Effects of reduced rebreathing time, in spontaneously breathing patients, on respiratory effort and accuracy in cardiac output measurement when using a partial carbon dioxide rebreathing technique: a prospective observational study

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Abstract

Introduction New technology using partial carbon dioxide rebreathing has been developed to measure cardiac output. Because rebreathing increases respiratory effort, we investigated whether a newly developed system with 35 s rebreathing causes a lesser increase in respiratory effort under partial ventilatory support than does the conventional system with 50 s rebreathing. We also investigated whether the shorter rebreathing period affects the accuracy of cardiac output measurement.

Method Once a total of 13 consecutive post-cardiac-surgery patients had recovered spontaneous breathing under pressure support ventilation, we applied a partial carbon dioxide rebreathing technique with rebreathing of 35 s and 50 s in a random order. We measured minute ventilation, and arterial and mixed venous carbon dioxide tension at the end of the normal breathing period and at the end of the rebreathing periods. We then measured cardiac output using the partial carbon dioxide rebreathing technique with the two rebreathing periods and using thermodilution.

Results With both rebreathing systems, minute ventilation increased during rebreathing, as did arterial and mixed venous carbon dioxide tensions. The increases in minute ventilation and arterial carbon dioxide tension were less with 35 s rebreathing than with 50 s rebreathing. The cardiac output measures with both systems correlated acceptably with values obtained with thermodilution.

Conclusion When patients breathe spontaneously the partial carbon dioxide rebreathing technique increases minute ventilation and arterial carbon dioxide tension, but the effect is less with a shorter rebreathing period. The 35 s rebreathing period yielded cardiac output measurements similar in accuracy to those with 50 s rebreathing.

Introduction

A partial carbon dioxide rebreathing technique has been developed to estimate cardiac output (CO) in mechanically ventilated patients undergoing surgery [1,2] or intensive care [3,4]. We previously reported that 50 s carbon dioxide rebreathing resulted in increased minute ventilation (VE) and an irregular respiratory pattern [4]. Recently, an improved system with a shorter rebreathing time (35 s) was developed and is replacing the 50 s rebreathing system. We reasoned that shortening the carbon dioxide rebreathing period would lessen the
increases in arterial carbon dioxide tension (PaCO₂) and respiratory effort during carbon dioxide rebreathing. We were concerned, however, that measurement of CO might be compromised by a shorter rebreathing period because there would be smaller changes in the measured variables, fewer sampled breaths and incomplete equilibrium [5]. We designed the present prospective study to investigate how, in spontaneously breathing patients, the shorter carbon dioxide rebreathing period affects respiratory effort during rebreathing and how it affects the accuracy of CO measurement.

Materials and methods
The study was approved by the ethics committee of the National Cardiovascular Center (Osaka, Japan), and written informed consent was obtained from each patient.

Patients
Thirteen consecutive patients (age 39–79 years) who had undergone elective cardiovascular surgery were enrolled in the study (Table 1). Enrolment criteria were similar to those of previous studies [3,4]: insertion of a pulmonary artery catheter, stable haemodynamics in the intensive care unit (ICU) and no leakage around the endotracheal tube. We excluded those patients who had central nervous system disorders, who might be adversely affected by induced hypercapnia, or who exhibited severe tricuspid regurgitation. After admission to the ICU each patient was ventilated with an 8400STi ventilator (Bird Corp., Palm Springs, CA, USA). Initial ventilatory settings were synchronized intermittent mandatory ventilation plus pressure support ventilation (PSV), volume controlled ventilation, tidal volume (VT) 10 ml/kg, respiratory rate 10 breaths/min, inspiratory time 1.0 s, positive end-expiratory pressure 4 cmH₂O, and PSV 10 cmH₂O. The inspired fraction of oxygen was adjusted by attending physicians to maintain arterial oxygen tension greater than 100 mmHg. Using an inspiratory hold technique, we measured the effective static compliance and resistance of the respiratory system (Table 1) [6]. In all patients, arterial blood pressure, heart rate, pulmonary artery pressure, central venous pressure and pulse oximeter signal (PM-1000; Nellcor Inc., Hayward, CA, USA) were continuously monitored. Patients were sedated with propofol (2–3 mg/kg per hour). After waiting 1–2 hours for haemodynamics to stabilize, we decreased the dosage of propofol to 1–2 mg/kg per hour.

Study protocol
As each patient recovered spontaneous breathing, we gradually decreased synchronized intermittent mandatory ventilation rates, finally changing the ventilatory mode to continuous positive airway pressure with PSV at 10 cmH₂O. The measurement protocol was started when the recruited patients satisfied the following conditions: recovery of cough reflex; VT ≥ 8 ml/kg and respiratory rate ≤ 20 breaths/min; arterial blood gas of pH 7.35–7.45; PaCO₂ 35–45 mmHg; and arterial oxygen tension ≥ 100 mmHg at an inspired fraction of oxygen ≤ 0.5. We applied two systems of noninvasive partial carbon dioxide rebreathing technique in a random order. After waiting for at least 15 min, we recorded respiratory and haemodynamic data. Because the stimuli of partial carbon dioxide rebreathing increased spontaneous breathing, we recorded the data as displayed on the graphic monitors of the ventilators for respiratory rate and VT at the end of the normal breathing period and at the end of the rebreathing periods (Fig. 1). At the same time arterial blood was drawn via radial artery cannulation and mixed venous blood via pulmonary artery catheter; samples were analyzed with a calibrated blood gas analyzer (ABL 505; Radiometer, Copenhagen, Denmark).

Cardiac output measurements
We randomly applied two systems of noninvasive partial carbon dioxide rebreathing technique to measure CO (CO_NI): 35 s rebreathing (version 4.5, fast mode; Novametrix Medical Systems Inc., Wallingford, CT, USA) and 50 s rebreathing (version 4.2, fast mode). Although the durations of carbon dioxide rebreathing were different, both the total cycle (3 min) and the calculation algorithm were the same. Sensors for noninvasive partial carbon dioxide rebreathing technique (NICO₂) were placed between the tracheal tube and Y-piece. The principle underlying this technique is described in detail elsewhere [3-5]. Briefly, carbon dioxide production (VCO₂) is calculated on a breath-by-breath basis and a differential Fick equation is

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**Table 1**

Patient profile at study enrolment

| Characteristic/parameter | Value |
|-------------------------|-------|
| Number of patients      | 13    |
| Male/female             | 8/5   |
| Age (years)             | 64 ± 12 |
| Height (cm)             | 160 ± 11 |
| Body weight (kg)        | 58 ± 14 |
| Operative time (min)    | 252 ± 50 |
| Intraoperative dose of fentanyl (µg/kg) | 21 ± 8 |
| Carbon dioxide production (ml/min per kg) | 2.6 ± 0.2 |
| Dead space fraction     | 0.48 ± 0.02 |
| Venous admixture fraction | 0.08 ± 0.02 |
| CO with thermodilution (l/min) | 5.3 ± 2.1 |
| Compliance of the respiratory system (ml/cmH₂O) | 49.8 ± 14.8 |
| Resistance of the respiratory system (cmH₂O s per l) | 12.0 ± 2.9 |
| Background disease      |       |
| Coronary artery disease | 6     |
| Acquired valve disease  | 6     |
| Thoracic aortic aneurysm| 1     |

Values are expressed as mean ± standard deviation. CO, cardiac output.
applied to establish the relationship between VCO₂ and CO as follows:

\[ VCO_2 = CO \times (CvCO_2 - CaCO_2) \quad (1) \]

Where \( CvCO_2 \) is the carbon dioxide content in mixed venous blood, and \( CaCO_2 \) is the carbon dioxide content in arterial blood. Assuming that both \( CO \) and \( CvCO_2 \) remains constant during carbon dioxide rebreathing and that the change in \( CaCO_2 \) between normal breathing and carbon dioxide rebreathing is proportional to the changes in \( PaCO_2 \) and end-tidal carbon dioxide pressure (PETCO₂), the following equation is substituted for the previous one:

\[ CO = \Delta VCO_2/(S \times \Delta PETCO_2) \quad (2) \]

Where \( \Delta VCO_2 \) is the change in \( VCO_2 \) and \( \Delta PETCO_2 \) is the change in PETCO₂ between normal breathing and carbon dioxide rebreathing, and \( S \) is the slope of the carbon dioxide dissociation curve from haemoglobin. After compensating, from the pulse oximeter signal, for the intrapulmonary shunt fraction, the partial carbon dioxide rebreathing technique obtains values for CO.

After we had acquired CONI data, we measured thermodilution CO (CO_TD) via a 7.5-Fr pulmonary artery catheter (Abbott Laboratories, North Chicago, IL, USA; Fig. 1). During the latter half of the normal breathing period, injection of 10 ml cold saline (0°C) was done three times and the values obtained were averaged. We carefully standardized the timing of bolus injections to after the first half of the expiratory phase [7].

**Statistical analysis**

Data are presented as mean ± standard deviation, or as the median and interquartile range if the data were skewed. Comparison of respiratory rate, \( V_E \), \( PaCO_2 \) and mixed venous partial carbon dioxide tension (PCO₂) between different conditions (35 s versus 50 s rebreathing, and normal breathing versus rebreathing) were conducted using the Friedman test and the Wilcoxon signed rank test. We evaluated the agreement among COₙₐ with 35 s rebreathing, COₙₐ with 50 s rebreathing and CO_TD using Bland-Altman analysis [8]. \( P < 0.05 \) was considered statistically significant.

**Results**

**Respiratory loads**

Respiratory and blood gas results are summarized in Table 2. There was no significant difference in respiratory rate, \( V_E \), \( PaCO_2 \) and mixed venous PCO₂ during normal breathing between 35 s rebreathing and 50 s rebreathing (Table 2). With either duration of rebreathing, respiratory rate and \( V_E \) increased during rebreathing. Similarly, the values for \( PaCO_2 \) and mixed venous PCO₂ were higher at the end of the rebreathing period. The changes in \( V_E \) and \( PaCO_2 \) due to rebreathing were significantly less with 35 s rebreathing than with 50 s rebreathing (Fig. 2).

**Cardiac output**

The results of Bland-Altman analysis for 35 s and 50 s rebreathing systems are summarized in Fig. 3. The CO measured using both systems exhibited similar agreement (bias and precision, respectively: 0.02 l/min and 1.06 l/min with 35 s rebreathing, and -0.34 l/min and 1.08 l/min with 50 s rebreathing) with values measured by thermodilution. When comparing the CO between 35 s rebreathing and 50 s rebreathing, bias was 0.26 l/min and precision was 0.51 l/min (Fig. 3c).

**Discussion**

The main findings of the present study, conducted in spontaneously breathing patients, are that respiratory rate, \( V_E \), \( PaCO_2 \) and mixed venous PCO₂ increased during the rebreathing period; that increases in \( V_E \) and \( PaCO_2 \) during carbon dioxide rebreathing were less with the shorter rebreathing period; and that the two systems, with different rebreathing periods, provided similarly accurate CO measurements.

The NICO₂ system is appealing as a noninvasive method for measuring CO in patients in whom pulmonary artery catheterization is not possible or desirable. Because it is now common for ICU patients to receive partial ventilatory support that allows spontaneous breathing [9], we must determine how the reduction in carbon dioxide rebreathing time affects respiratory effort and how accurate the NICO₂ system is in such patients.
One disadvantage of the partial carbon dioxide rebreathing technique is that rebreathing increases the respiratory effort of spontaneously breathing patients [4]. Consequently, the effect on respiratory effort of different durations of carbon dioxide rebreathing requires clarification. To our knowledge, no other investigations into this issue have been published. First, we found that the increase in PaCO₂ during 50 s rebreathing was 5.9 mmHg (median; Fig. 2). These increases were greater than values (2–5 mmHg) previously reported in applications of controlled mechanical ventilation [10,11]. We assume that the greater metabolic rate in awake and spontaneously breathing patients accounted for the higher increase in PaCO₂ during carbon dioxide rebreathing. Next, as we had conjectured, the shorter period of carbon dioxide rebreathing resulted in lesser increases in PaCO₂ and, as a result, reduced the increases in Vₑ during carbon dioxide rebreathing (Fig. 2). Although NICO₂ monitoring is relatively noninvasive under controlled mechanical ventilation, it increases PaCO₂ and respiratory effort under partial ventilatory support, even during 35 s rebreathing.

### Accuracy of cardiac output measurement

Although we previously found this technique to be less accurate when there were spontaneous breathing efforts [4], in the present study CO₅₌ correlated moderately well with CO_TD. We reason that we were able to obtain more stable Vₚ and Vₑ findings during CO measurement in the present study by using a larger dosage of propofol (1–2 mg/kg per hour) than in the previous study (0.5 mg/kg per hour). It is likely that stable Vₚ and Vₑ resulted in more accurate CO measurement. Gama de Abreu and coworkers [12], using a system different from ours, also reported that results were less precise when there was irregular spontaneous breathing than when respiratory rate and Vₑ were fixed.

Because of smaller changes in the measured variables, fewer sampled breaths and incomplete equilibrium, we expected that the shorter duration of rebreathing would lead to less accurate CO measurement [5]. However, CO measurement with 35 s rebreathing was as accurate as with 50 s rebreathing (Fig. 3). Although the exact reason is unknown, we speculate as follows: Because the CO₅₃ value is calculated from the ratio of change in VCO₂ and PETCO₂ during carbon dioxide rebreathing, the measurement is corrupted by noise and by variations in Vₑ and respiratory rate [5]. Smaller carbon dioxide stimuli during 35 s rebreathing probably result in a more stable ventilatory pattern, whereas the smaller changes in VCO₂ and PETCO₂ during 35 s rebreathing lead to a poorer signal-to-

### Table 2

**Respiratory parameters and blood gas analysis at normal breathing and rebreathing**

| Respiratory and blood gas parameters | 35 s system | 50 s system |
|-------------------------------------|-------------|-------------|
| **Respiratory rate (breaths/min)**   |             |             |
| Normal breathing                    | 16 (15–18)  | 17 (15–17)  |
| Rebreathing                         | 18* (16–22) | 19* (16–22) |
| **Minute ventilation (l/min)**      |             |             |
| Normal breathing                    | 6.6 (5.9–7.4) | 6.3 (6.2–7.3) |
| Rebreathing                         | 8.8* (8.0–11.6) | 9.5* (8.2–12.4) |
| **Arterial carbon dioxide tension (mmHg)** |         |             |
| Normal breathing                    | 42.1 (41.0–46.9) | 42.2 (39.6–48.6) |
| Rebreathing                         | 46.5* (43.5–52.5) | 47.2* (45.9–55.0) |
| **Mixed venous carbon dioxide tension (mmHg)** |         |             |
| Normal breathing                    | 46.2 (44.4–52.2) | 48.0 (43.9–52.2) |
| Rebreathing                         | 47.6* (46.1–52.9) | 49.0* (47.0–54.4) |

Values are expressed as median (interquartile range). *P < 0.05 versus normal breathing.

### Figure 2

(a) \( ΔV_E (l/min) \)  
(b) \( ΔPaCO₂ (mmHg) \)

Changes in respiratory values in each patient due to carbon dioxide rebreathing. (a) Increases in minute ventilation (\( V_E \)) due to carbon dioxide rebreathing. (b) Increases in arterial carbon dioxide tension (PaCO₂) due to carbon dioxide rebreathing. Medians (triangles) and interquartile ranges are also shown. *P < 0.05 versus 35 s rebreathing.
noise ratio. In the range of durations tested, these two factors might proportionally cancel each other out, resulting in similar accuracy between 35 s rebreathing and 50 s rebreathing.

Limitations
The present study has several limitations. First, we waited for 15 min after applying each NICO$_2$ system with 35 s and 50 s rebreathing. When spontaneous breathing effort is present and $V_E$ is changing, more time may be required to attain stable conditions and an accurate CO$_N$. The time course of the increase in PaCO$_2$ after a decrease in $V_E$ is much slower than the rate of decrease after an increase in $V_E$ [13]. Second, all of the patients included were sedated, but different levels of sedation may result in different responses to carbon dioxide rebreathing. Third, although the patients enrolled in this study exhibited normal lung mechanics (Table 1), critically ill patients with metabolic acidosis may respond differently to carbon dioxide rebreathing [14]. Although we speculate that our findings may be expanded to other patients with stable haemodynamics, and normal lung mechanics and gas exchange, further studies are needed to evaluate the accuracy and reproducibility of the NICO$_2$ system with various levels of sedation and various patient populations. Fourth, the sample size in the study was small and we did not conduct a power analysis to determine the needed sample size. Because we performed multiple measurements in the same individuals, the order of measurements might have affected the results. Finally, the NICO$_2$ algorithm assumes that mixed venous PCO$_2$ remains constant during partial carbon dioxide rebreathing [5]. However, we found that increases in mixed venous PCO$_2$ were larger than those previously reported (Table 2) [15,16]. When mixed venous PCO$_2$ increases during carbon dioxide rebreathing, this must lead to an underestimation in CO$_N$ [5]. Further study is needed to clarify the effects of the change in mixed venous PCO$_2$ on the accuracy of CO measurement.

Conclusion
When patients breathe spontaneously, CO measurement using partial carbon dioxide rebreathing technique increases PaCO$_2$ and $V_E$, although shortening the carbon dioxide rebreathing period causes a lesser increase. The two durations of rebreathing result in similar accuracy in measuring CO.

Key messages
- The NICO$_2$ monitor is claimed to measure CO noninvasively using the partial carbon dioxide rebreathing technique.
- When there are spontaneous breaths, partial carbon dioxide rebreathing increases $V_E$ and PaCO$_2$.
- Use of a shorter duration of rebreathing (35 s versus 50 s) has smaller effects on respiratory effort in spontaneously breathing patients.
- The shorter duration of carbon dioxide rebreathing system yields a CO measurement that is similar in accuracy to that obtained with the previously used, longer duration of rebreathing.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
KT designed the study, collected and analyzed the clinical data, and drafted the manuscript. HI designed the study, carried out data collection and analysis, and extensively revised the manuscript. MT designed the study and performed the statistical analysis. TN and YT participated in the analysis and interpretation of data. MN designed the study and extensively revised the manuscript. All authors read and approved the final manuscript.

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