**Background:** Recently, a new device has been developed to measure cardiac output noninvasively using partial carbon dioxide (CO2) rebreathing. Because this technique uses CO2 rebreathing, the authors suspected that ventilatory settings, such as tidal volume and ventilatory mode, would affect its accuracy; they conducted this study to investigate which parameters affect the accuracy of the measurement.

**Methods:** The authors enrolled 25 pharmacologically paralyzed adult post–cardiac surgery patients. They applied six ventilatory settings in random order: (1) volume-controlled ventilation with inspired tidal volume (VT) of 12 ml/kg; (2) volume-controlled ventilation with VT of 6 ml/kg; (3) pressure-controlled ventilation with VT of 12 ml/kg; (4) pressure-controlled ventilation with VT of 6 ml/kg; (5) inspired oxygen fraction of 1.0; and (6) high positive end-expiratory pressure. Then, they changed the maximum or minimum length of rebreathing loop and VT set at 12 ml/kg. After establishing steady-state conditions (15 min), they measured cardiac output using CO2 rebreathing and thermodilution 

**Results:** When VT was set at 12 ml/kg, cardiac output with the CO2 rebreathing technique correlated moderately with that measured by thermodilution (y = 1.02x, R = 0.63; bias, 0.28 l/min; limits of agreement, −1.78 to +2.34 l/min), regardless of ventilatory mode, oxygen concentration, or positive end-expiratory pressure. However, at a lower VT of 6 ml/kg, the CO2 rebreathing technique underestimated cardiac output compared with thermodilution (y = 0.70x; R = 0.70; bias, −1.66 l/min; limits of agreement, −3.90 to +0.58 l/min). When the loop was fully retracted, the CO2 rebreathing technique overestimated cardiac output.

**Conclusions:** Although cardiac output was underreported at small VT values, cardiac output measured by the CO2 rebreathing technique correlates fairly with that measured by the thermodilution method.

**Subjects and Methods**

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

**Patients**

Twenty-five adult patients aged 48–78 yr (median, 61 yr) who had undergone cardiac surgery (table 1) were enrolled in this study. Enrollment criteria were (1) insertion of a Swan-Ganz catheter; (2) stable hemodynamics from each patient.

Although there is controversy over the cost benefit of pulmonary artery catheterization, cardiac output (CO) is commonly monitored when treating critically ill patients. Recently, a new device, the NICO2 system (Noavametrix Medical Systems Inc., Wallingford, CT), has been developed to measure CO noninvasively using partial carbon dioxide (CO2) rebreathing. This device uses periodic partial CO2 rebreathing to create a CO2 disturbance, which is then used in a differential Fick CO2 equation to calculate CO.

There have been few studies to investigate how well the results obtained by CO2 rebreathing correlate with those obtained by the conventional thermodilution technique. Furthermore, it remains to be clarified which ventilatory or hemodynamic parameters affect the measured values when the CO2 rebreathing technique is used. Because noninvasive CO measurement depends on CO2 rebreathing and assumes constant dead space and mixed venous CO2 content through the CO2 rebreathing procedure, we suspected that change in ventilatory settings might affect accuracy of the CO measurement. Consequently, we performed a prospective comparative study to evaluate the effects of tidal volume (VT), ventilatory mode, inspired oxygen fraction (FiO2), and positive end-expiratory pressure (PEEP) on the accuracy of the measurement. The NICO2 system uses a rebreathing loop in which volume is adjustable according to tidal volume. We suspected that a too-short loop may affect the accuracy due to poor signal-to-noise ratio. Therefore, we investigated, as a factor of the machine itself, the effect of adjusting the length of the rebreathing loop.

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Table 1. Patient Profile

| No. of patients | 25 |
| M/F           | 19/6 |
| Age (yr)      | 61 ± 9 |
| Height (cm)   | 163 ± 7 |
| Body Weight (kg) | 63 ± 11 |
| Background diseases |
| Coronary artery disease | 11 |
| Acquired valve disease | 8 |
| Thoracic aortic aneurysm or dissection | 4 |
| Miscellaneous | 2 |

Measurements

We measured CO using two methods. Values for CO derived from a thermodilution technique (CO\textsubscript{2}ND) were obtained using a Swan-Ganz catheter (7.5 French; Abbott Laboratories, North Chicago, IL). Injection of 10 ml cold saline (0°C) was performed in triplicate, and the values were averaged. Because the CO measurement varies depending on when in the respiratory cycle the measurement is initiated,\textsuperscript{6} we standardized the timing of bolus injection after the first half of the expiratory phase. We confirmed the injection timing by watching the waveform of airway pressure versus time on the graphic monitor of a ventilator (Bird Corp., Palm Springs, CA). Noninvasive measurement of CO (CO\textsubscript{2}ND) was performed with a NICO\textsubscript{2} system (software version 3.1, fast mode). This procedure has been presented in detail elsewhere.\textsuperscript{3,4} Briefly, on a breath-by-breath basis, CO\textsubscript{2} production (V\textsubscript{CO2}) is calculated from the flow and CO\textsubscript{2} concentration at the airway opening. Then, to establish the relation between V\textsubscript{CO2} and CO, the Fick principle is applied as follows:

\[
\dot{V}_{CO2} = CO \times (C\dot{V}_{CO2} - C_{aco2}),
\]

where C\dot{V}_{CO2} and C_{aco2} represent the CO\textsubscript{2} content in mixed venous and arterial blood, respectively. In the NICO\textsubscript{2} system, CO\textsubscript{2} rebreathing is performed for 50 s every 3 min using a disposable sensor (Novametrix Medical Systems). A brief period of CO\textsubscript{2} rebreathing caused a change in Paco\textsubscript{2} and a change in V\textsubscript{CO2} but little or no change in C\dot{V}_{CO2} in anesthetized dogs,\textsuperscript{3} probably because the quantity of CO\textsubscript{2} stores in the body is large, and new equilibrium levels are attained after 20–30 min.\textsuperscript{3} Assuming that CO and C\dot{V}_{CO2} remain constant during the CO\textsubscript{2} rebreathing procedure, the following equation can be substituted for the previous one:

\[
\Delta \dot{V}_{CO2} = CO \times (-\Delta \text{C}_{aco2}),
\]

where \Delta \dot{V}_{CO2} is the change in V\textsubscript{CO2} between normal breathing and CO\textsubscript{2} rebreathing, and \Delta \text{C}_{aco2} is the change in arterial CO\textsubscript{2} content. Assuming here that dead space fraction (V\textsubscript{E}/V\textsubscript{T}) remains constant during the CO\textsubscript{2} rebreathing and that \Delta \text{C}_{aco2} is proportional to changes in arterial carbon dioxide pressure (Paco\textsubscript{2}) and end-tidal CO\textsubscript{2} pressure (PET\textsubscript{CO2}), the following equation can be plotted:

\[
CO = \Delta \dot{V}_{CO2} / S \times \Delta \text{PETCO2},
\]

where \Delta \text{PETCO2} is the change in PET\textsubscript{CO2} between normal breathing and CO\textsubscript{2} rebreathing, and S is the slope of the CO\textsubscript{2} dissociation curve from hemoglobin. The constant S can be expressed as a function of hemoglobin concentration and Paco\textsubscript{2} as follows:

\[
S = (1.34 \times [Hb] + 18.34) / (1 + 0.193 \times \text{Paco2})
\]

\[
\text{[ml CO2} \cdot 1^{-1} \text{blood} \cdot \text{mmHg}^{-1}],
\]

where [Hb] is hemoglobin concentration.

Before the start of the study protocol, the NICO\textsubscript{2} system was calibrated for zero CO\textsubscript{2} by opening the system to the atmosphere, according to the manufacturer’s instructions. We entered the results of arterial oxygen pressure (Pao\textsubscript{2}), Paco\textsubscript{2}, Fi\textsubscript{O2} (0.4–0.7), and hemoglobin concentrations (7.9–11.9 g/dl) into the machine when each patient was under the baseline ventilation. Inclusion of these parameters is used to calculate shunt fraction (Pao\textsubscript{2} and Fi\textsubscript{O2}), alveolar dead space (Paco\textsubscript{2}), and the slope of the CO\textsubscript{2} dissociation curve (hemoglobin).\textsuperscript{3,4}

Study Protocol

We used Bird 8400STi ventilators (Bird Corp.). At the time of admission to the intensive care unit, initial ventilatory settings were as follows: synchronized intermittent mandatory ventilation mode; volume-controlled ventilation (VCV); inspired V\textsubscript{T} of 10 ml/kg; decelerating flow pattern; respiratory rate of 10–12 breaths/min; and inspiratory time of 1.0 s. The Fi\textsubscript{O2} was adjusted by attending physicians to maintain a Pao\textsubscript{2} greater than 100 mmHg. Baseline PEEP was set at 4 cm H\textsubscript{2}O in 23 patients; because of hypoxemia, the remaining 2 patients needed PEEP of 6 and 8 cm H\textsubscript{2}O, respectively. With the patients maintained in the supine position, sedated with continuous intravenous injection of propofol (2–3 mg · kg\textsuperscript{-1} · h\textsuperscript{-1}), and paralyzed with bolus administration of vecuronium bromide (4–8 mg), we started the measurement protocol.

In random order, we applied six ventilatory settings to all of the 25 patients, and then we applied three additional settings in a fixed order (table 2). To test the effects of ventilatory mode and V\textsubscript{T}, we chose VCV with inspired V\textsubscript{T} of 12 or 6 ml/kg and pressure-controlled ventilation (PCV) with the same V\textsubscript{T} settings. The Fi\textsubscript{O2} and respiratory rate were fixed identical to baseline. The PEEP was also fixed identical to the baseline measurement (4 cm H\textsubscript{2}O in 23 patients, 6 cm H\textsubscript{2}O in 1, and 8 cm H\textsubscript{2}O in 1). The inspiratory time was set to 1.0 s for both VCV and PCV. The level of pressure control was adjusted

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to obtain the same $V_{T}$ during VCV. The rebreathing loop was sized according to the manufacturer’s instructions recommended for set tidal volume of 12 ml/kg.

Ventricular infusion was stopped. When the patient recovered stable spontaneous breathing, we switched the ventilatory mode to continuous positive airway pressure of 4 cm H2O plus pressure-support ventilation (PSV) of 10 cm H2O.

After establishing steady-state conditions (approximately 15 min) at each setting, we measured both CO2 and CO2. We limited ourselves perform only nine measurements (one measurement for each ventilating setting) per patient. Arterial blood samples were analyzed with a calibrated blood gas analyzer (ABL 50s, Radiometer, Copenhagen, Denmark). Hemodynamic data were also recorded. $V_{T}/V_{T}$ and venous admixture fraction

```
Table 2. Ventilatory Settings

<table>
<thead>
<tr>
<th>Ventilatory mode</th>
<th>VCV</th>
<th>VCV</th>
<th>PCV</th>
<th>PCV</th>
<th>VCV</th>
<th>VCV</th>
<th>PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspired tidal volume (ml/kg)</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>PaO2</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Rebreathing loop: † Long (400 ml) † Short (150 ml)

No. of patients: 25 25 25 25 25 25 17 17 23

Median values are presented for fraction of inspired oxygen (FiO2) and positive end-expiratory pressure (PEEP).

VCV = volume-controlled ventilation; PCV = pressure-controlled ventilation; PSV = pressure-support ventilation.

* In two patients, PEEP of 8 and 9 cm H2O was used because of hypoxemia. † The rebreathing loop was sized according to the manufacturer’s instructions recommended for set tidal volume of 12 ml/kg.

```

Table 3. Respiratory and Hemodynamic Parameters at Each Ventilatory Setting

<table>
<thead>
<tr>
<th>Ventilatory Setting</th>
<th>VCV</th>
<th>VCV</th>
<th>PCV</th>
<th>PCV</th>
<th>VCV</th>
<th>VCV</th>
<th>PSV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{T}$ (ml/kg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>13.0 ± 0.6</td>
<td>13.2 ± 0.8</td>
<td>12.9 ± 0.7</td>
<td>13.1 ± 0.8</td>
<td>8.8 ± 2.6†</td>
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</tr>
<tr>
<td>$V_{E}$ (l.min⁻¹.kg⁻¹)</td>
<td>0.13 ± 0.01</td>
<td>0.13 ± 0.01</td>
<td>0.13 ± 0.01</td>
<td>0.14 ± 0.04</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PIP (cm H2O)</td>
<td>27.5 ± 5.8</td>
<td>27.0 ± 6.4</td>
<td>27.2 ± 5.8</td>
<td>36.6 ± 7.1</td>
<td></td>
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</tr>
<tr>
<td>P/C (cm H2O)</td>
<td>4.2 ± 0.9</td>
<td>4.2 ± 0.9</td>
<td>4.2 ± 0.9</td>
<td>14.0 ± 1.7</td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7.45 ± 0.04</td>
<td>7.44 ± 0.05</td>
<td>7.44 ± 0.05</td>
<td>7.42 ± 0.04</td>
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<td></td>
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</tr>
<tr>
<td>PaCO2 (mmHg)</td>
<td>37.7 ± 5.4</td>
<td>39.2 ± 6.4</td>
<td>40.4 ± 6.4</td>
<td>38.8 ± 7.5</td>
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</tr>
<tr>
<td>P/F</td>
<td>292 ± 87</td>
<td>299 ± 88</td>
<td>376 ± 87†</td>
<td>357 ± 113†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate (mM)</td>
<td>2.0 ± 1.2</td>
<td>2.1 ± 1.2</td>
<td>2.1 ± 1.1</td>
<td>2.1 ± 1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO2 (l/min)</td>
<td>3.5 ± 1.2</td>
<td>5.0 ± 1.5</td>
<td>5.1 ± 1.5</td>
<td>5.3 ± 1.5</td>
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<td></td>
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</tr>
<tr>
<td>CO2 (l/min)</td>
<td>5.1 ± 1.36</td>
<td>5.60 ± 1.40</td>
<td>5.30 ± 1.45</td>
<td>4.82 ± 1.24</td>
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<tr>
<td>CO2 (l/min)</td>
<td>3.0 ± 0.3</td>
<td>3.1 ± 0.5</td>
<td>3.1 ± 0.4</td>
<td>3.0 ± 0.4</td>
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<tr>
<td>PTPCO2 (mmHg)</td>
<td>34.5 ± 3.8</td>
<td>35.4 ± 4.9</td>
<td>35.7 ± 4.7</td>
<td>36.7 ± 5.3</td>
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<tr>
<td>VD/VT</td>
<td>0.43 ± 0.09</td>
<td>0.43 ± 0.10</td>
<td>0.45 ± 0.13</td>
<td>0.51 ± 0.12</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q/VQ</td>
<td>0.05 ± 0.03</td>
<td>0.06 ± 0.04</td>
<td>0.03 ± 0.03</td>
<td>0.04 ± 0.03</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>HR (beats/min)</td>
<td>92 ± 7</td>
<td>96 ± 9</td>
<td>93 ± 8</td>
<td>94 ± 8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BP (mmHg)</td>
<td>79 ± 9</td>
<td>77 ± 10</td>
<td>79 ± 11</td>
<td>78 ± 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA (mmHg)</td>
<td>19.3 ± 5.6</td>
<td>18.6 ± 5.5</td>
<td>19.0 ± 6.1</td>
<td>20.2 ± 6.6</td>
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<tr>
<td>CVP (mmHg)</td>
<td>7.9 ± 2.5</td>
<td>7.5 ± 2.7</td>
<td>7.6 ± 2.6</td>
<td>10.4 ± 2.4†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>9.8 ± 2.2</td>
<td>9.6 ± 2.5</td>
<td>10.1 ± 2.5</td>
<td>11.8 ± 2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVR (dyn.s.cm⁻³)</td>
<td>158 ± 89</td>
<td>153 ± 100</td>
<td>143 ± 93</td>
<td>185 ± 105</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SVR (dyn.s.cm⁻³)</td>
<td>1,162 ± 372</td>
<td>1,145 ± 379</td>
<td>1,191 ± 315</td>
<td>1,237 ± 405</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVCO2 (%)</td>
<td>72 ± 7</td>
<td>73 ± 7</td>
<td>73 ± 7</td>
<td>73 ± 7</td>
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</tr>
</tbody>
</table>

* P < 0.05 versus volume-controlled ventilation (VCV)–large tidal volume (VT), pressure-controlled ventilation (PCV)–large VT, fraction of inspired oxygen (FiO2) 1.0, high positive end-expiratory pressure (PEEP), long loop, short loop, and pressure-support ventilation (PSV). † P < 0.05 versus other ventilatory settings. ‡ P < 0.05 versus VCV–small VT, PCV–small VT, and PSV. § P < 0.05 versus VCV–large VT, PCV–large VT, PCV–small VT, FiO2 1.0, and short loop, and PSV. †† P < 0.05 versus VCV–large VT and short loop. ††† P < 0.05 versus PCV–large VT and FiO2 1.0. ††† P < 0.05 versus VCV–large VT, PCV–large VT, high PEEP, and PSV.

Vν = minute ventilation; PIP = peak inspiratory pressure; PaCO2 = arterial carbon dioxide tension; P/F = ratio of arterial oxygen tension to FiO2; CO2 = cardiac output with thermolodation; CO2 = cardiac output with carbon dioxide rebreathing; CO2 = carbon dioxide production; PECTCO2 = end-tidal carbon dioxide pressure; VVT = dead-space fraction; Q/VQ = venous admixture fraction; HR = heart rate; BP = mean artery pressure; PA = mean pulmonary artery pressure; CVP = central venous pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; SVR = systemic vascular resistance; SVCO2 = mixed venous oxygen saturation.

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(\dot{Q}_S/\dot{Q}_T) were calculated using the following equations

\[ \frac{V_D}{V_T} = 1 - (0.863 \cdot \dot{V}_{CO_2})/(\dot{V}_E \cdot P_{aco_2}) \] (5)

and

\[ \frac{\dot{Q}_S}{\dot{Q}_T} = (C_c'O_2 - C_aO_2)/(C_c'O_2 - C_{vO_2}), \] (6)

where \( \dot{V}_E \) is minute ventilation, \( C_c'O_2 \) is oxygen content at the pulmonary capillary, \( C_aO_2 \) is arterial oxygen content, and \( C_{vO_2} \) is mixed venous blood oxygen content. Assuming that pulmonary capillary blood is fully saturated with oxygen and that oxygen content is roughly proportional to oxygen saturation, the second equation can be revised as follows:

\[ \frac{\dot{Q}_S}{\dot{Q}_T} = (1 - Sao_2)/(1 - S_{vO_2}), \] (7)

where \( Sao_2 \) and \( S_{vO_2} \) are oxygen saturation at the artery and mixed venous blood, respectively.

**Statistical Analysis**

Data are presented as mean ± 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.\(^\text{12,13}\) To investigate which parameters contributed to the discrepancy between \( CO_{NI} \) and \( CO_{TD} \), we also performed linear multiple regression analysis among \( F_{io2} \), \( V_T \), \( V_E \), \( PEEP \), peak inspiratory pressure, \( pH \), \( PaO_2 \), \( P_{aco_2} \), \( PETCO_2 \), \( V_{CO_2} \), and \( S_{vO_2} \). Statistical significance was set at \( P < 0.05 \).

**Results**

Blood gas and hemodynamic results are summarized in table 3. Minute ventilation was stable at all 12-ml/kg \( V_T \) settings. Regardless of ventilatory mode, the 6-ml/kg \( V_T \) settings resulted in higher \( PaCO_2 \), higher \( PETCO_2 \), and less \( V_{CO_2} \), compared with the 12-ml/kg \( V_T \) settings. During PSV, \( V_T \) values (8.8 ± 2.6 ml/kg) decreased to between those for 12- and 6-ml/kg \( V_T \) settings, whereas minute ventilation was similar to that at the 12-ml/kg \( V_T \) settings. \( CO_{TD} \) values were similar at each 12-ml/kg \( V_T \) setting, although \( CO_{TD} \) values at the 6-ml/kg \( V_T \) settings were slightly larger in comparison. At high PEEP, \( CO_{TD} \) values were lower.
Levels of pressure control were 24±7 (16–36) cm H₂O with inspired Vₚ of 12 ml/kg and 13±4 (8–22) cm H₂O with Vₚ of 6 ml/kg. As a result, there was no difference in peak inspiratory pressure for VCV and PCV at either Vₚ setting (table 3).

Results of Bland-Altman analysis and linear regression analysis are shown in table 4 for each ventilatory setting. When Vₚ values were the same, Bland-Altman analysis characteristics between CO_TD and CO_NI were almost identical (bias and precision: 12-ml/kg Vₚ VCV, 0.18 and 1.04; 12-ml/kg Vₚ PCV, 0.37 and 1.17; 6-ml/kg Vₚ VCV, −1.67 and 1.06; and 6-ml/kg Vₚ PCV, −1.64 and 1.19, table 4). Consequently, for the same Vₚ values, CO data during both VCV and PCV were analyzed together.

When Vₚ was 12 ml/kg, a fair correlation was observed between CONI and COTD (fig. 1). The slope of linear regression was 1.02 (R = 0.63, fig. 1), and bias was small (0.28 l/min, fig. 2), although limits of agreement were wide (−1.78 to +2.34 l/min, fig. 2). This is the case with ventilatory setting of high FIO₂ or high PEEP (table 4). By contrast, when Vₚ was small (6 ml/kg), the CO_NI underestimated the CO_TD with a slope of 0.70 (fig. 1), a bias of −1.66 l/min, and limits of agreement of −3.9 to +0.58 l/min (fig. 2). During PSV, the correlation between CO_NI and CO_TD was also close to identical (slope = 1.07, R = 0.63, bias = 0.52 l/min, table 4). With the loop maximally expanded, the CO_NI correlated moderately with CO_TD (slope = 1.05, bias = 0.48, table 4); however, with the loop fully retracted, CO_NI overestimated CO_TD (slope = 1.23, bias = 1.30, table 4). Linear multiple regression analysis revealed that the setting most affecting the discrepancy between CO_NI and CO_TD was minute ventilation (R = 0.616).

Figure 3 shows a relation between changes in cardiac output measurements obtained by CO₂ rebreathing technique and those obtained by thermodilution technique when positive end-expiratory pressure was increased. Ventilatory settings are volume-controlled and 12 ml/kg tidal volume. When positive end-expiratory pressure was increased from 4.2 to 14.0 cm H₂O, both CO_TD and CO_NI decreased. Both values moved in identical directions in all patients but one. Equations and result curves for linear regression analysis are also shown.

**Discussion**

The main findings of this study are as follows. (1) During mechanical ventilation with large constant Vₚ or during PSV, CO measurements obtained by CO₂ rebreathing technique correlate with those obtained by thermodilution method. (2) When minute ventilation is large, the accuracy of the CO₂ rebreathing technique is not affected by a selection of VCV, PCV, spontaneous breathing (PSV), PEEP, or FIO₂. (3) When Vₚ and minute ventilation are reduced, the CO₂ rebreathing technique...
underreports CO. (i) CO measurements are accurate when the rebreathing loop is maximally expanded but is overestimated when the loop is fully retracted.

**Clinical Implications**

Using partial CO₂ rebreathing, CO can be measured noninvasively. However, there have been few clinical reports, on the accuracy of this technique. We need to confirm that it provides effective monitoring for critically ill patients and discover parameters that might affect accuracy. Our results suggest that at a large Vₚ setting and with constant minute ventilation, CO measurements obtained from this technology correlate fairly with those from the thermodilution method. When inspired Vₚ is set at 12 ml/kg and respiratory rate is set at 10–12 breaths/min, which results in an actual minute ventilation of 0.13–0.14 l·min⁻¹·kg⁻¹, the linear regression slopes for CO₉NI and CO₉TD were almost identical (1.01:1.05). Bias analysis also indicated small bias and moderate precision (fig. 2), while accuracy was consistent regardless of ventilatory mode (VCV or PCV), PEEP, or FIO₂. Correlation of results from CO₉NI and CO₉TD was also satisfactory during PSV (table 4). These observations suggest that this CO₂ rebreathing technique is reliable both with large constant Vₚ and during PSV. In addition, because the maximally expanded loop did not affect accuracy (table 4), rather than it being necessary to strictly adjust the loops, there may be some leeway in adjusting them for the maximal expected Vₚ. In contrast, when the rebreathing loop was set too short for a given Vₚ, CO₉NI measurements had greater values than those obtained by CO₉TD (table 4). This may be due to the small changes in PETCO₂ that occur with the shortest loop during CO₂ rebreathing, when a slight amount of noise would likely generate large errors.

To our surprise, when Vₚ was small (6 ml/kg), CO₉NI measurements showed consistently lower values than those produced by CO₉TD, resulting in a linear regression slope of 0.70 and a negative value of bias (figs. 1 and 2). Low Vₚ (6 ml/kg) is currently recommended for ventilator management in acute respiratory failure, so attention needs to be drawn to the lack of reliable measurement using CO₉NI at the low Vₚ setting. Reasons for these discrepant results have not been clarified, but there are several possible explanations.

First, after we adjusted the length of rebreathing loops for high Vₚ, when Vₚ was decreased, results may have been affected because the loop had become relatively too long. However, we found that the maximally expanded loop did not make CO₉NI measurements less accurate (table 4). This finding suggests that the combination of long loop and small Vₚ are unlikely to impair the accuracy of CO₉NI.

Second, at small Vₚ settings, PETCO₂ increased to almost 60 mmHg in several patients. The software (version 3.1) that we used suspends rebreathing when the base-line PETCO₂ is greater than 65 mmHg or PETCO₂ is greater than 80 mmHg during CO₂ rebreathing. It could be that the linearity between CaCO₂ and PETCO₂ is less accurate when PETCO₂ is extremely high.

Finally, the assumed constancy of mixed venous CO₂ content may be false for some time after Vₚ and minute ventilation are changed. The measured values of VCO₂ were smaller at low Vₚ than at high Vₚ (table 3). Although we waited for 15 min, this may not have been enough time for CO₂ stores to reach a steady state, which is 100 times larger than oxygen stores. In addition, the time course of the increase in PaCO₂ after abrupt decrease of ventilation is much slower than the rate of decrease after abrupt increase of ventilation. These facts suggest that CO₂ stores and mixed venous CO₂ content may continue to change even after PaCO₂ and PETCO₂ seem to have reached plateau values. If this is the case, the accuracy of the CO₂ rebreathing technique may be compromised when there are abrupt changes in minute ventilation and VCO₂. Further study is needed to find out exactly what happens after these sudden changes and whether these mechanisms affect the accuracy of the CO₂ rebreathing technique.

**Limitations**

The current study has several limitations. First, the patients in our study were sedated and paralyzed initially, resulting in constant Vₚ and stable VCO₂. Even during PSV, they breathed quietly with small variation in Vₚ. Therefore, our results may not be directly extrapolated to populations of patients whose Vₚ and VCO₂ are changing. Secondly, our patients had relatively normal lung mechanics (respiratory system compliance, 45.4 ± 12.8 ml/cmH₂O; resistance, 11.2 ± 4.1 cm H₂O·s·l⁻¹), and their hemodynamics had been stabilized at time of entry into the study. In more seriously compromised patients, the accuracy may be quite different. To corroborate the relevance of our findings for acutely ill and ventilator-dependent patients, it is prudent to perform further studies. Third, we did not examine how the ventilatory pattern alterations affect the assumptions underlying the fundamental equation of the NICO₂ technique: e.g., constant Vₚ/Vₚ, constant CO₂, and constant mixed venous CO₂ content during the CO₂ rebreathing procedure. Finally, it remains to be clarified whether the impaired accuracy of CO₉NI with small Vₚ results from small Vₚ itself or from reduced minute ventilation during PSV, when Vₚ was smaller (8.8 ± 2.6 ml/kg) but minute ventilation was similar to that at the high Vₚ settings, CO₉NI and CO₉TD values correlated fairly (y = 1.07x); we speculate that if normocapnia is sustained by adjusting the respiratory rate, the accuracy of the CO₉NI technique can be maintained at small Vₚ.

In conclusion, noninvasive measurement of CO using CO₂ rebreathing is reliable with a bias of less than 0.5 l/min and a precision of 1 l/min when the tidal

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volume is large and constant, regardless of ventilatory modes. However, at small tidal volume, the rebreathing system underreports CO₂, compared with the conventional thermodilution technique.

References