Noninvasive Cardiac Output Measurement Using Partial Carbon Dioxide Rebreathing Is Less Accurate at Settings of Reduced Minute Ventilation and When Spontaneous Breathing Is Present

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Background: Although evaluation of cardiac output by the partial carbon dioxide rebreathing technique is as accurate as thermodilution techniques under controlled mechanical ventilation, it is less accurate at low tidal volume. It is not clear whether reduced accuracy is due to low tidal volume or low minute ventilation. The effect of spontaneous breathing on the accuracy of partial carbon dioxide rebreathing measurement has not been fully investigated. The objectives of the current study were to investigate whether tidal volume or minute ventilation is the dominant factor for the accuracy, and the accuracy of the technique when spontaneous breathing effort is present.

Methods: The authors enrolled 25 post–cardiac surgery patients in two serial protocols. First, the authors applied three settings of controlled mechanical ventilation in random order: large tidal volume (12 ml/kg), the same minute ventilation with a small tidal volume (6 ml/kg), and 50% decreased minute ventilation with a small tidal volume (6 ml/kg). Second, when the patient recovered spontaneous breathing, the authors applied three conditions of partial ventilatory support in random order: synchronized intermittent mandatory ventilation–pressure support ventilation, pressure support ventilation with an appropriately adjusted rebreathing loop, and pressure support ventilation with the shortest available loop. After establishing steady state conditions, the authors measured cardiac output using both partial carbon dioxide rebreathing and thermodilution methods. The correlation between the data yielded by the two methods was determined by Bland–Altman analysis and linear regression.

Results: Cardiac output with the carbon dioxide rebreathing technique correlated moderately with that measured by thermodilution when minute ventilation was set to maintain normocapnia, regardless of tidal volumes. However, when minute ventilation was set low, the carbon dioxide rebreathing technique underreported cardiac output ($r = 0.70x$; correlation coefficient, 0.54; bias, $-1.73$ l/min; precision, 1.27 l/min; limits of agreement, $-4.27$ to $+0.81$ l/min). When there was spontaneous breathing, the correlation between the two cardiac output measurements became worse. Carbon dioxide rebreathing increased spontaneous tidal volume and respiratory rate (20% and 30%, respectively), during pressure support ventilation) when the rebreathing loop was adjusted for large tidal volume.

Conclusions: During controlled mechanical ventilation, minute ventilation rather than tidal volume affected the accuracy of cardiac output measurement using the partial carbon dioxide rebreathing technique. When spontaneous breathing is present, the carbon dioxide rebreathing technique is less accurate and increases spontaneous tidal volume and respiratory rate.

Because pulmonary artery catheterization is expensive and brings adverse effects such as venous thrombosis and catheter-related infection, a less expensive device has been developed to noninvasively measure cardiac output (CO) based on the partial carbon dioxide rebreathing technique. In comparison with CO data obtained by the thermodilution technique (CO$_{TD}$), CO readings obtained by the carbon dioxide rebreathing system (CO$_{NI}$) have proved reliable when tidal volume ($V_T$) is constant and set to maintain normocapnia. This accuracy is maintained without regard to several key factors, such as whether ventilatory mode is pressure- or volume-controlled ventilation, inspired oxygen fraction ($F_{IO_2}$), or positive end-expiratory pressure (PEEP). However, when $V_T$ is reduced at a constant respiratory rate, CO$_{NI}$ underreports CO. The reason for this underreporting remains unknown.

Using a differential Fick equation, the partial carbon dioxide rebreathing technique calculates CO from the change in carbon dioxide production ($V_{CO_2}$) and the change in end-tidal carbon dioxide pressure ($PETCO_2$) when periodic partial carbon dioxide rebreathing creates a carbon dioxide disturbance. Therefore, the accuracy of the technique depends on accurate measurement of both the change in $V_{CO_2}$ and the change in $PETCO_2$. Once a patient starts breathing spontaneously, $V_{CO_2}$ and $PETCO_2$ vary from breath to breath. We speculate that irregular spontaneous breaths may affect the accuracy of the partial carbon dioxide rebreathing technique. Moreover, CO$_{NI}$ measurement may increase the work of breathing because, during the partial rebreathing phase, there is an increase in $PETCO_2$. Therefore, we designed this prospective study with three objectives: to investigate (1) whether small $V_T$ or small minute ventilation ($V_E$) results in the underestimation of CO$_{NI}$, (2) the accuracy of the partial carbon dioxide rebreathing technique when spontaneous breaths are supported by partial ventilatory support, such as synchronized intermit-
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

Twenty-five adult patients aged 19–75 yr (median age, 63 yr) who had undergone cardiac surgery were enrolled in this study (table 1). They were consecutively admitted patients whose cases matched the following criteria: insertion of a pulmonary artery catheter, stable hemodynamics in the intensive care unit, and no leakage around the endotracheal tube. We excluded candidates who had central nervous system disorders, might be adversely affected by induced hypercapnia, or demonstrated severe tricuspid regurgitation. Arterial blood pressure, heart rate, pulmonary artery pressure, central venous pressure, and pulse oximeter signal (PM-1000; Nellcor Inc., Hayward, CA) were continuously monitored in all patients. After waiting 1–2 h for hemodynamics to stabilize after surgery, we started the measurements. First, using an inspiratory-hold technique, we measured the effective static compliance and resistance of the respiratory system.

Measurements

We measured CO using two methods: thermodilution (CO_TJ) and noninvasive partial carbon dioxide rebreathing technique (CO_N). CO_TJ was obtained using a 7.5-French pulmonary artery catheter (Abbott Laboratories, North Chicago, IL). Injection of 10 ml cold saline (0°C) was performed in triplicate, and the values were averaged. We standardized the timing of bolus injection after the first half of the expiratory phase. CO_N measurement was performed with the partial carbon dioxide rebreathing technique (NICO2 software version 3.1, fast mode; Novametrix Medical Systems Inc., Wallingford, CT). This procedure has been described in detail elsewhere. Briefly, VCO2 is calculated on a breath-by-breath basis, and the differential Fick equation is applied to establish the relation between VCO2 and CO as follows:

\[ V_{CO2} = CO \times (C_{vCO2} - C_{aCO2}) \]

where \( C_{vCO2} \) represents the carbon dioxide content in mixed venous blood, and \( C_{aCO2} \) represents the carbon dioxide content in arterial blood. In the NICO2 system of the current version, carbon dioxide rebreathing is performed for 50 s every 3 min. Assuming that CO remains constant during the carbon dioxide rebreathing procedure, the following equation is substituted for the previous one:

\[ \Delta V_{CO2} = CO \times (\Delta C_{vCO2} - \Delta C_{aCO2}) \]

where \( \Delta V_{CO2} \) is the change in VCO2 between normal breathing and carbon dioxide rebreathing, \( \Delta C_{vCO2} \) is the change in mixed venous carbon dioxide content, and \( \Delta C_{aCO2} \) is the change in arterial carbon dioxide content. Then, assuming that \( C_{vCO2} \) also remains constant during the carbon dioxide rebreathing procedure, the following equation is introduced:

\[ \Delta V_{CO2} = CO \times (\Delta C_{aCO2}) \]

When end-capillary content (Ccco2) is used in place of Caco2, pulmonary capillary blood flow (PCBF), the blood flow that participates in alveolar gas exchange, is measured rather than CO, and the following equation is plotted:

\[ \Delta V_{CO2} = PCBF \times (\Delta C_{cco2}) \]

Assuming here that \( \Delta C_{cco2} \) is proportional to changes in PetCO2, the following equation can be plotted:

\[ PCBF = \Delta V_{CO2} / (S \times \Delta PetCO2), \]

where \( \Delta PetCO2 \) is the change in PetCO2 between normal breathing and carbon dioxide rebreathing, and S is the slope of the carbon dioxide dissociation curve from hemoglobin. CO is the sum of PCBF and intrapulmonary shunt flow (Qs); then, CO is expressed in the following equation:

\[ CO = PCBF / (1 - Qs/Qe) \]

where \( Qs/Qe \) is the intrapulmonary shunt fraction. The noninvasive method for estimating shunt fraction in the NICO2 system is adapted from Nunn’s iso-shunt plots, which are a series of continuous curves indicating the relation between arterial oxygen pressure (Pao2) and Fio2 for different levels of shunt.
arterial blood oxygen saturation (SaO₂), which is non-invasively determined using the pulse oximeter signal. Before the start of the study protocol, the NICO₂ system was calibrated for zero CO₂. We entered the results of PaO₂, arterial carbon dioxide tension (Paco₂), FiO₂, and hemoglobin concentration into the machine when each patient was undergoing the baseline ventilation.

Study Protocol

After admission to the intensive care unit, each patient was ventilated with an 8400STi ventilator (Bird Corp., Palm Springs, CA). Initial ventilatory settings were as follows: SIMV, volume-controlled ventilation, inspired VT of 10 ml/kg, respiratory rate of 10 breaths/min, inspiratory time of 1.0 s, PEEP of 4 cm H₂O, and pressure support of 10 cm H₂O. The FiO₂ settings were adjusted by attending physicians to maintain PaO₂ greater than 100 mmHg. With the patients maintained in the supine position, sedated with continuous intravenous injection of propofol (2 to 3 mg · kg⁻¹ · h⁻¹), we started the measurements.

We performed the two protocols serially. In the first protocol, to prevent spontaneous breathing, if needed, we administered bolus vecuronium bromide (4–8 mg). We applied three settings of volume-controlled ventilation in random order as follows: (1) inspired VT of 12 ml/kg and respiratory rate of 10 breaths/min; (2) VT of 6 ml/kg and respiratory rate of 20 breaths/min; and (3) VT of 6 ml/kg and respiratory rate of 10 breaths/min. The first and second settings should result in identical VT, and the last setting should result in half the VT value. At each setting, the rebreathing loop was size adjusted according to the manufacturer’s instructions recommended for a VT setting of 12 ml/kg. PEEP and FiO₂ identical to baseline were used throughout the measurement period. After establishing steady state conditions (approximately 15 min) and confirming stable values of CO NI (< 5% change in the successive readings), we measured both CO TD and CO NI. The values of expired VT and V̇E were recorded from the digital display of the ventilator. Arterial blood samples were analyzed with a calibrated blood gas analyzer (ABL 505; Radiometer, Copenhagen, Denmark). Hemodynamic data were also recorded. Dead space fraction (V̇E/VT) and venous admixture fraction (Q̇̇S/Q̇̇T) were calculated as described elsewhere.

In the second protocol, we examined the measurement of CO when there was spontaneous breathing effort. We stopped the infusion of vecuronium and decreased the propofol infusion rate to 0.5 mg · kg⁻¹ · h⁻¹. When the patient recovered spontaneous breathing and satisfied our extubation criteria (recovery of cough reflex; VT ≥ 8 ml/kg and respiratory rate ≤ 20 breaths/min under pressure support of 10 cm H₂O; arterial blood gas of pH, 7.35–7.45; PaCO₂, 35–45 mmHg; and PaO₂ ≥ 100 mmHg at FiO₂ ≤ 0.5), we started the measurements. In random order, we applied three settings of partial

Table 2. Respiratory and Hemodynamic Parameters during Controlled Mechanical Ventilation

<table>
<thead>
<tr>
<th>Ventilatory Setting</th>
<th>V̇E, l · min⁻¹ · kg⁻¹</th>
<th>pH</th>
<th>Paco₂, mmHg</th>
<th>P/F</th>
<th>CO TD, l/min</th>
<th>CO NI, l/min</th>
<th>V̇co₂, ml · min⁻¹ · kg⁻¹</th>
<th>PEO₂, mmHg</th>
<th>VT/V̇E</th>
<th>Q̇̇S/Q̇̇T</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT 12 ml/kg</td>
<td>0.13 ± 0.01</td>
<td>7.46 ± 0.04</td>
<td>35.5 ± 4.5</td>
<td>7.41 ± 0.05</td>
<td>5.51 ± 1.23</td>
<td>5.60 ± 1.13</td>
<td>2.9 ± 0.5</td>
<td>33.0 ± 4.5</td>
<td>0.41 ± 0.08</td>
<td>0.06 ± 0.04</td>
</tr>
<tr>
<td>RR 10 breaths/min</td>
<td>(n = 25)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VT 6 ml/kg</td>
<td>0.14 ± 0.01</td>
<td>7.41 ± 0.05</td>
<td>41.1 ± 5.4</td>
<td>7.33 ± 0.04</td>
<td>5.75 ± 1.25</td>
<td>5.08 ± 1.09</td>
<td>2.9 ± 0.4</td>
<td>36.7 ± 5.3</td>
<td>0.50 ± 0.07*</td>
<td>0.09 ± 0.05</td>
</tr>
<tr>
<td>RR 20 breaths/min</td>
<td>(n = 25)</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>VT 6 ml/kg</td>
<td>0.07 ± 0.01†</td>
<td>7.33 ± 0.04†</td>
<td>51.9 ± 6.8*</td>
<td>6.13 ± 1.45</td>
<td>4.40 ± 1.09*</td>
<td>4.72 ± 7.0*</td>
<td>2.1 ± 0.7*</td>
<td>47.2 ± 7.0*</td>
<td>0.47 ± 0.12</td>
<td>0.10 ± 0.07</td>
</tr>
</tbody>
</table>

* P < 0.05 vs. VT 12 ml/kg, RR 10 breaths/min. † P < 0.05 vs. VT 6 ml/kg, RR 20 breaths/min.

CO TD = cardiac output with carbon dioxide rebreathing; CO TD = cardiac output with thermodilution; PaCO₂ = arterial carbon dioxide tension; PEO₂ = end-tidal carbon dioxide production; P/F = ratio of arterial oxygen tension to inspired oxygen fraction; Q̇̇S/Q̇̇T = venous admixture fraction; RR = respiratory rate; V̇E = tidal volume; VT = tidal volume.

Table 3. Results of Bland-Altman Analysis and Regression Analysis during Controlled Mechanical Ventilation

<table>
<thead>
<tr>
<th>Ventilatory Setting</th>
<th>V̇E, l · min⁻¹ · kg⁻¹</th>
<th>pH</th>
<th>Paco₂, mmHg</th>
<th>P/F</th>
<th>CO TD, l/min</th>
<th>CO NI, l/min</th>
<th>V̇co₂, ml · min⁻¹ · kg⁻¹</th>
<th>PEO₂, mmHg</th>
<th>VT/V̇E</th>
<th>Q̇̇S/Q̇̇T</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT 12 ml/kg</td>
<td>0.09</td>
<td>7.41 ± 0.05</td>
<td>41.1 ± 5.4</td>
<td>7.33 ± 0.04</td>
<td>5.75 ± 1.25</td>
<td>5.08 ± 1.09</td>
<td>2.9 ± 0.4</td>
<td>36.7 ± 5.3</td>
<td>0.50 ± 0.07*</td>
<td>0.09 ± 0.05</td>
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<tr>
<td>RR 10 breaths/min</td>
<td>(n = 25)</td>
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</tr>
<tr>
<td>VT 6 ml/kg</td>
<td>−0.67</td>
<td>7.41 ± 0.05</td>
<td>41.1 ± 5.4</td>
<td>7.33 ± 0.04</td>
<td>5.75 ± 1.25</td>
<td>5.08 ± 1.09</td>
<td>2.9 ± 0.4</td>
<td>36.7 ± 5.3</td>
<td>0.50 ± 0.07*</td>
<td>0.09 ± 0.05</td>
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<tr>
<td>RR 20 breaths/min</td>
<td>(n = 25)</td>
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<td></td>
<td></td>
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<tr>
<td>VT 6 ml/kg</td>
<td>−1.73</td>
<td>7.41 ± 0.05</td>
<td>41.1 ± 5.4</td>
<td>7.33 ± 0.04</td>
<td>5.75 ± 1.25</td>
<td>5.08 ± 1.09</td>
<td>2.9 ± 0.4</td>
<td>36.7 ± 5.3</td>
<td>0.50 ± 0.07*</td>
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<tr>
<td>RR 10 breaths/min</td>
<td>(n = 25)</td>
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</table>

Bias, l/min: −1.91 to +2.09; Precision, l/min: 1.00; Limits of agreement, l/min: −2.13 to +0.79; Slope of linear regression: 1.00; Correlation coefficient, R: 0.47.

V̇E = tidal volume; RR = respiratory rate.

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ventilatory support: (1) SIMV plus PSV, mandatory breath rate of 5 breaths/min, mandatory VT of 12 ml/kg, and 6 cm H2O of pressure support; (2) continuous positive airway pressure plus PSV, 10 cm H2O of pressure support; and (3) the same setting of PSV with the shortest length of rebreathing loop. In the first and second settings, the rebreathing loop was sized according to the manufacturer’s instructions recommended for a VT setting of 12 ml/kg; at the other setting, the loop was fully retracted (150 ml). After establishing steady state, we measured both COTD and CONI. Because VT, respiratory rate, and \( V_{\dot{E}} \) increased according to the stimulus of carbon dioxide rebreathing, we recorded VT, respiratory rate, and \( V_{\dot{E}} \) at the end of the normal breathing period and at the end of the carbon dioxide rebreathing period. We limited ourselves to performing a single measurement for each ventilatory setting per patient.

Statistical Analysis

Data are presented as mean \( \pm SD \). Using analysis of variance with repeated measures, mean values were compared across different settings. When significance was observed, the mean values were tested by multiple comparison with the Bonferroni correction. We evaluated the correlation between \( CO_{NI} \) and \( CO_{TD} \) with linear regression and Bland-Altman analysis. Statistical significance was set at \( P < 0.05 \).

Results

Patients had respiratory system compliance of 48.4 \( \pm 8.7 \) ml/cm H2O and resistance of 9.6 \( \pm 2.8 \) cm H2O \( \cdot s \cdot l^{-1} \). All patients safely underwent all the measurements and were extubated within 1 h after the measurement protocol.

Controlled Mechanical Ventilation

Table 2 shows respiratory and hemodynamic results during controlled mechanical ventilation. Although \( V_{\dot{E}} \) was identical, there was higher PaCO2 and \( VD/VT \) at the ventilatory setting of VT of 6 ml/kg and respiratory rate of 20 breaths/min than at VT of 12 ml/kg and respiratory rate of 10 breaths/min. When \( V_{\dot{E}} \) was set to a smaller value (VT of 6 ml/kg and respiratory rate of 10 breaths/min), PaCO2 and PETCO2 were significantly higher, and \( CO_{NI} \) and \( VCO2 \) were significantly lower, compared with the other two settings that provided twice as much \( V_{\dot{E}} \). The values of \( CO_{TD} \), a ratio of Pao2 to FIO2, and \( Q_{S}/Q_{T} \) did not differ significantly at any of ventilatory settings.

The results of Bland-Altman analysis and regression analysis are summarized in table 3 and figures 1 and 2. \( CO_{NI} \) correlated moderately with \( CO_{TD} \) when \( V_{\dot{E}} \) was high, regardless of the VT (figs. 1 and 2). However, when \( V_{\dot{E}} \) was set at half, \( CO_{NI} \) underestimated \( CO_{TD} \) (by \( y = 0.70x; \) bias, \(-1.73 \) l/min) and the correlation coefficient (R) was small (0.34; table 3). Analysis of the results obtained at the setting of 6 ml/kg VT and 20 breaths/min respiratory rate showed bias values and slope of linear regression between those of the other two ventilatory settings.

Spontaneous Breathing

Table 4 shows respiratory and hemodynamic results when patients had spontaneous breaths. At the phase of normal breathing, all of the three ventilatory settings...
showed similar \( V_{\text{E}} \) (mean value of 0.11 l \( \cdot \) min\(^{-1} \cdot \) kg\(^{-1} \)) and respiratory rate (12.3–12.4 breaths/min). When the ventilatory mode was PSV, \( V_T \) at the phase of normal breathing was similar for different sizes of rebreathing loop. When PSV was applied with the rebreathing loop adjusted for 12 ml/kg \( V_T \), at the phase of carbon dioxide rebreathing, \( V_{\text{E}} \) increased by 46%, \( V_T \) increased by 20%, and respiratory rate increased by 30%. Similarly, when SIMV–PSV was applied with the same size of rebreathing loop, at the phase of carbon dioxide rebreathing, \( V_{\text{E}} \) increased by 28%, \( V_T \) of spontaneous breaths increased by 23%, and total respiratory rate increased by 28%. By contrast, when the shortest rebreathing loop was used with PSV, carbon dioxide rebreathing caused smaller increases in \( V_{\text{E}} \) (+17%), \( V_T \) (+10%), and respiratory rate (+10%). There were no significant differences at the three ventilatory settings in blood gas analysis data, \( V_{\text{CO}_2} \), \( \dot{V}_{\text{ETCO}_2} \), \( V_{\text{E}}/V_T \), and \( Q_{\text{S}}/Q_{\text{T}} \).

The results of Bland-Altman analysis and regression analysis when spontaneous breathing were present are summarized in table 5 and figures 3 and 4. During SIMV–PSV mode, the correlation between the CO\(_{\text{NI}}\) and CO\(_{\text{TD}}\) was poor (precision, 1.41 l/min and R = 0.23). When PSV was applied with the rebreathing loop adjusted for 12 ml/kg \( V_T \), the correlation was moderate (precision, 1.26 l/min and R = 0.75). When the shortest rebreathing loop was used during PSV, CO\(_{\text{NI}}\) overestimated CO\(_{\text{TD}}\) (bias, 1.2 l/min and slope = 1.19) with large precision (1.80 l/min).

### Discussion

The main findings of this study are as follows. (1) Rather than small \( V_T \), low \( V_{\text{E}} \) led to less accuracy of CO\(_{\text{NI}}\). (2) When spontaneous breathing effort was present, CO\(_{\text{NI}}\) was less accurate than during controlled mechanical ventilation. (3) During carbon dioxide rebreathing, spontaneous breathing \( V_T \) and respiratory rate increased. (4) Shortening the rebreathing loop reduced the accuracy of CO\(_{\text{NI}}\), although causing less increase in \( V_T \) and respiratory rate during carbon dioxide rebreathing.

### Controlled Mechanical Ventilation

We had previously shown that, when \( V_T \) is constant during controlled mechanical ventilation, CO\(_{\text{NI}}\) correlates well with CO\(_{\text{TD}}\), regardless of inspired oxygen fraction, PEEP, or whether ventilation was pressure or volume controlled.\(^4\) At constant respiratory rate, however, reduced \( V_T \) results in an underestimation of CO\(_{\text{NI}}\), and

### Table 4. Respiratory and Hemodynamic Parameters when Spontaneous Breathing is Present

<table>
<thead>
<tr>
<th>Ventilatory Setting</th>
<th>SIMV/PSV (n = 25)</th>
<th>PSV/Long Loop (n = 25)</th>
<th>PSV/Short Loop (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal breathing</td>
<td>CO(_{\text{E}}) rebreathing</td>
<td>Normal breathing</td>
</tr>
<tr>
<td>( V_{\text{E}} \cdot \text{l} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} )</td>
<td>0.11 ± 0.02</td>
<td>0.14 ± 0.03*</td>
<td>0.11 ± 0.02</td>
</tr>
<tr>
<td>( V_T \cdot \text{ml/kg} )</td>
<td>6.9 ± 2.5</td>
<td>8.5 ± 3.1*</td>
<td>9.3 ± 2.3†</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>12.3 ± 3.1</td>
<td>15.8 ± 3.5*</td>
<td>12.4 ± 3.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.38 ± 0.03</td>
<td>7.38 ± 0.03</td>
<td>7.38 ± 0.03</td>
</tr>
<tr>
<td>Paco(_2), mmHg</td>
<td>44.2 ± 4.1</td>
<td>44.1 ± 4.6</td>
<td>44.2 ± 4.8</td>
</tr>
<tr>
<td>P/F</td>
<td>286 ± 101</td>
<td>289 ± 106</td>
<td>279 ± 97</td>
</tr>
<tr>
<td>CO(_{TD}), l/min</td>
<td>5.96 ± 1.33</td>
<td>6.32 ± 1.59</td>
<td>6.07 ± 1.42</td>
</tr>
<tr>
<td>CO(_{NI}), l/min</td>
<td>6.14 ± 1.46</td>
<td>7.12 ± 1.95</td>
<td>7.27 ± 2.24</td>
</tr>
<tr>
<td>Vco(_2), ml \cdot \text{min}^{-1} \cdot \text{kg}^{-1} )</td>
<td>3.0 ± 1.0</td>
<td>3.6 ± 1.1</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>( \dot{V}_{\text{ETCO}_2} ), mmHg</td>
<td>44.5 ± 4.1</td>
<td>43.8 ± 5.2</td>
<td>44.1 ± 4.2</td>
</tr>
<tr>
<td>( V_{\text{E}}/V_T )</td>
<td>0.42 ± 0.18</td>
<td>0.35 ± 0.13</td>
<td>0.37 ± 0.13</td>
</tr>
<tr>
<td>( Q_{\text{S}}/Q_{\text{T}} )</td>
<td>0.08 ± 0.05</td>
<td>0.09 ± 0.05</td>
<td>0.08 ± 0.05</td>
</tr>
</tbody>
</table>

\* P < 0.05 vs. Normal breathing. † P < 0.05 vs. SIMV/PSV. ‡ P < 0.05 vs. PSV/long loop.

CO\(_{\text{NI}}\) = cardiac output with carbon dioxide rebreathing; CO\(_{\text{TD}}\) = cardiac output with thermodilution; Paco\(_2\) = arterial carbon dioxide tension; \( \dot{V}_{\text{ETCO}_2} \) = end-tidal carbon dioxide pressure; P/F = ratio of arterial oxygen tension to inspired oxygen fraction; PSV = pressure support ventilation; PSV/Long Loop = PSV (10 cm H\(_2\)O) with the rebreathing loop adjusted for \( V_T \) of 12 ml/kg; PSV/Short Loop = PSV (10 cm H\(_2\)O) with the rebreathing loop fully retracted; \( Q_{\text{S}}/Q_{\text{T}} \) = venous admixture fraction; RR = respiratory rate; SIMV = synchronized intermittent mandatory ventilation; SIMV/PSV = mandatory breath rate of 5 breaths/min and PSV (6 cm H\(_2\)O); Vco\(_2\) = carbon dioxide production; \( V_{\text{E}}/V_T \) = dead-space fraction; \( V_{\text{E}} \) = minute ventilation; \( V_T \) = tidal volume (recorded during PSV).

### Table 5. Results of Bland-Altman Analysis and Regression Analysis when Spontaneous Breathing is present

<table>
<thead>
<tr>
<th>Ventilatory Setting</th>
<th>SIMV/PSV (n = 25)</th>
<th>PSV/Long Loop (n = 25)</th>
<th>PSV/Short Loop (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bias, l/min</td>
<td>0.18</td>
<td>0.80</td>
<td>1.20</td>
</tr>
<tr>
<td>Precision, l/min</td>
<td>1.41</td>
<td>1.26</td>
<td>1.80</td>
</tr>
<tr>
<td>Limits of agreement, l/min</td>
<td>-2.64 to +3.00</td>
<td>-1.72 to +3.32</td>
<td>-2.40 to +4.80</td>
</tr>
<tr>
<td>Slope of linear regression</td>
<td>1.01</td>
<td>1.12</td>
<td>1.19</td>
</tr>
<tr>
<td>Correlation coefficient, R</td>
<td>0.23</td>
<td>0.75</td>
<td>0.58</td>
</tr>
</tbody>
</table>

PSV = pressure support ventilation; SIMV = synchronized intermittent mandatory ventilation.

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We designed the first part of this study to investigate whether VT or V̇E is the dominant factor for the accuracy of CONI. For VT, when V̇E of volume-controlled ventilation was set to maintain normocapnia, a correlation between CONI and CO TD was clinically acceptable (bias < 1 l/min, precision ≤ 1 l/min), whether VT was large or small (table 3). The percentage error, which was calculated from the precision divided by the mean CO value, was also acceptable (18% for large VT setting, 13% for small VT setting) because acceptable range is reported to be less than 20%. By contrast, when V̇E was reduced to half, CONI underestimated CO TD with worse precision (1.27 l/min) and percentage error (29%). These findings clearly indicate that V̇E is more important than VT for CONI accuracy. The NICO2 system, by using the following equation, assumes that Cv̅CO2 is constant during the measurement period:

\[
( - \Delta \text{VCO}_2) = \text{CO} \times (\Delta \text{Caco}_2 - \Delta \text{VCO}_2)
\]

Cv̅CO2 may increase during carbon dioxide rebreathing, however, when V̇E/V̇T is large and alveolar ventilation is low. When using the above equation, the neglecting of \( \Delta \text{VCO}_2 \) could lead to an underestimation of CO. At the end of the 50-s rebreathing period in the NICO2 system, mixed venous Pco2 was reported to increase by 0.53 mmHg (median) or by 2.5% (average) from the initial value. Even at identical V̇E, we observed that CO_NI underestimated CO at a high respiratory rate (20 breaths/min) and small VT, compared to ventilation at a low respiratory rate (10 breaths/min) and large VT (table 3). We speculate that increased V̇E/VT and decreased alveolar V̇E at high respiratory rate leads to this inaccuracy and that a change in VT can also affect CO_NI accuracy by this mechanism. It is clear that controlled mechanical ventilation with constant V̇E and constant VT provides more reliable CO_NI measurement.

**Spontaneous Breathing Efforts**

There have been few clinical reports on the accuracy of the NICO2 system when spontaneous breathing is allowed. It is now common for patients receiving intensive care to be ventilated with modes that allow some spontaneous breathing. Consequently, we need to confirm whether the NICO2 technique provides effective monitoring when spontaneous breathing is present, such as during mixed ventilation consisting of spontaneous breaths and mandatory ventilation. Although several reports have compared CO_NI with continuous CO_TD measurement under mixed ventilation, actual ventilatory settings were not specified, and modified algorithms were used. Meanwhile, using a system different from the NICO2, Gama de Abreu et al. have reported that the intraindividual variability of CO measured by partial..
carbon dioxide rebreathing technique was significantly larger during irregular spontaneous breathing than when respiratory rate and VT were fixed. In this study, when spontaneous breathing effort was present, precision (1.26–1.80 l/min) and percentage error (20–30%) were large, indicating less accuracy of the NICO2 system.8 The exact reason for this inaccuracy remains unknown, but there are several plausible reasons.

First, under the influence of spontaneous breathing, 

\[ \dot{V}_{E} \]

may both drift by time and increase in response to carbon dioxide rebreathing. These changes in \( \dot{V}_{E} \) may foul the assumption of constant \( C_{\dot{V}CO_2} \) and affect accuracy of the NICO2 system.9,10 Second, it may be possible that the stimulus of carbon dioxide rebreathing increases CO in spontaneously breathing patients. Because only minimal dosage of propofol (0.5 mg · kg⁻¹ · h⁻¹) was used in our experiment, it is likely that the sympathetic nerve of the patient, as well as the respiratory center, is stimulated during carbon dioxide rebreathing. Third, when there is spontaneous breathing effort, \( \dot{V}_{T} \) changes breath by breath, which may affect accurate measurement of \( \dot{V}_{CO_2} \) or \( PETCO_2 \).

Figure 5 shows representative \( \dot{V}_{CO_2} \) and \( PETCO_2 \) traces from a patient during controlled mechanical ventilation, SIMV–PSV, and PSV. During controlled mechanical ventilation, both \( \dot{V}_{CO_2} \) per breath and \( PETCO_2 \) produced a stable plateau during normal breathing and carbon dioxide rebreathing. On the other hand, during SIMV–PSV, the \( \dot{V}_{CO_2} \) per breath changed drastically on a breath-by-breath basis because of the variation in \( \dot{V}_{T} \) between mandatory breaths (830 ml) and spontaneous breaths (540–620 ml). In the NICO2 system, values for \( \dot{V}_{CO_2} \) and \( PETCO_2 \) during 60-s baseline normal ventilation were calculated as the average of samples of 33–60 s, and those during the 50-s rebreathing period were calculated for intervals of 25–50 s.3 Because \( CO_{NI} \) is derived from changes in \( \dot{V}_{CO_2} \) and \( PETCO_2 \), during SIMV–PSV, the presence of marked breath-by-breath changes in \( \dot{V}_{CO_2} \) and \( PETCO_2 \) may affect \( CO_{NI} \) accuracy. During PSV, breath-by-breath changes in \( \dot{V}_{CO_2} \) or \( PETCO_2 \) are smaller than during
SIMV–PSV. Even so, neither $\dot{V}_{\text{CO}_2}$ nor $\text{PetCO}_2$ produced a steady plateau during normal breathing or rebreathing periods, probably because $V_E$ changed under the influence of carbon dioxide rebreathing. Worse precision during SIMV–PSV and PSV supports the speculation that irregular spontaneous breathing affects the accuracy of the current version of the NICO$_2$ system. In fact, a correlation between $\text{CO}_{\text{NI}}$ and $\text{CO}_{\text{TD}}$ was better even during PSV in the previous study$^4$ than in the current one, probably because the patients had been sedated more deeply with 2 to 3 mg · kg$^{-1}$ · h$^{-1}$ propofol, resulting in more regular spontaneous breathing.$^4$

**Rebreathing Loop Length and Respiratory Efforts**

Once the rebreathing loop is adjusted for a given $V_T$, it is possible that an awake patient may increase $V_T$, making the rebreathing loop relatively too short. In light of this, it may be rational to adjust the rebreathing loop for the largest anticipated $V_T$. In this case, however, when the rebreathing loop is adjusted for large $V_T$, carbon dioxide rebreathing stimulates the respiratory center of the patient, resulting in increased $V_T$, respiratory rate, and $V_E$. The increase in $V_E$ was 28% during SIMV–PSV and 46% during PSV (table 4), suggesting that respiratory efforts increase during carbon dioxide rebreathing. Although fully retracting the rebreathing loop minimized respiratory efforts due to carbon dioxide rebreathing, minimal loops resulted in overestimation and poor correlation (table 5).

**Limitations**

The current study has several limitations. First, we waited for approximately 15 min to establish steady state after each change of ventilatory condition. However, when spontaneous breathing effort is present and $V_T$ is changed, more time may be required to attain stable conditions and more accurate $\text{CO}_{\text{NI}}$, which impairs clinical usefulness of NICO$_2$ monitoring. Second, all patients in this study were sedated, but awake patients may respond differently to carbon dioxide rebreathing. Third, effects of gas compression on the $V_E$ or $V_T$ measurement should be considered in patients with low compliance or high resistance, although the patients enrolled in this study showed normal lung mechanics. Finally, the range of CO measured in this study was relatively small (3.26–9.6 l/min) and only one steady state CO was studied in each patient. Further study is needed to evaluate the accuracy and reproducibility of the NICO$_2$ system under various hemodynamic conditions.

In conclusion, the change in $V_E$ or alveolar ventilation rather than $V_T$ affects the accuracy of CO measurement using noninvasive partial carbon dioxide rebreathing. When spontaneous breathing efforts are present, the CO measurement using the partial carbon dioxide rebreathing method becomes less accurate. Moreover, during the carbon dioxide rebreathing phase, the respiratory efforts during SIMV–PSV or PSV mode increase.

**References**


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