CO₂ artificial pneumothorax on coagulation and fibrinolysis during thoracoscopic esophagectomy

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Abstract
Background: CO₂ artificial pneumothorax creates a sufficient operative field for thoracoscopic esophagectomy. However, it has potential complications and continuous CO₂ insufflation may impede coagulation and fibrinolysis. We sought to compare the effects of CO₂ artificial pneumothorax on perioperative coagulation and fibrinolysis during thoracoscopic esophagectomy.

Methods: We investigated patients who underwent thoracoscopic esophagectomy with (group P, n = 24) or without CO₂ artificial pneumothorax (group N, n = 24). The following parameters of coagulation-fibrinolysis function: intraoperative bleeding volume; serum levels of tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1), thromboelastogram (TEG), D-Dimer; and arterial blood gas levels were compared with two groups.

Results: Group P showed higher levels of PaCO₂, reaction time (R) value and kinetics (K) value, but significantly lower pH value, alpha (α) angle and Maximum Amplitude (MA) value at 60 minutes after the initiation of CO₂ artificial pneumothorax than group N (P < .05, all). The t-PA level after CO₂ insufflation for 60 minutes was significantly higher in group P than in group N (P < .05), but preoperative levels were gradually restored on cessation of CO₂ insufflation for 30 min (P > .05). There was no significant difference in D-dimer.

Conclusion: CO₂ artificial pneumothorax during thoracoscopic esophagectomy had a substantial impact on coagulation and fibrinolysis, inducing significant derangements in pH and PaCO₂.

Trial registration: The study was registered at the Chinese clinical trial registry (ChiCTR1800019004)

Abbreviations: ABP = arterial blood pressure, ASA = American society of anesthesiology, α angle = alpha angle, MA = maximum amplitude, t-PA = tissue plasminogen activator, BP = non-invasive cuff blood pressure, ECG = electrocardiogram, HR = heart rate, I/E = inspiration-expiration ratio, K = kinetics, PAI-1 = plasminogen activator inhibitor, R = reaction time, SD = standard deviation, SpO₂ = pulse oxygen saturation, TEG = thromboelastogram, TNM = tumor node metastasis

Keywords: thoracoscopic esophagectomy, artificial capnothorax, coagulation and fibrinolysis, acidosis

1. Introduction
Thoracoscopic esophagectomy is the mainstay in the treatment of esophageal cancer.[1] However, this procedure requires complete lung collapse and a broad surgical field. In the past, the main ventilation mode for collapsed lung was intubation of double-lumen bronchial catheter and one-lung ventilation, but this method had many drawbacks. The establishment of CO₂ artificial pneumothorax has been shown to provide better surgical field.[2] The current method of choice for lung ventilation during thoracoscopic esophagectomy is single-lumen endotracheal tube intubation with the establishment of a CO₂ artificial pneumothorax and bilateral lung ventilation. In 2006, Palanivelu et al introduced CO₂ artificial pneumothorax, which is an approach of anesthesia intubation in thoracoscopic esophagectomy with the two-lung ventilation approach.[3] Since then, there has been growing interest in CO₂ artificial pneumothorax. In 2011, Ninomiya et al[4] reported the use of intrathoracic CO₂ insufflation for thoracoscopic esophagectomy in the left lateral position. Studies have shown that artificial pneumothorax is beneficial for maintaining stable hemodynamics and oxygenation.[5,6] However, the technique is not widely applied because it can lead to complications such as arterial hypercapnia, CO₂ embolism, and hypotension, resulting from impaired venous return,[7] as well as derangements in the coagulation and fibrinolysis system due to continuous CO₂ insufflation. Data on the latter are scarce. On the basis of experimental data, some researchers have concluded that as long as the intrathoracic pressure is controlled to no more than 10 mmHg, artificial pneumothorax will not have any significant impact on the body.

[8,9] According to our clinical observation and review of relevant literature, we found that as long as the flow rate and pressure of
artificial pneumothorax are well controlled, artificial pneumothorax will not significantly affect the patient’s respiratory and circulatory systems, nor cause serious complications, which indicates that it can be safely applied in clinical practice.\(^5,^{10}\)

Therefore, in this study, we compared the perioperative levels of various parameters associated with coagulation and fibrinolysis in esophageal cancer patients undergoing thoracoscopic esophagectomy with and without CO\(_2\) artificial pneumothorax. With these data, we sought to evaluate the risk of bleeding or thrombosis during the perioperative period and accordingly develop a theoretical basis for whether interventional measures are necessary.

2. Material and methods

2.1. Study design

We enrolled 48 patients who underwent thoracoscopic esophagectomy for esophageal cancer, at our center between November 2017 and March 2018. This study was approved by the ethics committee of Daping Hospital [ethics batch: (2017) No. 67], and all the subjects signed informed consent.

2.2. Patients

Of these 48 patients, 35 were men and 13 were women, with their ages ranging from 53 to 67 years [mean±standard deviation, (SD) = 60.06±7.13 years]. The criteria for inclusion in this study were as follows: preoperative gastroscopy confirmed a pathological diagnosis of esophageal squamous cell carcinoma; TNM stage was below T3a; no significant abnormality detected in cardiopulmonary function, liver and kidney function, or coagulation function; no history of the use of drugs affecting coagulation function within two weeks before the operation; no acute or chronic infection, no metabolic or endocrine diseases; American Society of Anesthesiologists (ASA) grade II-III.

By using the random number table method, the 48 enrolled patients were classified into two equal groups with (group P) or without (group N) the establishment of CO\(_2\) artificial pneumothorax. All patients underwent surgery under general anesthesia.

2.3. Surgical procedures

2.3.1. Anesthesia

Once the patients were placed in the appropriate position on the operating table, their vital monitors were continuously monitored: electrocardiogram (ECG), heart rate (HR), non-invasive cuff blood pressure (BP), pulse oxygen saturation (Sp\(_{O_2}\)), body temperature (T). After administration of local anesthesia, catheters were inserted into the right internal jugular vein and left radial artery. Thereafter, invasive arterial blood pressure (ABP) was continuously monitored. For all patients, general anesthesia was induced and intubation was performed. For patients in group P, a single-lumen endotracheal tube (diameter: 7 mm, females; 7.5 mm, males) was inserted under the guidance of a video laryngoscope. For patients in group N, the left double-lumen endobronchial tube (size: 35F, female; 37F, male) was inserted into the left side under the guidance of a fiberoptic bronchoscope. After successful intubation, the connections of the anesthesia machine were established, and the respiratory parameters were adjusted as appropriate. In group P, bilateral lung ventilation was initiated, with tidal volume of 8 mL/kg, respiratory rate, 12 times/min, and inspiration-expiration ratio (I/E) of 1/2. In group N, one-lung ventilation was established, with tidal volume of 6mLkg, respiratory rate of 15 times/min, I/E of 1/2. These values were maintained both before and after the operation. The volume of fluid infusion and the depth of anesthesia were adjusted according to the hemodynamic status during the operation, and care was taken to ensure that the blood pressure fluctuation was not more than 20% before the operation.

2.4. CO\(_2\) insufflation

The patient was positioned and covered with towels; the operative area was sterilized. After inserting trocars the patient was connected with a CO\(_2\) pneumoperitoneum machine to inflate the peritoneum at a speed of 12 L/min, while maintaining the intrathoracic pressure at 6 to 8 mmHg; this resulted in lung collapse on the affected side. Thoracoscopic and laparoscopic esophagectomy was performed after the establishment of the CO\(_2\) artificial pneumothorax.

2.5. Monitoring indicators

Blood samples were collected at different time points: 60 minutes before induction of anesthesia (T1), 60 minutes after the initiation of CO\(_2\) artificial pneumothorax establishment or 60 minutes after one-lung ventilation (T2), 30 minutes after the termination of CO\(_2\) artificial pneumothorax or 30 minutes after bilateral pulmonary ventilation (T3), and the first and the third postoperative days (T4,T5). The major parameters measured during the perioperative period were as follows: arterial blood gas analysis; thromboelastogram (TEG) parameters, including reaction time (R value), which represents the time from the beginning of measurement until clot formation, and is related to the change of coagulation factor function, clot formation rate (K value and \(\alpha\) Angle), which represents the speed and clot formation and are closely related to fibrinogen level, and maximum amplitude (MA), which represents the clot strength and is related to the function of platelet aggregation; serum levels of tissue plasminogen activator (t-PA), which catalyzes the conversion of plasminogen to plasmin to degrade fibrin(ogen) and some coagulation factors and is the key substance of the fibrinolytic system; plasminogen activator inhibitor (PAI-1), which is also known as endothelial plasminogen activator inhibitor and is the key protein regulating fibrinolytic activity; D-dimer; and intraoperative bleeding volume (using the weighing method). The rate of postoperative complications, including anastomotic fistula, pulmonary infection, arrhythmia, incision infection, and chylothorax, were also recorded.

2.6. Statistical analysis

The sample size was determined as follows: The primary outcome was R value of the coagulation factor in the TEG. According to our preliminary experiment, the R value was 7.1 minutes in the experimental group and 6.2 minutes in the control group, with SD of 1.1. We set \(\alpha = 0.05\) and \(\beta = 0.8\). The sample size was 42, with 21 in each group. Considering a 10% drop-off rate, we finally enrolled 24 patients in each group.

The SPSS 19 software was used for data analysis. Countable data were analyzed using the \(\chi^2\) test, and all measurements were expressed as \(x \pm s\). Intra-group comparisons were made by repeated-measurement analysis of variance. The Bonferroni method was used for comparisons at each time point, and
inter-group comparisons were made using multivariate analysis of variance. \( P < .05 \) was considered to indicate statistical significance.

3. Results

3.1. Demographics and clinicopathologic factors

The study population comprised of 48 patients equally divided into two groups. The duration of operation in group P was significantly less than that in group N (\( P < .05 \)). There were no significant intergroup differences in the age, sex, weight, intraoperative bleeding volume, and pathological stage (\( P > .05 \)). (Table 1).

3.2. Perioperative morbidity and mortality

Postoperative complications were observed in 2 cases (8.33%) in group N and in 3 cases (12.5%) in group P two weeks after thoracoscopic esophagectomy. There was no death in either group. No significant intergroup difference was observed in terms of complications and mortality (\( P > .05 \)). Intervention did not increase morbidity or mortality (Table 2).

3.3. Blood gas analysis

In group P, the pH value decreased significantly 60 minutes after the initiation of CO2 artificial pneumothorax (\( P < .05 \)) while the PaCO2 increased significantly (\( P < .05 \)). These findings suggest that the blood H+ level increased significantly after the beginning of CO2 artificial pneumothorax. However, 30 minutes after the termination of CO2 artificial pneumothorax, the pH value and PaCO2 were restored quickly to the preoperative level (\( P > .05 \)) (Fig. 1).

3.4. TEG comparison

Group P showed significantly longer R value 60 minutes after the start of CO2 artificial pneumothorax (\( P < .05 \)), thereby suggesting that time of initiation of coagulation was prolonged. The K value was significantly prolonged and the alpha angle was significantly decreased (\( P < .05 \)). This suggested that the rate of blood clot formation was decreased. Further, the MA value was significantly decreased (\( P < .05 \)), suggesting that the strength of blood clotting was decreased. The changes in the R, K, \( \alpha \) angle, and MA values were the same even 30 minutes after the termination of artificial pneumothorax; the levels were still different from that the pre-anesthesia values (\( P < .05 \)), and were restored to preoperative levels only on postoperative days 1 and 3. In addition, there were significant difference in R value, K value, \( \alpha \) angle and MA between group P and group N at T2 and T3. There were no significant differences in the TEG levels at different time points in group N (Fig. 2).

3.5. Changes in t-PA and PAI-1

The t-PA in group P at 60 minutes after the initiation of CO2 pneumothorax was higher than in group N (\( P < .05 \)) and gradually returned to the preoperative level at 30 minutes after the cessation of CO2 pneumothorax. No significant intergroup difference was noted in terms of the PAI-1 (Fig. 3).

3.6. D-Dimer

The levels of D-dimer in both group P and group N were increased on the 1st and 3rd postoperative days (\( P < .05 \)), but there were no significant differences between the values in the 2 groups (Fig. 4).

4. Discussion

Our results indicated that during the establishment of CO2 artificial pneumothorax, obvious changes occurred in the arterial blood gas levels, the pH value decreased, and PaCO2 increased. Together, these changes manifested as respiratory acidosis and hypercapnia. The proportion of patients with moderate or high degree of hypercapnia (PaCO2 > 50mmHg) accounted for 70% of the total study population. Studies such as those by Brock et al.[11] investigating the effects of different CO2 artificial pneumothorax pressures on hemodynamics have revealed that although CO2 artificial pneumothorax has some effects on circulation, it does not induce any significant changes in the PaCO2. Similarly, Sancheti et al.[12] showed that no significant change occurred in the PaCO2 in patients who underwent thoracoscopic pulmonary wedge resection with single-lumen

### Table 1

| Project                      | Group P (n=24) | Group N (n=24) | \( P \) |
|------------------------------|---------------|---------------|-------|
| Age (yr)                     | 62±7.31       | 58.13±6.54    | .059  |
| Gender (m/f)                 | 17.7          | 18.6          | .745  |
| Weight (kg)                  | 62.04±9.51    | 61.60±4.73    | .633  |
| Pathological staging (T1:T2:T3) | 5:14:5     | 6:15:3        | .731  |
| Operative blood loss (mL)    | 127.09±48.85  | 125.42±32.30  | .890  |
| Operation time (min)         | 239.33±35.69  | 271.88±31.31  | .002  |

### Table 2

| Groups                      | Anastomotic fistula | Pulmonary infection | Arrhythmia | Incision infection | Chylothorax | Overall complication rate | Death |
|-----------------------------|---------------------|---------------------|------------|-------------------|-------------|--------------------------|-------|
| Group N (n=24)              | 1 (4.16%)           | 1 (4.16%)           | 0          | 0                 | 2 (8.33%)   | 0                        | 0     |
| Group P (n=24)              | 1 (4.16%)           | 1 (4.16%)           | 1 (4.16%)  | 0                 | 3 (12.5%)   | 0                        | 0     |
| P value                     | 1.000               | 1.000               | 0.312      | 1.000             | 0.637       | 1.000                    |       |
Endotracheal intubation or double-lumen bronchial intubation with establishment of CO\textsubscript{2} artificial pneumothorax. On the other hand, the results reported by Tran et al\textsuperscript{[13]} are similar to those reported in the current study. The possible discrepancy between the results of the abovementioned studies may be attributed to the following factors: The dispersion rate of CO\textsubscript{2} in human body is 25 times that of O\textsubscript{2}, whereas the absorption rate is faster. For the resection of esophageal cancer, a large surgical wound is required and the pressure of CO\textsubscript{2} in the thoracic cavity becomes positive during CO\textsubscript{2} artificial pneumothorax, which in turn increases the rate of CO\textsubscript{2} absorption in the blood. Only a few respiratory parameters were assessed in this experiment, those assessed were within the acceptable permissible hypercapnia range and indicated a protective pulmonary ventilation strategy.

Acidosis is known to be an important cause of coagulation dysfunction, but the specific underlying mechanism is still unclear\textsuperscript{[14–16]} Coagulation is initiated by the activation of coagulation factors, which can transform prothrombin into thrombin and fibrinogen into fibrin, in the presence of thrombin; this is accompanied by platelet activation and the formation of
blood clots through adhesion and aggregation with fibrin. Thus, the formation rate and stability of blood clots, which are the final products of the coagulation process, are important factors influencing coagulation. The levels of TEG can provide a fair assessment of the entire process of coagulation–fibrinolysis and affords a rapid and comprehensive evaluation of coagulation factors, platelet energy, fibrinogen, and fibrinolysis. Further, the R value reflects the time required for the initial blood clot formation in the presence of coagulation factors, while the K value and α angle reflect the process of coagulation under the combined action of fibrinogen and platelets. The rate and value of MA reflect the maximum strength of blood clots, which is mainly influenced by the number and function of platelets (20%) and fibrin (80%). In the present study, the R value in group P was significantly increased at 60 minutes after the imitation of CO₂ artificial pneumothorax (P < 0.05), and the time of initiation of coagulation was also prolonged. These findings suggest that the coagulation function was decreased. On the other hand, the significant increase in the K value, significant decrease in the angle of alpha (P < 0.05), and decrease in the rate of blood clot formation indicate that the function of fibrinogen was decreased and the synthesis of blood clot was inhibited in group P. This may be because thrombin, which promotes the formation of blood clots, is affected by the acidic environment in the body. Meng et al.[20] showed that at a pH value of 7.0, the rate of prothrombin activation is decreased by 55% to 70%. Martini et al.[18] measured the changes in the plasma thrombin–antithrombin III complex content at different time points and showed a significant decrease in the rate of thrombin generation during acidosis. This suggests that acidosis causes a decrease in the rate of thrombin generation, thereby leading to a decrease in coagulation function. In addition, the significant decrease in the MA value in group P at 60 minutes after the initiation of CO₂ artificial pneumothorax (P < 0.05) and the consequent decrease in the strength and stability of blood clot together suggest a decrease in the functions of fibrinogen and platelet aggregation. This may be explained by the fact that abnormal platelet function in an acidic environment leads to a decrease in the cross-linking strength between platelet and fibrins, which in turn weakens the strength of the blood clot. Studies[19] have shown that in the presence of acidosis, the internal structure and shape of platelets undergo certain changes such as loss of pseudopodia, change of shape to globular, which results in a decrease in their hemostatic function. In this experiment, at the end of 30 minutes after the termination of artificial pneumothorax, the corresponding values of R, K, α angle and MA also were restored to some extent with the return of the PaCO₂ and pH values to the pre-anesthesia levels; however, the levels of the former group of parameters were still different from those recorded before the operation (P < 0.05) and only normalized on postoperative day 1. These findings suggest that with the correction of acidic environment in vivo, there is a gradual improvement in the coagulation function, but the effect of acidic environment on coagulation function persists for a certain period of time. Studies have shown that correcting the pH value once acidosis has occurred does not completely reverse the acidosis-induced damage to coagulation function.[20,21]

T-PA is mainly synthesized and released by endothelial cells and is widely expressed by various tissues of the body. T-PA is an important index of the fibrinolytic activity in the fibrinolytic
the initiation of CO2 artifcial pneumothorax during thoracoscopic esophagectomy had a significant impact on coagulation and fibrinolysis. CO2 artifcial pneumothorax may result in signifcant derangements in pH and PaCO2, and the resultant respiratory acidosis and hypercapnia may increase the risk of intraoperative bleeding.

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