Monitoring of exhaled carbon monoxide and carbon dioxide during lung cancer operation

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Abstract

OBJECTIVE: Carbon monoxide (CO) is expelled mainly via the lungs, so that exhaled carbon monoxide (Ex-CO) concentration reflects endogenous production. Recent reports have shown that Ex-CO levels are increased in critically ill patients and after anaesthesia and surgery. However, there has been no investigation of the changes in Ex-CO level during a lung operation. We continuously monitored Ex-CO and exhaled carbon dioxide (Ex-CO2) concentrations during surgery for lung cancer.

METHODS: Eighteen lung cancer patients who underwent elective lung cancer lobectomy were enrolled in this study. All patients were endotracheally intubated and ventilated under general anaesthesia. Ex-CO and Ex-CO2 concentrations were separately monitored and recorded continuously using two sets of Carbolyzer® breath analysers (Taiyo Inc., Osaka, Japan).

RESULTS: Ex-CO concentration increased rapidly in response to changes in body position from supine to decubitus and was significantly decreased when patients were once again lying back (supine 2). Upon restarting bilateral ventilation, Ex-CO concentration in the operated lung was significantly higher than that in the breathing lung. In the lateral decubitus position, Ex-CO2 concentration showed the same pattern of increase as seen for Ex-CO. In the operated lung, the Ex-CO2 concentrations changed significantly at clamping, declamping and supine 2. In the re-ventilated, operated lung, the Ex-CO2 concentration was significantly lower than in the breathing lung. In the breathing lung, the Ex-CO2 concentration did not exhibit any significant changes over the course of the operation.

CONCLUSIONS: When breathing was restarted, the Ex-CO level of the target lung was significantly higher than that of the breathing lung. The Ex-CO concentration was also affected by the surgical body position and this change was marked and transient.

Keywords: Exhaled carbon monoxide • Monitoring • Lung cancer operation • Mechanical ventilation

INTRODUCTION

Carbon monoxide (CO) is expelled mainly via the lungs, so that the exhaled carbon monoxide (Ex-CO) concentration reflects endogenous production. CO is a product of organic oxidation processes and arises in vivo during cellular metabolism, most notably haem degradation. CO binds to the haem iron of most haemoproteins. Haem oxygenase (HO) produces carbon monoxide (CO) during the breakdown of haem molecules. Thus the Ex-CO levels could reflect the induction of HO. Increases in exhaled carbon monoxide presumably reflect changes in systemic and airway haem metabolic activity from the action of haem oxygenase enzyme [1–3].

The Ex-CO concentration has been reported to increase in oxidative tissue injuries, such as systemic inflammation, and is thought to reflect increased breakdown in the affected organ. Ex-CO concentrations have also been shown to be increased in inflammatory airway diseases, such as upper respiratory tract infections (URTIs), lower respiratory tract infection, asthma, seasonal allergic rhinitis, cystic fibrosis and severe sepsis [4–9].

Ex-CO concentrations are significantly increased in critically ill patients, compared with those in healthy controls. Increased haem breakdown has been observed in critically ill patients and increased CO, arterial carboxyhaemoglobin (COHb) and serum total bilirubin concentration may be novel and useful markers of critically ill conditions. Morimatsu et al. compared Ex-CO concentrations between survivors and non-survivors, and survivors tended to have higher Ex-CO concentrations than non-survivors. However, the poorer outcome of non-survivors may have been due to their limited capacity to produce CO or induce HO-1 [10].

Ex-CO concentrations have also been shown to be increased after surgery under both general and spinal anaesthesia, probably due to oxidative stress caused by anaesthesia or surgery. Ex-CO concentrations were increased on the day after surgery, irrespective of whether general or spinal anaesthesia was used. Consistent with the increase in Ex-CO concentration, arterial COHb levels
were increased in both the spinal and general anaesthesia group for surgery. Moreover, during living donor liver transplantation (LDLT) surgery, the Ex-CO concentration is significantly increased after reperfusion, probably due to increases in haem breakdown and endothelial cell injury in the grafted liver [11, 12]. In this study, we considered separately the changes in exhaled gas under bilateral and one-lung ventilation and compared the monitoring of the breathing (dependent) and operated (target) lungs.

**MATERIALS AND METHODS**

The study protocol was approved by the Institutional Review Board at the University Hospital of Tokushima, Japan, and data was collected between June 2008 to November 2009.

**Patients’ characteristics**

Measurements were performed in 18 patients (8 female, 10 male, aged 66.4 ± 7.7 years) who underwent elective lobectomy for lung cancer. Right lung lobectomy patients were predominant in our patient population (83.3%; 15/18 cases).

Cancer types were squamous cell carcinoma in 27.8% (5/18) and adenocarcinoma in 72.2% (13/18) of patients. The procedures were right upper lobectomy in 50% (9/18), right middle lobectomy in 16.7% (3/18), right lower lobectomy in 16.7% (3/18), left upper lobectomy in 11.1% (2/18) and left lower lobectomy in 5.5% (1/18). Respiratory types were normal type in 66.7% (12/18), obstructive type in 27.8% (5/18) and restrictive type in 5.5% (1/18). In the present study we enrolled only 15 patients who underwent right lung lobectomy.

All patients received general anaesthesia with endotracheal intubation. Respiratory conditions were kept constant during the operation in all patients by using anaesthetic drugs with muscle relaxants. Throughout the entire surgical period, we simultaneously recorded the fraction of inspired oxygen (FiO₂), end tidal carbon dioxide (etCO₂), heart rate (HR), blood pressure (BP) and saturation oxygen pressure (sPO₂). The characteristics of the patients are listed in Table 1. Exhaled carbon monoxide concentrations could be monitored easily in all patients during the operation.

**Exhaled carbon monoxide and carbon dioxide measurements**

Ex-CO concentrations were continuously measured in gas sampled at 200 ml/min, separately in the left and right lungs, by using a highly sensitive CO and CO₂ analyser (Carbolyzer® mBA-2000; Taiyo Instruments Inc., Osaka, Japan). This machine is equipped with a gas sensor based on the controlled potential electrolysis method. The Carbolyzer has sensitivity of ±0.1 ppm, unit measuring range of 0–50 ppm and is capable of continuous side-stream sampling at a rate of 0.2 l/min. A sampling adaptor was attached to the respiratory circuit for exhaled air sampling [10, 13]. We used two Carbolyzers [Fig. 1A]; one machine was used to measure the right lung Ex-CO and Ex-CO₂ levels and the other to measure the left lung Ex-CO and Ex-CO₂ levels. During operation, the Ex-CO and Ex-CO₂ concentrations were continuously monitored (every second) with a focus on the following six time points:

(i) Supine 1—lying on the back (before operation)
(ii) Decubitus—lateral decubitus body position and start of operation
(iii) Clamping—operation side tube clamping and one-lung ventilation
(iv) Cut out—removing lobes of the lung (target)
(v) Declamping—restarting bilateral ventilation
(vi) Supine 2—lying on the back again (end of operation)

**Measurement equipment**

The measurement was carried out after 1.0 min at each time point and the mean Ex-CO and Ex-CO₂ levels were calculated using a special software package (Carbolyzer DataBox, Taiyo Inc., Osaka, Japan). The CO level in the inspired air was confirmed as zero before measurement in every patient.

Simultaneously, the exhaled carbon dioxide (Ex-CO₂) concentrations were also measured by a non-dispersive infrared absorption sensor included in the Carbolyzer machines. Calibrations of both Carbolyzer machines were performed using a standard gas mixture at a concentration of CO = 48.9 ppm and CO₂ = 5.1% (produced by Taiyo Inc., Osaka, Japan) before each measurement.

Tracheally intubated double-lumen tubes (left) (Portex® Blue Line® Endobronchial Tube; Smiths Medical International, Ltd.) were used for all patients. The correct double-lumen tube position was ascertained by fibre-optic bronchoscopy, firstly in the supine and then in the lateral decubitus position [Fig. 1B]. Subsequently, the Carbolyzer was connected to the endobronchial tube via an extension tube (size: X2WL 100 × 4; Top Inc., Tokyo, Japan) and separate lung ventilation was performed with an artificial ventilator (Aestiva5 Datex-Ohmeda (GEMSIT), Philips, Tokyo, Japan).

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**Table 1: Patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>68 ± 6.5</td>
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<tr>
<td>Gender (female/male)</td>
<td>8/7</td>
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<tr>
<td>Body (weight/height)</td>
<td>55 kg/158.1 cm</td>
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<tr>
<td>Smoking status:</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (cessation 1 month before)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>6</td>
</tr>
<tr>
<td>Never smoked</td>
<td>6</td>
</tr>
<tr>
<td>Mean tumour size (mm)</td>
<td>31.4 ± 16.7</td>
</tr>
<tr>
<td>Involved side: Right lung</td>
<td></td>
</tr>
<tr>
<td>P-stage</td>
<td>RUL-9, RML-3, RLL-3</td>
</tr>
<tr>
<td>Forced expiratory volume (FEV/FEV%)</td>
<td>2170 ± 4.5/74.6 ± 6.01%</td>
</tr>
<tr>
<td>Vital capacity (VC/ VC%)</td>
<td>2798 ± 533/106 ± 19.44%</td>
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<tr>
<td>Diffusion lung carbon monoxide (D_{LCO})</td>
<td>96.41 ± 29 ml/mmHg</td>
</tr>
<tr>
<td>Respiratory disorder type:</td>
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</tr>
<tr>
<td>Normal</td>
<td>12</td>
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<tr>
<td>Obstructive</td>
<td>2</td>
</tr>
<tr>
<td>Restrictive</td>
<td>1</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>267.6 ± 125.5</td>
</tr>
<tr>
<td>Blood transfusion/complication</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Table 1:** Patient characteristics.
From the time of clamping to the time of declamping, the endobronchial tube of operated side was clamped and disconnected from the breathing system in the operated lung.

Statistical analysis

Results were analysed by a Prism 5.0 statistical package (Graph-Pad Software, San Diego, CA, USA). All data were expressed as the mean ± standard error (SEM) or the mean ± standard deviation (SD). Differences in Ex-CO and Ex-CO\(_{2}\) concentrations at different time points were analysed by one-way repeated measures analysis of variance (ANOVA) corrected for multiple comparisons by Bonferroni's method compare all pairs of columns. Mean values were compared by unpaired \(t\)-Test with Welch's correction. Significance was defined as \(P \leq 0.05\).

RESULTS

Fifteen patients undergoing right lobectomy for lung cancer between June 2008 and November 2009, were examined: seven men (46.7%) and eight women (53.3%) aged 68.0 ± 6.5 years (mean ± SD). A total of nine (60%) patients were former smokers (cessation for more than one month prior to the operation) and six patients had never smoked. The mean operation time was 267.6 ± 125.5 min. All patients had primary lung cancer [pathological stage IA (nine patients), IB (five patients) and IIIB (one patient), respectively]. The most common cancer type was adenocarcinoma (12 patients; 80%), followed by squamous carcinoma (3 patients; 20%). The underlying types of lung resections were right upper lobectomy (9 patients; 60%), right middle lobectomy (3 patients; 20%) and lower lobectomy (3 patients; 20%). The mean tumour size was 31.4 ± 16.7 mm. Lung function tests showed a forced expiratory volume (FEV) of 2170 ± 4.5 ml/min, predicted FEV% of 74.6 ± 6%, forced vital capacity (FVC) of 2798 ± 533 ml/min, predicted FVC% of 106 ± 19.4% and diffusing capacity of the lung for CO (DLCO) of 96.4 ± 29 ml/min/mmHg. The characteristics of these patients are listed in Table 1. All patients had a fraction of inspired oxygen (FiO\(_2\)) concentration of 0.7–1.0, a level that remained constant throughout the study.

Exhaled CO concentrations were increased after a change of body position from supine to decubitus during surgery. During the supine period, the Ex-CO concentrations were similar in the operated (right) and breathing (left) lungs and then after the change of body position to decubitus the Ex-CO level in the breathing lung was higher than that on the operated side (11.4 ± 4.0 vs. 10.5 ± 3.3 ppm). However, none of these differences were statistically significant [Fig. 2A and B].

Operated side (right lung) exhaled carbon monoxide monitoring

Ex-CO concentrations in the operated lung (right) increased from 9.3 ± 2.72 ppm under the supine 1 body position to 10.5 ± 3.3 ppm under decubitus in 86.7% of cases (13/15). The increased Ex-CO concentrations returned to baseline (8.9 ± 3.3 ppm) at the time of clamping. In the period from clamping to declamping, Ex-CO concentration increased from 8.9 ± 3.3 ppm to 9.5 ± 3.2 ppm. Thereafter, the Ex-CO concentration rapidly decreased from the time of declamping (9.5 ± 3.2 ppm) to supine 2 (again lying on the back) (6.8 ± 2.8 ppm) and this phenomenon was detected in 93.3% of cases (14/15), but the difference was not statistically significant. Ex-CO concentrations were significantly decreased from 10.5 ± 3.3 ppm at the time of decubitus (start of operation) to 6.8 ± 2.77 ppm at the time of supine 2 (end of operation) in 14 out of 15 cases (\(P < 0.05\)) [Fig. 2A].

Ex-CO concentrations at the time of supine 2 (end of operation) tended to be lower than those at the time of supine 1 (before operation). These changes were detected in 80% of cases (12/15).

Breathing side (left lung) exhaled carbon monoxide monitoring

Ex-CO concentrations in the breathing lung increased from 9.8 ± 3.2 ppm at the start of the supine 1 period to a peak value of 11.4 ± 4.0 ppm at the time of decubitus (i.e. within a few minutes) and then returned rapidly to 10.0 ± 4.5 upon clamping. After a change of body position from supine 1 to decubitus, in 73.3% of cases (11/15), Ex-CO concentrations increased rapidly and then significantly decreased from 11.4 ± 4.0 ppm at the time of decubitus to 6.8 ± 1.7 ppm at supine 2 in 86.7% of cases (13/15; \(P < 0.005\)).
In 86.7% of cases (13/15) exhaled carbon monoxide concentrations decreased significantly from 11.4 ± 4.0 ppm at decubitus, to 7.4 ± 2.5 ppm at cut-out (*P < 0.005), 7.4 ± 2.3 ppm at declamping (**)P < 0.005) and to 6.8 ± 1.7 ppm at supine 2 (**P < 0.005) [Fig. 2B].

Exhaled carbon dioxide monitoring

In the operated (right) lung, Ex-CO2 concentrations at the time of clamping, (4.7 ± 1.4%) were significantly higher than at the time of declamping (3.7 ± 0.9%) in 73.3% of cases (11/15; *P < 0.05). Comparing the point of declamping (at the restart of bilateral ventilation) and supine 2 (the end of the operation), the Ex-CO2 concentration increased significantly from 3.7 ± 0.9% to 5.0 ± 1.6% in 86.7% of cases (13/15; **P < 0.05) [Fig. 3A].

The Ex-CO2 concentration in the breathing (left) lung was essentially stable and did not show any differences over the six time points of the lung cancer operation [Fig. 3B].

Exhaled carbon monoxide and carbon dioxide concentrations compared with operated (right) and breathing (left) sides at the time of declamping

In comparison between the operated (right) lung and breathing (left) lung at the time of declamping (start of one-lung ventilation), the Ex-CO concentration in the operated side (9.5 ± 3.2 ppm) was significantly higher than that in the breathing side (7.5 ± 2.3 ppm) and this change was detected in 86.7% of cases (13/15; P < 0.02) [Fig. 4A].

At the same time point of declamping (the restart of bilateral ventilation), we also found that Ex-CO2 concentration in the operated lung (3.7 ± 0.8%) was significantly lower than in the breathing lung (4.4 ± 1.3%); this change was detected in 80% of cases (12/15; P < 0.03) [Fig. 4B].

DISCUSSION

In this study, we separately monitored changes of Ex-CO and Ex-CO2 concentration in mechanically ventilated patients during lung cancer lobectomy. No complications were observed in any of the patients and no blood transfusion was performed during the measurements. Carbon monoxide (CO), a product of organic oxidation processes, arises in vivo during cellular metabolism, most notably haem degradation. The rate of endogenous CO production in the human body is estimated at 0.42 ml/hour and endogenous CO accounts for 0.4–0.96% of blood carboxyhaemoglobin (COHb) in the absence of significant environmental background CO. Endogenous CO is mainly derived from haem catabolism in the HO reaction. Increases in Ex-CO presumably
CO lung excretion is dependent on many variables, such as the CO lung diffusing capacity, alveolar ventilation, oxygen pressure in the lung capillaries, carboxyhaemoglobin concentration, endogenous CO production and CO catabolism. Coburn et al. reported that endogenously produced CO does not accumulate within the body. CO is almost exclusively eliminated through the lungs [12, 14]. However, as seen in the present study, CO may accumulate within the clamped lung during operation. Our data indicate that a significant release of endogenous CO occurs in the clamped lung. When bilateral ventilation is restarted by declamping on the operated side (target lung), the Ex-CO concentration becomes significantly higher than that on the breathing side (dependent lung).

The initial changes of exhaled CO levels may have been due to a change of mean oxygen tension in the pulmonary capillaries, suggesting that the lung blood circulation and respiratory condition may result in a systemic increase in CO concentration. CO and oxygen bind to the same site on haemoglobin and therefore compete against each other; it is well established that oxygen competes with CO for the same haemoglobin-binding site [15]. As shown in Fig. 2, the Ex-CO concentration showed a tendency to immediately increase after changes of surgical body position and reached a maximum. However, the increase in Ex-CO concentration between the supine and decubitus positions was not significantly different.

Increases in pulmonary elimination of CO were markedly but transiently influenced by FiO2. Oxygen therapy for critically ill patients can temporarily increase Ex-CO because of facilitating CO release from COHb and a recent study also reported that an increase in FiO2 from 0.5 to 1.0 did not influence the exhaled CO concentration [16, 17]. In our study, FiO2 was mainly controlled from 0.7 to 1.0 during the operations, based on the decision of the individual anaesthesiologist. There was no case with FiO2 of less than 0.7 during operation. Therefore, the influence of changing FiO2 in relation to the exhaled CO concentration was less in this research than in previous studies.

Hypoventilation and hyperventilation can influence Ex-CO measurements. This hypothesis was only partially confirmed because hypoventilation decreased Ex-CO, but to a much lesser extent than end tidal CO2 (etCO2). In practice, Ex-CO decreased by 10% while etCO2 decreased by 25%. Hypoventilation had an even smaller effect, causing a small and clinically negligible (3%) Ex-CO increase while etCO2 increased by 25% [18].

In thoracic surgery in the lateral position, arterial oxygenation is influenced by numerous factors during the period of one-lung ventilation. Lung resection lobectomy requires one-lung ventilation and pulmonary artery clamping procedures that may produce profound haemodynamic and gas exchange abnormalities. Presumably, these changes are more pronounced in patients with COPD, since their ventilation and haemodynamics are more severely compromised. Considering the present tendency to offer surgery to patients with greater lung function impairment, a higher incidence of intra-operative gas exchange and haemodynamic abnormalities might be expected. In addition to the obligatory right-to-left shunt through the non-ventilated lung, the alveolar pressure in the dependent (ventilated) lung may also influence arterial oxygenation [19, 20]. The results of this study clearly showed that the Ex-CO concentration at the start of operation (lateral decubitus) was significantly larger than that at the end of operation (supine 2) for both the operated and breathing lungs. Thereafter, the Ex-CO concentration gradually decreased and reached a low concentration (baseline level) by the time the patients lay on their backs again. Similar changes in Ex-CO concentration were observed for both the target and dependent lung [Fig. 2A and B].

The Ex-CO level has, significantly, been positively correlated with daily cigarette consumption and thus the Ex-CO level provides an easy and immediate way of assessing a subject’s smoking status. However, in this study we did not have current smokers or those who had stopped smoking less than one month before operation.
COPD patients have increased lung volumes due to pulmonary hyperinflation and, in the end-inspiratory pause, the end-inspiratory lung volume is increased. In this study, the pattern of change in the Ex-CO concentration in patients with mild obstructive respiratory disorder was similar to the pattern in patients with normal respiratory function.

Further, we did not find a correlation between Ex-CO concentrations and Ex-CO2 concentrations, so that Ex-CO2 concentrations may not be estimated from Ex-CO concentrations. The Ex-CO2 concentration remained stable throughout the experiment in the breathing (left) lung, whereas it decreased after re-breathing fresh air in the operated lung and it increased after a change in surgical body position from decubitus to supine 2.

CONCLUSION

In this study, we continuously monitored CO concentrations in exhaled gas under bilateral and one-lung ventilation separately during lung cancer operations. No study like this has ever been reported. Ex-CO concentrations could be easily monitored in tracheally intubated lung cancer patients. When breathing was restarted, the Ex-CO level of the operated lung was higher than that of the breathing lung. Higher CO level in the operated lung could be due to accumulation of CO during non-ventilation during surgery on the lung. The Ex-CO concentration was also affected by the surgical body position.

However, because there were no complications in any of the present procedures and thus no need for blood transfusions, additional studies will be needed to examine the Ex-CO concentration patterns during more problematic surgeries for lung cancer.

We will also be interested to use this non-invasive method in lung cancer operations with pulmonary reconstructions that present the need for clamping of the pulmonary artery and reperfusion of the lung. It might be a useful method to evaluate lung damage during pulmonary operations.

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Conflict of interest: none declared.

REFERENCES