0.018 | 0.050 |
| 60 min | 0.83 ± 0.02 | 0.81 ± 0.01 | 0.022 | −0.009 to 0.035 | 0.020 |
| 90 min | 0.82 ± 0.01 | 0.81 ± 0.004 | 0.016 | 0.006 to 0.026 | 0.004 |
| 120 min | 0.85 ± 0.03 | 0.82 ± 0.01 | 0.032 | 0.011 to 0.053 | 0.005 |
| 150 min | 0.83 ± 0.02 | 0.80 ± 0.01 | 0.016 | 0.002 to 0.030 | 0.010 |
| 180 min | 0.84 ± 0.01 | 0.82 ± 0.01 | 0.016 | 0.003 to 0.029 | 0.017 |
| 210 min | 0.88 ± 0.02 | 0.82 ± 0.02 | 0.068 | 0.050 to 0.090 | <0.001 |
| T2 | 0.78 ± 0.01 | 0.77 ± 0.02 | 0.004 | −0.009 to 0.017 | 0.520 |
| $F_{ICO_2}$ | | | | | |
| T1 | 0.00 ± 0.000 | 0.06 ± 0.007 | −0.058 | −0.063 to −0.053 | <0.001 |
| 30 min | 0.00 ± 0.000 | 0.05 ± 0.006 | −0.048 | −0.053 to −0.043 | <0.001 |
| 60 min | 0.00 ± 0.000 | 0.04 ± 0.006 | −0.040 | −0.044 to −0.036 | <0.001 |
| 90 min | 0.00 ± 0.000 | 0.03 ± 0.004 | −0.032 | −0.035 to −0.039 | <0.001 |
| 120 min | 0.00 ± 0.000 | 0.04 ± 0.006 | −0.040 | −0.043 to −0.037 | <0.001 |
| 150 min | 0.00 ± 0.000 | 0.03 ± 0.008 | −0.030 | −0.035 to −0.025 | <0.001 |
| 180 min | 0.00 ± 0.000 | 0.04 ± 0.004 | −0.038 | −0.041 to −0.035 | <0.001 |
| 210 min | 0.00 ± 0.000 | 0.03 ± 0.004 | −0.030 | −0.030 to −0.040 | <0.001 |
| T2 | 0.00 ± 0.000 | 0.00 ± 0.000 | 0.000 | 0.000 to 0.000 | 1.00 |
| $Pa_{O_2}$ (mmHg) | | | | | |
| T1 | 304.6 ± 16.6 | 305.0 ± 49.1 | −0.4 | −34.80 to 34.10 | 0.98 |
| 30 min | 276.5 ± 30.7 | 292.3 ± 50.6 | −15.8 | −55.10 to 23.50 | 0.41 |
| 60 min | 261.8 ± 34.5 | 272.8 ± 41.7 | −11.0 | −46.00 to 24.90 | 0.52 |
| 90 min | 262.1 ± 34 | 273.6 ± 46.1 | −11.5 | −49.50 to 26.50 | 0.53 |
| 120 min | 238 ± 25.7 | 250.9 ± 34.3 | −12.9 | −41.40 to 15.60 | 0.35 |
| 150 min | 244.6 ± 38.7 | 260 ± 39.3 | −15.4 | −52.10 to 21.30 | 0.39 |
| 180 min | 238.7 ± 28.5 | 247.5 ± 48.7 | −8.8 | −46.30 to 28.70 | 0.62 |
| 210 min | 210.9 ± 37.4 | 225.2 ± 38.2 | −14.3 | −49.80 to 21.20 | 0.41 |
| T2 | 288.4 ± 38.1 | 295.1 ± 40.7 | −6.7 | −43.70 to 30.30 | 0.71 |
| End-tidal carbon dioxide (mmHg) | | | | | |
| T1 | 37.5 ± 4.4 | 38.4 ± 4.3 | −0.9 | −4.98 to 3.18 | 0.64 |
| 30 min | 38.4 ± 4.3 | 64.4 ± 4.1 | −26.0 | −29.90 to −22.10 | <0.001 |
| 60 min | 40.6 ± 4.5 | 67.5 ± 4.1 | −26.9 | −30.90 to −22.80 | <0.001 |
| 90 min | 41.2 ± 5 | 66.1 ± 5.4 | −24.9 | −29.70 to −20.00 | <0.001 |
| 120 min | 39.2 ± 5.2 | 65.6 ± 5.3 | −26.4 | −31.30 to −21.40 | <0.001 |
| 150 min | 38.3 ± 4.3 | 67.0 ± 4.2 | −28.7 | −32.70 to −24.60 | <0.001 |
| 180 min | 38.0 ± 3.9 | 66.6 ± 5.5 | −27.6 | −31.90 to −23.20 | <0.001 |
| 210 min | 37.8 ± 3.3 | 64.5 ± 3.9 | −26.7 | −30.10 to −23.20 | <0.001 |
| T2 | 38.9 ± 4.1 | 42.2 ± 4.1 | −3.3 | −6.90 to 0.75 | 0.11 |
| pH | | | | | |
| T1 | 7.38 ± 0.03 | 7.38 ± 0.04 | 0.01 | −0.03 to 0.04 | 0.69 |
| 30 min | 7.38 ± 0.04 | 7.22 ± 0.07 | 0.16 | 0.11 to 0.22 | <0.001 |
| 60 min | 7.38 ± 0.02 | 7.17 ± 0.06 | 0.21 | 0.15 to 0.27 | <0.001 |
| 90 min | 7.36 ± 0.04 | 7.17 ± 0.09 | 0.18 | 0.12 to 0.25 | <0.001 |
| 120 min | 7.36 ± 0.03 | 7.18 ± 0.08 | 0.17 | 0.11 to 0.24 | <0.001 |
| 150 min | 7.39 ± 0.06 | 7.22 ± 0.08 | 0.17 | 0.10 to 0.24 | <0.001 |
| 180 min | 7.41 ± 0.06 | 7.24 ± 0.06 | 0.16 | 0.10 to 0.22 | <0.001 |
| 210 min | 7.42 ± 0.05 | 7.23 ± 0.04 | 0.17 | 0.12 to 0.22 | <0.001 |
| T2 | 7.4 ± 0.06 | 7.39 ± 0.05 | 0.01 | −0.04 to 0.06 | 0.72 |
| $Pa_{CO_2}$ (mmHg) | | | | | |
| T1 | 41.3 ± 3.3 | 40.8 ± 3.9 | 0.5 | −2.92 to 3.92 | 0.76 |
| 30 min | 42.0 ± 2.9 | 68.6 ± 3.7 | −26.6 | −29.73 to −23.46 | <0.001 |
| 60 min | 43.1 ± 2.9 | 69.9 ± 3.8 | −26.8 | −29.96 to −23.63 | <0.001 |
| 90 min | 43.7 ± 3.5 | 68.7 ± 4.2 | −25.0 | −25.83 to −21.46 | <0.001 |
| 120 min | 42.2 ± 4.8 | 68.2 ± 4.6 | −26.0 | −30.41 to −21.58 | <0.001 |

*(Continued)*

**Table 4.** Continued

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | Mean Difference | 95% CI* | *P* Value† |
|---|---|---|---|---|---|
| 150 min | 41.4 ± 3.4 | 69.3 ± 3.6 | −27.9 | −31.23 to −24.56 | <0.001 |
| 180 min | 41.5 ± 3.5 | 68.6 ± 4.1 | −27.1 | −30.67 to −23.52 | <0.001 |
| 210 min | 41.4 ± 2.9 | 67.8 ± 3.1 | −26.4 | −29.23 to −23.56 | <0.001 |
| T2 | 42.0 ± 3.0 | 44.6 ± 3.1 | −2.6 | −5.49 to 0.29 | 0.07 |
| Hemodynamic measures | | | | | |
| MAP (mmHg) | | | | | |
| T1 | 77.7 ± 0.6 | 76.4 ± 5.8 | 1.3 | −4.9 to 6.1 | 0.82 |
| 30 min | 81.2 ± 5.6 | 83.3 ± 4.3 | −2.2 | −7 to 2.8 | 0.38 |
| 60 min | 82.4 ± 5.7 | 86.1 ± 4.5 | −3.7 | −8.4 to 1.1 | 0.12 |
| 90 min | 85.3 ± 7.5 | 90.2 ± 6.2 | −4.9 | −11.3 to 1.5 | 0.11 |
| 120 min | 83.2 ± 7.6 | 86.7 ± 7.1 | −3.5 | −10.3 to 3.3 | 0.29 |
| 150 min | 78.2 ± 6.3 | 83.2 ± 8.1 | −5 | −11.7 to 1.7 | 0.13 |
| 180 min | 79.1 ± 5.4 | 82.7 ± 6.1 | −3.6 | −9.1 to 1.6 | 0.16 |
| 210 min | 78.4 ± 4.3 | 81.3 ± 5.9 | −2.9 | −7.5 to 2.1 | 0.25 |
| T2 | 79.2 ± 6.3 | 79.4 ± 5.1 | −1.2 | −6.7 to 3.9 | 0.58 |
| Heart rate (beats/min) | | | | | |
| T1 | 66.7 ± 4.9 | 67.2 ± 7.4 | −0.5 | −6.4 to 5.4 | 0.86 |
| 30 min | 68.3 ± 5.8 | 71.4 ± 6.7 | −3.1 | −9.1 to 2.2 | 0.22 |
| 60 min | 70.8 ± 6.8 | 74.8 ± 5.3 | −3.2 | −8.9 to 2.5 | 0.25 |
| 90 min | 75.7 ± 7.1 | 79.4 ± 6.8 | −3.7 | −10.1 to 2.8 | 0.24 |
| 120 min | 73.3 ± 7.5 | 80.3 ± 6.1 | −5.8 | −12.4 to 0.8 | 0.08 |
| 150 min | 73.8 ± 5.8 | 77.2 ± 7.1 | −3.4 | −9.4 to 2.6 | 0.25 |
| 180 min | 70.5 ± 5.4 | 73.6 ± 6.2 | −3.1 | −8.5 to 2.3 | 0.24 |
| 210 min | 69.8 ± 4.8 | 72.5 ± 6.6 | −2.5 | −8.1 to 2.7 | 0.31 |
| T2 | 70.8 ± 5.7 | 73.1 ± 4.9 | −2.3 | −7.3 to 2.7 | 0.35 |
| Expired volume (ml) | | | | | |
| T1 | 487.9 ± 39.3 | 483.5 ± 39.7 | 4.4 | −32.2 to 42.1 | 0.78 |
| 30 min | 360.8 ± 30.2 | 358.7 ± 28.5 | 2.1 | −26.3 to 28.9 | 0.92 |
| 60 min | 365.5 ± 24.3 | 370.1 ± 33.4 | −4.6 | −32.1 to 22.8 | 0.73 |
| 90 min | 367.6 ± 29.8 | 369.8 ± 25.1 | −1.4 | −27.2 to 24.4 | 0.91 |
| 120 min | 370.8 ± 26.8 | 373.5 ± 26.3 | −2.7 | −29.1 to 23.6 | 0.83 |
| 150 min | 364.7 ± 30.1 | 374.5 ± 27.9 | −9.8 | −36.5 to 17.9 | 0.48 |
| 180 min | 366.1 ± 30.9 | 370.9 ± 30.3 | −4.8 | −33.5 to 23.9 | 0.73 |
| 210 min | 369.3 ± 34.4 | 364.2 ± 35.1 | 5.1 | −27.3 to 37.9 | 0.74 |
| T2 | 478.3 ± 41.9 | 485.7 ± 42.6 | −7.4 | −47.4 to 32.0 | 0.68 |

Data are presented as mean ± SD.

* 95% CI of the difference between means of the two groups. † Bonferroni adjusted.

$FICO_2$ = fraction of inspired carbon dioxide; $FIO_2$ = fraction of inspired oxygen; MAP = mean arterial pressure; $PaCO_2$ = arterial partial pressure of carbon dioxide; $PaO_2$ = arterial partial pressure of oxygen; pH = potential of hydrogen; T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

Given that OLV is associated with ALI, our findings may provide a new basis for the design of therapeutic strategies to prevent ALI and manage patients undergoing a lobectomy.

Although ALI is rare, it is a serious complication. During OLV, many factors can induce severe inflammation and pulmonary edema, and they include oxidative damage, surgical procedures to repair a collapsed lung, the stretched and overdistended shear forces induced by repeated tidal collapse and reopening of alveolar, compression of alveolar vessels, and increased pulmonary vascular resistance in the ventilated lung. Previous studies have shown that permissive hypercapnia or therapeutic hypercapnia can reduce the incidence of lung injury.[5–8] Unlike passive respiratory acidosis of permissive hypercapnia, in the current study, we investigated the effect of therapeutic hypercapnia (60 to 70 mmHg) on OLV-related lung injury. We found that therapeutic hypercapnia reduced the levels of peak and plateau pressures in the lungs and increased lung compliance. During OLV, the surgical procedure, hypoxemia, decrease of lung volume, inflammation in lung tissue, and alveolar recruitment can increase airway resistance and decrease compliance.[17] The effect of therapeutic hypercapnia on airway pressure and compliance may be due to the stimulation of sympathetic nerves by carbon dioxide. Indeed, carbon dioxide can stimulate the sympathetic nerves, which mediate the relaxation of airway smooth muscles and then expand the airway, thereby decreasing the resistance of ventilation and increasing the dynamic compliance. Moreover, the improvement in compliance may also be associated with the antiinflammatory effects of hypercapnia.

We found that therapeutic hypercapnia slightly increased the $Pao_2/FIO_2$ during OLV although the difference was not statistically significant. The insignificance of the difference in the

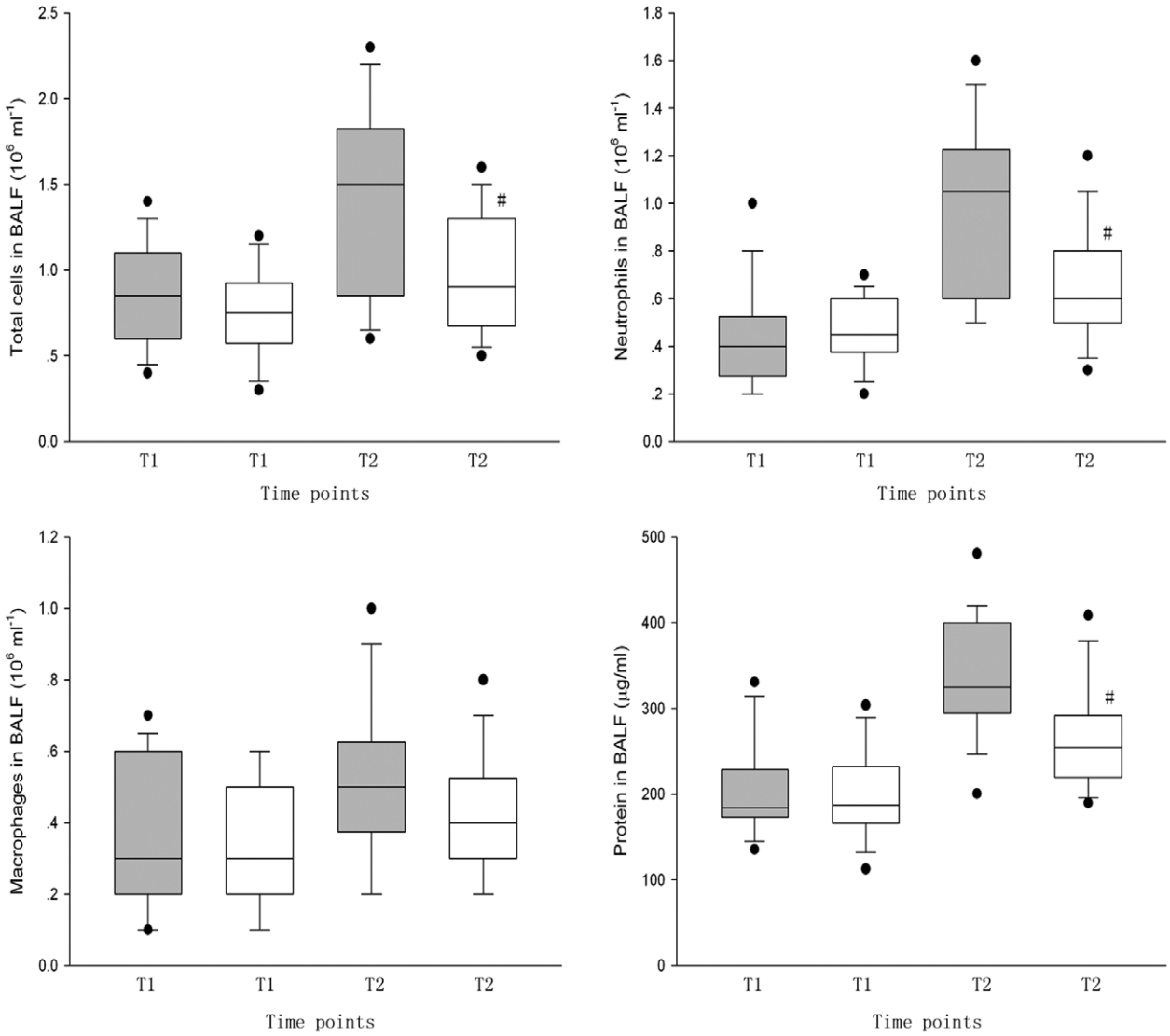


**Fig. 4.** Cell infiltration in bronchoalveolar lavage fluid (BALF). The numbers of total cells, macrophages, and neutrophils as well as the concentrations of total protein in the BALF from individual patients at T1 and T2 were measured. Data are expressed as box plots of the median, interquartile range, and range of each group (n = 25). The *black dots* indicate the outliers in each group. *Filled rectangle* and *open rectangle* represent the air and carbon dioxide groups, respectively. #$P < 0.05$ compared with air group. T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

$Pa_{O_2}/F_{I_{O_2}}$ between these two groups may have resulted because we performed volume-controlled ventilation in all patients, leading to similar minute ventilation volumes between patients in these two groups. The slightly increased values of the $Pa_{O_2}/F_{I_{O_2}}$ in the carbon dioxide group may be due to a Bohr effect because the increased concentrations of carbon dioxide and hydrogen may shift the hemoglobin–oxygen dissociation curve to the right (a Bohr effect). Furthermore, we detected lower numbers of total cells and neutrophils as well as lower concentrations of proteins and proinflammatory cytokines and mediators in the BALF from the carbon dioxide group. It is possible that therapeutic hypercapnia may protect the epithelial and endothelial cells, decrease the pulmonary capillary permeability, and then improve gas exchange among alveolar cells.

In a thoracic surgery, many factors can induce endothelial and epithelial cell injury by activating nuclear factor-κB[18] and then increase the expression of proinflammatory cytokines and chemokines, such as TNF-α, IL-1β, IL-6, and IL-8. These chemokines are important chemoattractants for the recruitment of neutrophils and alveolar macrophages and are positively upregulated during lung injury.[19] TNF-α is an important inflammatory mediator, and BALF TNF-α has been widely used as a marker of lung inflammation.[16,20] Several studies suggested that airway epithelial cells can express and secrete TNF-α and IL-1, *etc.*[21,22] After OLV, the TNF-α increased in BALF[16,20,23] and promoted the recruitment of neutrophils[19,24] and then aggravate the local inflammation. Neutrophils can produce inflammatory mediators, such as elastase, leukotrienes, and free

**Table 5.** The BALF Concentrations of Inflammatory Factors between the Two Groups

| | Air Group (n = 25) | Carbon Dioxide Group (n = 25) | *P* Value* |
|---|---|---|---|
| Inflammatory cytokines | | | |
| TNF-α (pg/ml) | | | |
| T1 | 32.9 (15.2–65.6) | 29.3 (19.8–63.6) | 0.639 |
| T2 | 71.2 (44.8–92.7) | 51.1 (42.8–76.6) | 0.034 |
| IL-1β (pg/ml) | | | |
| T1 | 8.5 (2.8–19.5) | 10.2 (3.4–17.4) | 0.972 |
| T2 | 26.8 (21.7–34.3) | 14.9 (9.8–20.7) | <0.001 |
| IL-6 (pg/ml) | | | |
| T1 | 18.5 (10.8–42.9) | 23.2 (10.4–34.8) | 0.838 |
| T2 | 43.1 (26.6–63.3) | 30.6 (14.6–46.1) | 0.001 |
| IL-8 (pg/ml) | | | |
| T1 | 200.2 (40.7–420.1) | 225.4 (49.6–430.5) | 0.619 |
| T2 | 510.4 (320.8–950.1) | 360.5 (120.8–640.6) | 0.040 |
| IL-10 (pg/ml) | | | |
| T1 | 10.9 (3.7–32.8) | 15.8 (4.8–34.5) | 0.764 |
| T2 | 29.6 (13.4–76.8) | 50.9 (18.6–98.2) | 0.033 |
| C3a (μg/ml) | | | |
| T1 | 70.9 (47.9–95.3) | 68.1 (45.0–96.8) | 0.877 |
| T2 | 88.9 (55.6–109.2) | 75.9 (55.8–105.2) | 0.308 |
| CRP (ng/ml) | | | |
| T1 | 970.5 (913.3–1,277.6) | 983.7 (930.3–1,140.9) | 0.393 |
| T2 | 1,145.5 (994.5–1,198.5) | 1,050.8 (850.8–1,353.7) | 0.528 |
| Total cells ($10^6 \cdot ml^{-1}$) | | | |
| T1 | 0.8 (0.4–1.4) | 0.7(0.3–1.2) | 0.233 |
| T2 | 1.5 (0.6–2.3) | 0.9 (0.5–1.5) | 0.029 |
| Neutrophils ($10^6$ $ml^{-1}$) | | | |
| T1 | 0.4 (0.2–1.0) | 0.5 (0.2–0.7) | 0.612 |
| T2 | 1.1 (0.5–1.6) | 0.6 (0.3–1.2) | 0.014 |
| Macrophages ($10^6$ $ml^{-1}$) | | | |
| T1 | 0.3 (0.1–0.7) | 0.3 (0.1–0.6) | 0.688 |
| T2 | 0.5 (0.2–1.0) | 0.4 (0.2–0.8) | 0.219 |
| Total protein (μg/ml) | | | |
| T1 | 184.1 (135.7–330.8) | 188.9 (112.7–303.6) | 0.777 |
| T2 | 324.4 (200.4–480.6) | 254.2 (189.7–408.6) | 0.001 |

Data are presented as median (range).

* Bonferroni adjusted.

BALF = bronchoalveolar lavage fluid; CRP = C-reactive protein; C3a = complement 3a; IL = interleukin; TNF = tumor necrosis factor; T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

radicals, which may damage the lung tissue.[25] This inflammatory process is positively regulated by complement activation.[26] We found that therapeutic hypercapnia effectively reduced the numbers of total BALF cells and neutrophils as well as the concentrations of total proteins and decreased the levels of BALF and serum proinflammatory mediators after surgery. Our data are consistent with those of a previous observation[20] and suggest that neutrophils may play a major role in the pathogenesis of OLV-related lung injury. Our data extend previous findings in animal models[7–9] and suggest that therapeutic hypercapnia can attenuate inflammation and injury in rodents and humans. Several studies have indicated that therapeutic hypercapnia can significantly limit TNF-α in various lung injuries.[27–30] The antiinflammatory effect of therapeutic hypercapnia may stem from its role in inhibiting nuclear factor-κB activation, which thus decreases proinflammatory cytokine expression.[31] Therapeutic hypercapnia can also reduce neutrophil adhesion to endothelial cells[31] and inhibit neutrophil infiltration and activity *via* acidosis. In addition, the antiinflammatory effect of hypercapnia may be also associated with its inhibition of complement activity. Moreover, we detected higher levels of IL-10 in patients who received therapeutic hypercapnia. Given that IL-10 is a potent inhibitor of inflammation,[32,33] the enhanced IL-10 responses in the lung may contribute to the therapeutic effect of therapeutic hypercapnia on OLV-related inflammation. More interestingly, we found that therapeutic hypercapnia reduced the concentrations of proinflammatory cytokines and increased the levels of antiinflammatory IL-10 in both the collapsed and ventilated lungs. Apparently, the effect of therapeutic hypercapnia on lung inflammation may be mainly associated with respiratory acidosis, but not carbon dioxide.[34] In addition, we found no statistically significant differences in the levels of serum cytokines tested at T2 between the two groups, consistent with the results of a previous report.[16] The

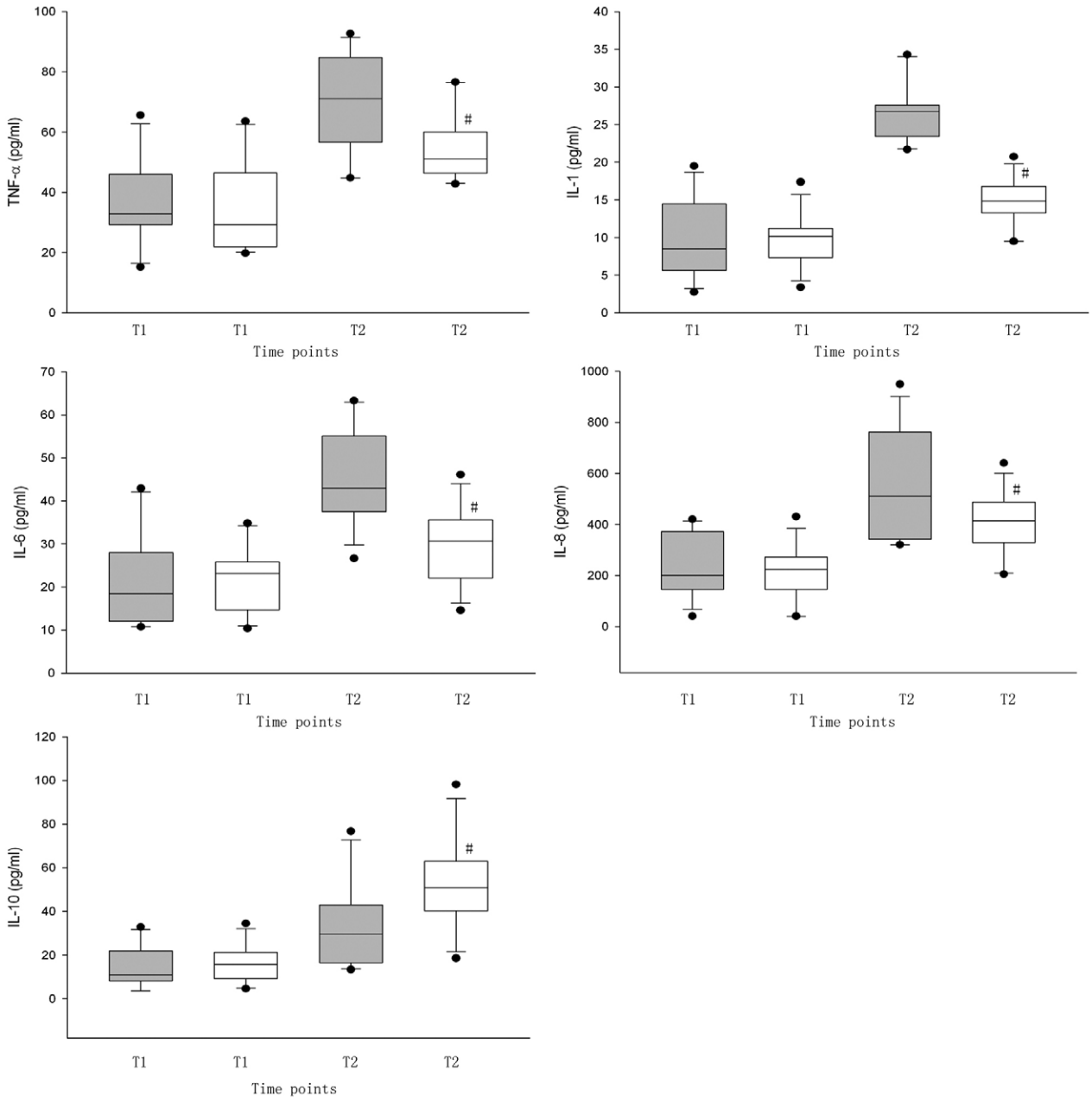


**Fig. 5.** Cytokine concentrations in the bronchoalveolar lavage fluid. The levels of bronchoalveolar lavage fluid tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and IL-10 in individual patients at T1 and T2 were determined. Data are expressed as the median, interquartile range, and range of each group (n = 25). The *black dots* indicate the outliers in each group. *Filled rectangle* and *open rectangle* represent the air and carbon dioxide groups, respectively. #*P* < 0.05 compared with air group. T1 = before one-lung ventilation; T2 = 30 min after reexpansion.

insignificant differences in the levels of serum cytokines support the notion that systemic inflammation in peri-OLV is seldom affected by a short period of ventilation.[35] However, we found that therapeutic hypercapnia improved systemic inflammation after surgery, which may stem from reduced lung inflammation and respiratory acidosis.

Although hypercapnia can reduce various types of injury,[7–9,36] recent studies suggest that the therapeutic effect of hypercapnia may depend mainly on acidosis rather than carbon dioxide.[34,36] In this study, patients received therapeutic hypercapnia by inhaling carbon dioxide only during OLV, which would induce a short period of acidosis that might not be compensated by the kidney. In addition, all patients received intravenous anesthesia with propofol, which has been demonstrated to inhibit inflammation and reduce lung injury induced by ischemia–reperfusion, oleic acid, and endotoxin.[37–39] Although the propofol may provide additional protection against lung inflammation after

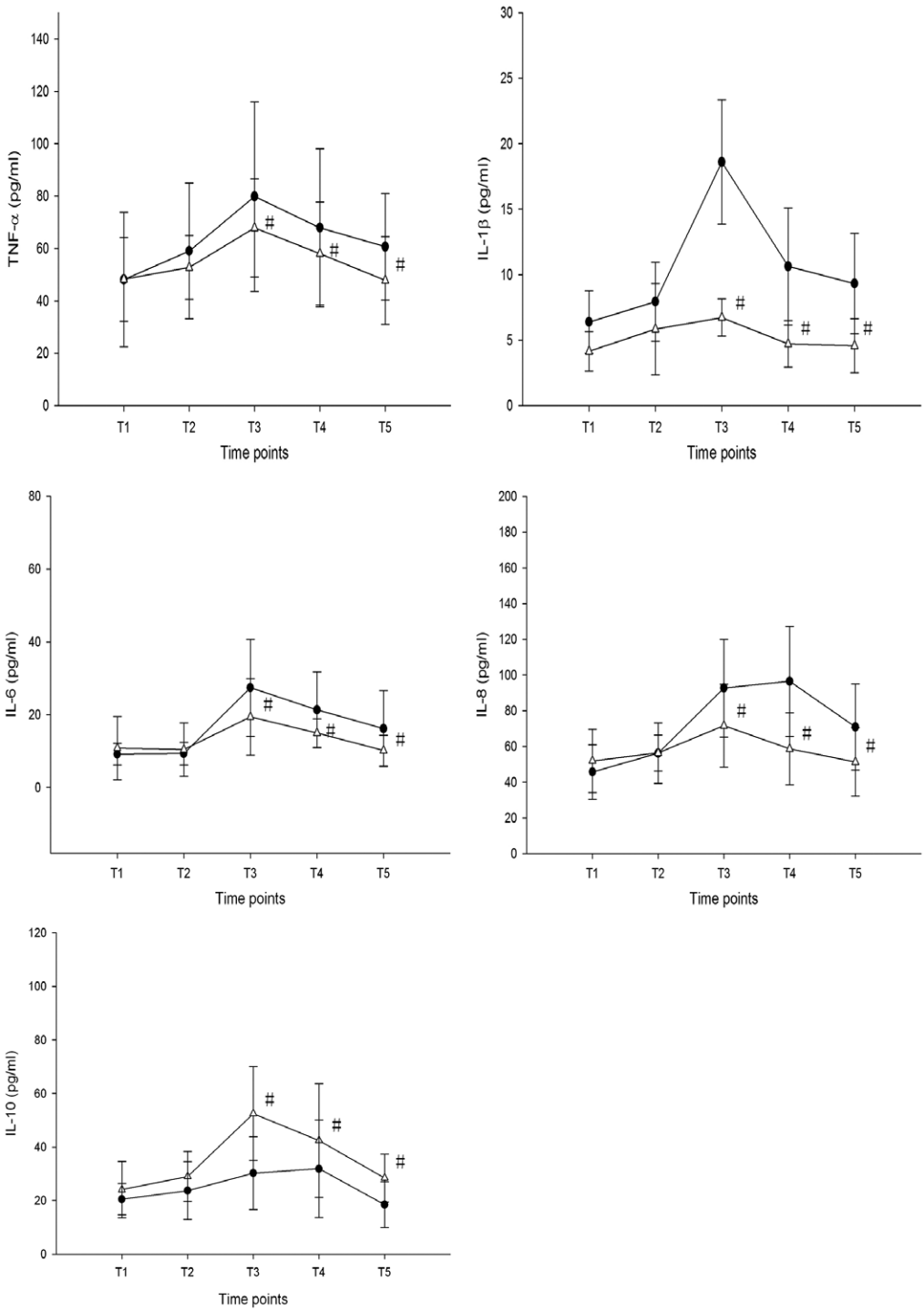


**Fig. 6.** Concentrations of serum cytokines. The concentrations of serum tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, and IL-10 in individual patients were measured. Data are expressed as the mean ± SD for each group of patients (n = 25). *Filled circle* and *triangle* represent the air and carbon dioxide groups, respectively. #$P < 0.05$ compared with air group. T1 = before one-lung ventilation; T2 = 30 min after reexpansion; T3 = 24 h postoperation; T4 = 48 h postoperation; T5 = 72 h postoperation.

OLV in this study, we cannot draw this conclusion due to the lack of proper controls for comparison.

Interestingly, we did observe 10 patients with increased blood pressure and heart rate during OLV, and the increase in blood pressure was transient and self-limited after OLV. More importantly, we did not observe other adverse effects in these patients. Our findings support the notion that therapeutic hypercapnia is a safe procedure for the management of patients undergoing a lobectomy,[40] and lower blood pH less than 7.2 can be tolerated by patients.[41]

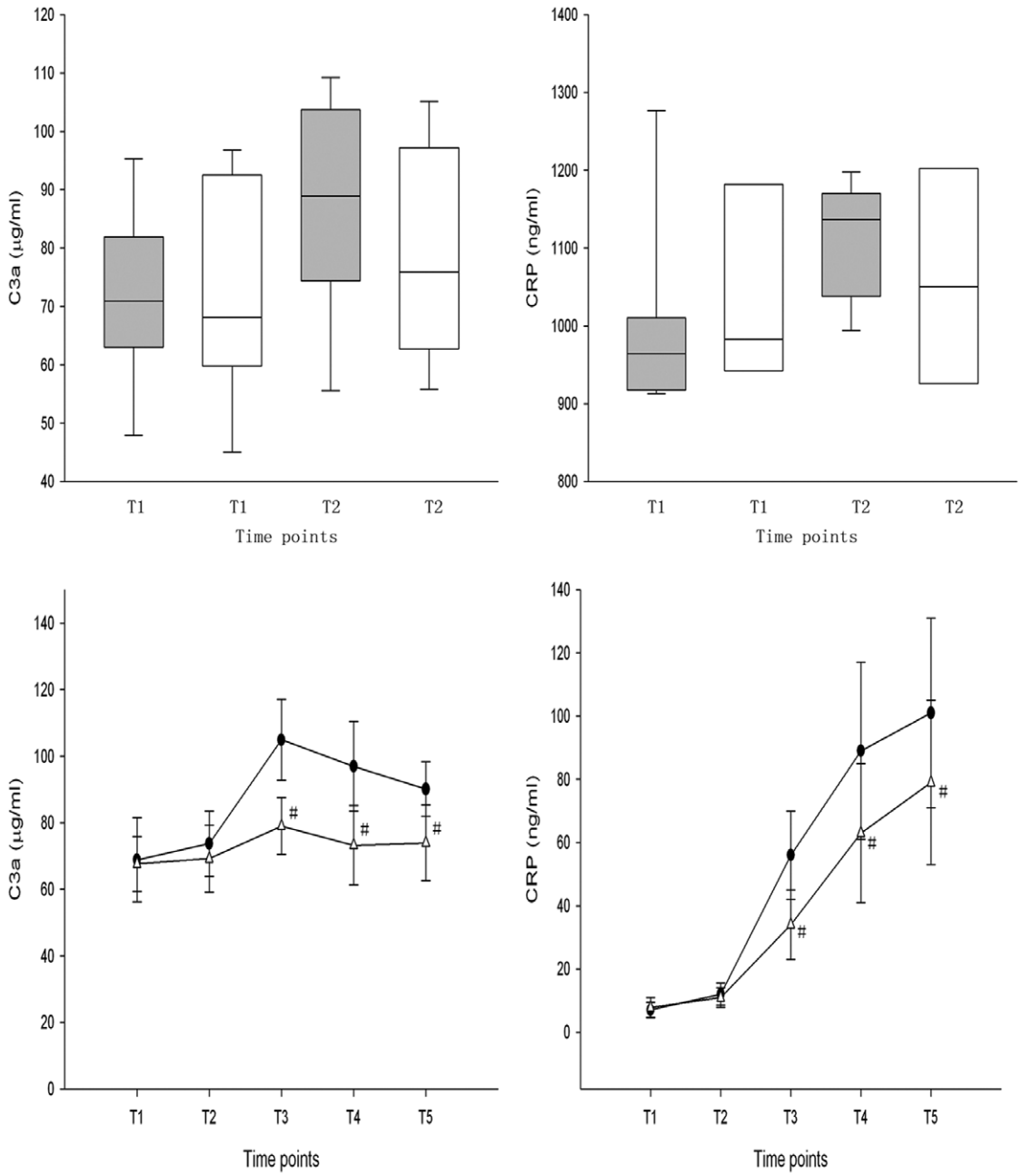


**Fig. 7.** Concentrations of bronchoalveolar lavage fluid (BALF) and serum complement 3a (C3a) and C-reactive protein (CRP). The concentrations of BALF and serum C3a and CRP in individual patients were measured. Data are expressed as the median, interquartile range, and range or mean ± SD of each group (n = 25). There were no statistically significant differences in the levels of BALF and serum C3a and CRP between the two groups of patients at T1 and T2. The levels of C3a and CRP in the carbon dioxide group from T3–T5 were lower than those in the air group. *Filled rectangle* and *filled circle* represent the air group; *open rectangle* and *triangle* represent the carbon dioxide group. #$P < 0.05$ compared with air group. T1 = before one-lung ventilation; T2 = 30 min after reexpansion; T3 = 24 h postoperation; T4 = 48 h postoperation; T5 = 72 h postoperation.

In summary, under intravenous anesthesia, the induction of therapeutic hypercapnia by continual inhalation of carbon dioxide during OLV improves respiratory function and mitigates the OLV-related lung and systemic inflammation in patients undergoing a lobectomy. More importantly, no severe adverse events occurred related to therapeutic hypercapnia in these patients. It is well known that severe inflammation can cause lung injury. Although we do not know the exact benefits and the clinical relevance of reduced inflammation induced by therapeutic hypercapnia, the statistically significant reduction in the levels of local and systemic inflammation by therapeutic hypercapnia may benefit patients by speeding recovery and reducing potential complications in the clinic.

**Table 6.** The BALF Concentrations of Inflammatory Cytokines and Cells between Ventilated and Nonventilated Lungs in the Two Groups after OLV

| | Air Group (n = 25) | | | Carbon Dioxide Group (n = 25) | | |
|---|---|---|---|---|---|---|
| | Nonventilated Lung | Ventilated Lung | *P* Value* | Nonventilated Lung | Ventilated Lung | *P* Value* |
| Inflammatory cytokines | | | | | | |
| TNF-α (pg/ml) | | | | | | |
| T1 | 16.6 (7.4–32.1) | 19.2 (8.1–33.5) | 0.619 | 13.5 (8.2–36.4) | 14.3 (6.2–30.1) | 0.815 |
| T2 | 39.4 (22.2–42.4) | 37.4 (14.1–50.2) | 0.807 | 28.5 (18.4–41.4) | 25.4 (14.2–40.1) | 0.581 |
| IL-1β (pg/ml) | | | | | | |
| T1 | 4.7 (0.9–8.5) | 4.8 (1.8–11.2) | 0.585 | 5.2 (2.1–10.1) | 4.6 (1.3–7.3) | 0.344 |
| T2 | 13.8 (8.6–22.1) | 12.2 (8.1–20.1) | 0.957 | 7.6 (5.3–12.2) | 7.5 (4.1–9.4) | 0.304 |
| IL-6 (pg/ml) | | | | | | |
| T1 | 8.3 (4.4–19.5) | 8.2 (4.5–23.7) | 0.911 | 11.8 (6.3–17.4) | 10.4 (4.1–18.6) | 0.672 |
| T2 | 21.1 (12.6–35.7) | 22.6 (34.1) | 0.791 | 15.8 (8.3–20.1) | 14.8 (6.3–20.1) | 0.377 |
| IL-8 (pg/ml) | | | | | | |
| T1 | 110.7 (24.3–200.4) | 91.2 (16.4–221.6) | 0.967 | 99.6 (14.6–218.7) | 107.1(26.1–2,118) | 0.862 |
| T2 | 295.6.4 (156.3–558.8) | 204.8 (136.5–414.3) | 0.281 | 185.6 (58.5–369.8) | 163.3(62.3–326.4) | 0.467 |
| IL-10 (pg/ml) | | | | | | |
| T1 | 7.6 (1.7–15.3) | 5.4 (1.1–17.5) | 0.925 | 6.6 (1.9–16.7) | 7.73 (1.9–17.9) | 0.813 |
| T2 | 12.7 (5.5–48.6) | 15.7(3.8–28.2) | 0.492 | 23.6 (12.5–46.7) | 27.7 (6.1–52.6) | 0.782 |
| C3a (μg/ml) | | | | | | |
| T1 | 30.5 (24.3–44.2) | 38.2 (23.6–57.1) | 0.181 | 38.5 (23.4–49.4) | 35.0 (21.6–49.4) | 0.804 |
| T2 | 42.5 (30.1–58.5) | 40.4 (25.4–59.8) | 0.784 | 35.2 (28.5–57.2) | 39.5 (27.3–52.4) | 0.883 |
| CRP (ng/ml) | | | | | | |
| T1 | 514.6 (397.3–742.6) | 506.8 (358.1–580.7) | 0.416 | 489.7 (426.3–698.9) | 491.5 (379.3–775.1) | 0.993 |
| T2 | 588.3 (489.4–688.9) | 549.6 (410.8–672.3) | 0.279 | 475.8 (447.8–681.7) | 520.3 (403.2–765.8) | 0.387 |
| Total cells ($10^6 \cdot ml^{-1}$) | | | | | | |
| T1 | 0.8 (0.3–1.2) | 0.7 (0.3–1.7) | 0.588 | 0.8 (0.2–1.2) | 0.6 (0.2–1.6) | 0.536 |
| T2 | 1.3 (0.5–1.8) | 1.4 (0.4–2.9) | 0.402 | 0.9 (0.4–1.5) | 0.9 (0.4–1.9) | 0.628 |
| Neutrophils ($10^6$ $ml^{-1}$) | | | | | | |
| T1 | 0.4 (0.1–1.2) | 0.4 (0.1–0.8) | 0.551 | 0.3 (0.1–0.8) | 0.4 (0.1–0.9) | 0.381 |
| T2 | 0.8 (0.4–1.9) | 0.9 (0.2–1.5) | 0.801 | 0.6 (0.2–1.1) | 0.5 (0.3–1.3) | 0.994 |
| Macrophages ($10^6$ $ml^{-1}$) | | | | | | |
| T1 | 0.3 (0.1–0.8) | 0.4 (0.1–0.7) | 0.868 | 0.3 (0.1–0.7) | 0.3 (0.1–0.8) | 0.917 |
| T2 | 0.5 (0.1–1.0) | 0.5 (0.1–0.8) | 0.863 | 0.4 (0.2–0.8) | 0.4 (0.2–0.9) | 0.914 |
| Total protein (μg/ml) | | | | | | |
| T1 | 97.9 (65.7–186.6) | 94.2 (70.1–182.3) | 0.916 | 94.9 (48.7–179.5) | 89.2 (56.9–158.1) | 0.866 |
| T2 | 176.6 (99.4–278.5) | 160.3 (100.9–214.2) | 0.645 | 126.4 (94.5–215.6) | 122.9 (90.2–210.1) | 0.972 |

Data were presented as median (range).

* Bonferroni adjusted.

BALF = bronchoalveolar lavage fluid; CRP = C-reactive protein; C3a = complement 3a; IL = interleukin; OLV = one-lung ventilation; TNF = tumor necrosis factor; T1 = before OLV; T2 = 30 min after reexpansion.

This study had some limitations. First, due to patients' unwillingness to permit continual testing, we did not continue to study the long-term effects of therapeutic hypercapnia on lung inflammation after surgery. Moreover, we excluded patients with severe obstructive lung disease due to potentially chronic hypercapnia. In fact, these patients may benefit from moderate hypercapnia during OLV. We are interested in further investigating the long-term effect of therapeutic hypercapnia on lung inflammation and examining whether therapeutic hypercapnia has any favorable effect on patients with impaired lung function and more complex conditions during OLV. Second, in a prospective, randomized study, De Conno *et al.*[42] observed that anesthesia with intravenously administered propofol was associated with higher levels of inflammatory mediators and worse clinical outcomes in patients with OLV during thoracic surgery, compared with the volatile anesthetic sevoflurane. These findings suggest that the protective effects of carbon dioxide observed with propofol in the current study may not be seen when a volatile anesthetic is used. Thus, further investigation using a volatile anesthetic is required.

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## Competing Interests

The authors declare no competing interests.

## Correspondence

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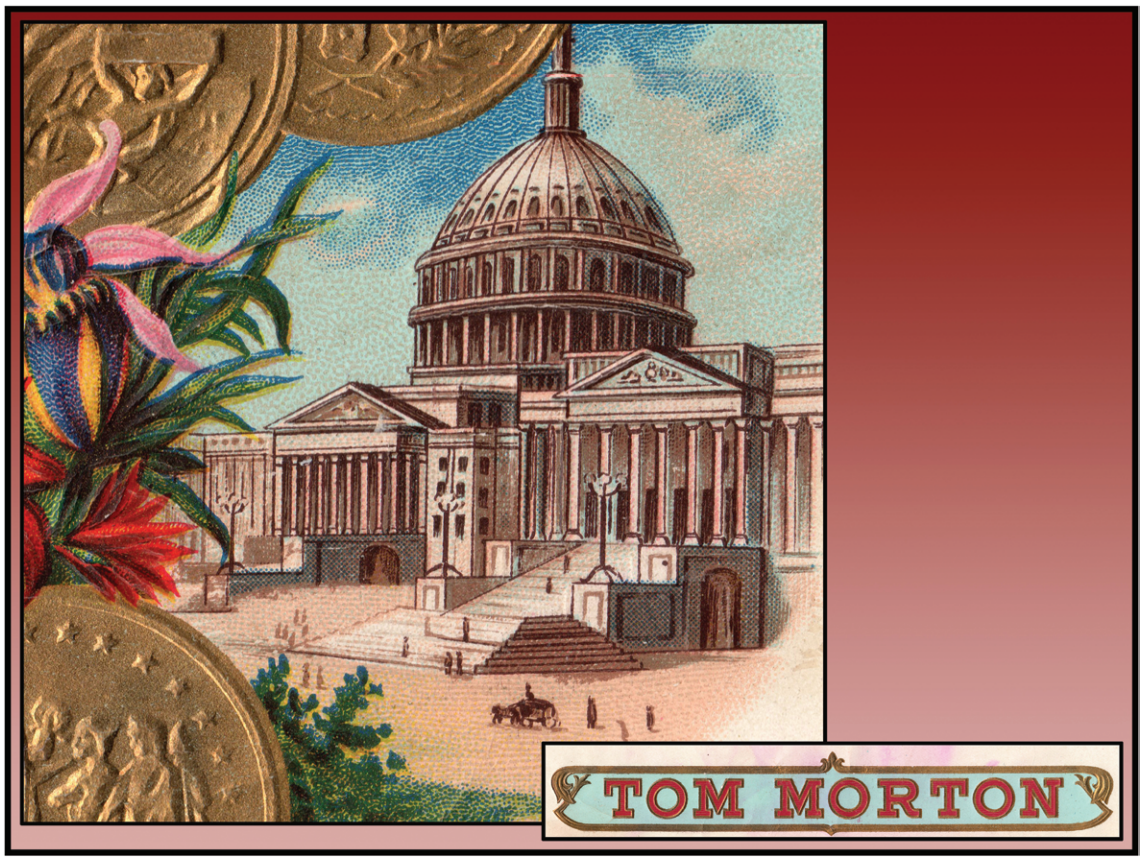
# Capitol Hill Bill: "Tom Morton" Cigar Box Label, Part II




The right side of the "Tom Morton" cigar box label featured the U.S. Capitol Building (*above*). Never nicknamed "Tom," perhaps ether pioneer William Thomas Green Morton (WTGM) should have been dubbed "Capitol Hill Bill" for all of the efforts by his advocates and himself to persuade the U.S. Congress to pass a "Capitol Hill bill." Such a bill would have aimed to reward WTGM monetarily for popularizing ether as a general anesthetic. Lithographs of the faces of both WTGM and the Capitol Building were conveniently available to the Wisconsin printers (the Henschel Family) of this label. However, since WTGM's friends referred to the etherist as "Willie" but never as "Tom," linking a cigar called "Tom Morton" to WTGM seems a clumsy advertisement for reaching the smoking public. (Copyright © the American Society of Anesthesiologists, Inc.)

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