

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 ($y = 0.70x$; correlation coefficient, 0.34; 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,¹ a less expensive device has been developed to noninvasively measure cardiac output (CO) based on the partial carbon dioxide rebreathing technique.^{2,3} 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).⁴ 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 (\dot{V}_{CO_2}) and the change in end-tidal carbon dioxide pressure (P_{ETCO_2}) when periodic partial carbon dioxide rebreathing creates a carbon dioxide disturbance.² Therefore, the accuracy of the technique depends on accurate measurement of both the change in \dot{V}_{CO_2} and the change in P_{ETCO_2} . Once a patient starts breathing spontaneously, \dot{V}_{CO_2} and P_{ETCO_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 P_{ETCO_2} . Therefore, we designed this prospective study with three objectives: to investigate (1) whether small V_T or small minute ventilation (\dot{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-

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Table 1. Patient Profile

No. patients	25
Male/female	21/4
Age, yr	60 ± 14
Height, cm	162 ± 7
Body weight, kg	63 ± 11
Background diseases	
Coronary artery disease	14
Acquired valve disease	10
Constrictive pericarditis	1

tent mandatory ventilation (SIMV) and pressure support ventilation (PSV); and (3) how respiratory efforts change during carbon dioxide rebreathing when spontaneous breathing is present. Our hypothesis is that the partial carbon dioxide rebreathing technique is less accurate when \dot{V}_E is unstable or when patients are spontaneously breathing and that the carbon dioxide rebreathing increases respiratory efforts in spontaneous breathing patients.

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.⁴ 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,⁵ we measured the effective static compliance and resistance of the respiratory system.

Measurements

We measured CO using two methods: thermodilution (CO_{TD}) and noninvasive partial carbon dioxide rebreathing technique (CO_{NI}). CO_{TD} 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.⁶ CO_{NI} measurement was performed with the partial carbon dioxide rebreathing technique (NICO₂ software version 3.1, fast mode; Novamatrix Medical Systems Inc., Wallingford, CT). This procedure has been described in detail elsewhere.^{1,2} Briefly, \dot{V}_{CO_2} is calculated on a breath-by-breath basis, and the differential Fick equation is applied to establish the relation between \dot{V}_{CO_2} and CO as follows:

$$\dot{V}_{CO_2} = CO \times (C\bar{v}CO_2 - Caco_2)$$

where $C\bar{v}CO_2$ represents the carbon dioxide content in mixed venous blood, and $Caco_2$ 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:

$$\Delta\dot{V}_{CO_2} = CO \times (\Delta C\bar{v}CO_2 - \Delta Caco_2)$$

where $\Delta\dot{V}_{CO_2}$ is the change in \dot{V}_{CO_2} between normal breathing and carbon dioxide rebreathing, $\Delta C\bar{v}CO_2$ is the change in mixed venous carbon dioxide content, and $\Delta Caco_2$ is the change in arterial carbon dioxide content. Then, assuming that $C\bar{v}CO_2$ also remains constant during the carbon dioxide rebreathing procedure, the following equation is introduced:

$$\Delta\dot{V}_{CO_2} = CO \times (-\Delta Caco_2)$$

When end-capillary content (C_{CCO_2}) is used in place of $Caco_2$, 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:

$$\Delta\dot{V}_{CO_2} = PCBF \times (-\Delta C_{CCO_2})$$

Assuming here that ΔC_{CCO_2} is proportional to changes in P_{ETCO_2} , the following equation can be plotted:

$$PCBF = \Delta\dot{V}_{CO_2} / (S \times \Delta P_{ETCO_2}),$$

where ΔP_{ETCO_2} is the change in P_{ETCO_2} 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 (\dot{Q}_s); then, CO is expressed in the following equation:

$$CO = PCBF / (1 - \dot{Q}_s / \dot{Q}_T)$$

where \dot{Q}_s / \dot{Q}_T 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 (P_{aO_2}) and F_{IO_2} for different levels of shunt.³ P_{aO_2} is a function of

Table 2. Respiratory and Hemodynamic Parameters during Controlled Mechanical Ventilation

Ventilatory Setting	V _T 12 ml/kg RR 10 breaths/min (n = 25)	V _T 6 ml/kg RR 20 breaths/min (n = 25)	V _T 6 ml/kg RR 10 breaths/min (n = 25)
\dot{V}_E , l · min ⁻¹ · kg ⁻¹	0.13 ± 0.01	0.14 ± 0.01	0.07 ± 0.01††
pH	7.46 ± 0.04	7.41 ± 0.05*	7.33 ± 0.04*†
Paco ₂ , mmHg	35.5 ± 4.5	41.1 ± 5.4*	51.9 ± 6.8*†
P/F	319 ± 109	289 ± 95	263 ± 68
CO _{TD} , l/min	5.51 ± 1.23	5.75 ± 1.25	6.13 ± 1.45
CO _{NI} , l/min	5.60 ± 1.13	5.08 ± 1.09	4.40 ± 1.09*
\dot{V}_{CO_2} , ml · min ⁻¹ · kg ⁻¹	2.9 ± 0.5	2.9 ± 0.4	2.1 ± 0.7*†
PETCO ₂ , mmHg	33.0 ± 4.5	36.7 ± 5.3	47.2 ± 7.0*†
V _D /V _T	0.41 ± 0.08	0.50 ± 0.07*	0.47 ± 0.12
\dot{Q}_S/\dot{Q}_T	0.06 ± 0.04	0.09 ± 0.05	0.10 ± 0.07

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

CO_{NI} = cardiac output with carbon dioxide rebreathing; CO_{TD} = cardiac output with thermodilution; Paco₂ = arterial carbon dioxide tension; PETCO₂ = end-tidal carbon dioxide pressure; P/F = ratio of arterial oxygen tension to inspired oxygen fraction; \dot{Q}_S/\dot{Q}_T = venous admixture fraction; RR = respiratory rate; \dot{V}_{CO_2} = carbon dioxide production; V_D/V_T = dead-space fraction; V_E = minute ventilation; V_T = tidal volume.

arterial blood oxygen saturation (SaO₂), which is noninvasively 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 pressure (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 V_T 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 V_T of 12 ml/kg and respiratory rate of 10 breaths/min; (2) V_T of 6 ml/kg and respiratory rate of 20 breaths/min; and (3)

V_T of 6 ml/kg and respiratory rate of 10 breaths/min. The first and second settings should result in identical \dot{V}_E , and the last setting should result in half the \dot{V}_E value. At each setting, the rebreathing loop was size adjusted according to the manufacturer's instructions recommended for a V_T 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 V_T and \dot{V}_E 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 (V_D/V_T) and venous admixture fraction (\dot{Q}_S/\dot{Q}_T) were calculated as described elsewhere.⁴

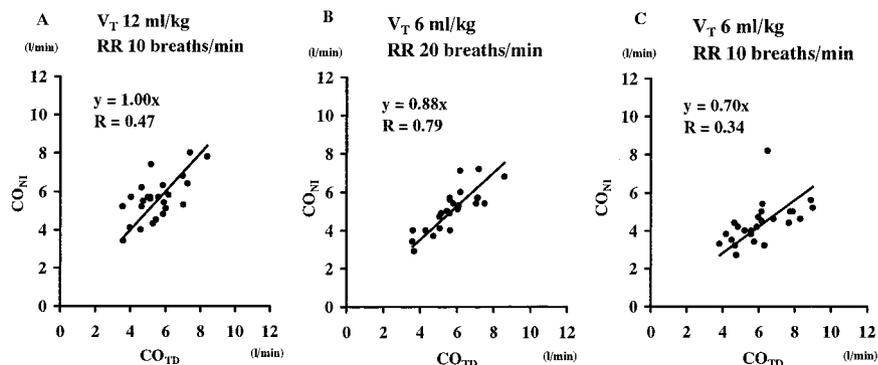
In the second protocol, we examined the measurement of CO when there was spontaneous breathing effort. We stopped the infusion of vecuronium and decreased the propofol infusion rate to 0.5 mg · kg⁻¹ · h⁻¹. When the patient recovered spontaneous breathing and satisfied our extubation criteria (recovery of cough reflex; V_T ≥ 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 3. Results of Bland-Altman Analysis and Regression Analysis during Controlled Mechanical Ventilation

Ventilatory Setting	V _T 12 ml/kg RR 10 breaths/min (n = 25)	V _T 6 ml/kg RR 20 breaths/min (n = 25)	V _T 6 ml/kg RR 10 breaths/min (n = 25)
Bias, l/min	0.09	-0.67	-1.73
Precision, l/min	1.00	0.73	1.27
Limits of agreement, l/min	-1.91 to +2.09	-2.13 to +0.79	-4.27 to +0.81
Slope of linear regression	1.00	0.88	0.70
Correlation coefficient, R	0.47	0.79	0.34

V_T = tidal volume; RR = respiratory rate.

Fig. 1. Agreement between cardiac output measurements obtained by carbon dioxide rebreathing (CO_{NI}) and those obtained by thermodilution technique (CO_{TD}) during controlled mechanical ventilation. (A) Large tidal volume (V_T, 12 ml/kg) with respiratory rate (RR) of 10 breaths/min. (B) Small tidal volume (6 ml/kg) with respiratory rate of 20 breaths/min. (C) Small tidal volume (6 ml/kg) with respiratory rate of 10 breaths/min. Equations and result curves for linear regression analysis are also shown.



ventilatory support: (1) SIMV plus PSV, mandatory breath rate of 5 breaths/min, mandatory V_T 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 V_T setting of 12 ml/kg; at the other setting, the loop was fully retracted (150 ml). After establishing steady state, we measured both CO_{TD} and CO_{NI}. Because V_T, respiratory rate, and \dot{V}_E increased according to the stimulus of carbon dioxide rebreathing, we recorded V_T, respiratory rate, and \dot{V}_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.

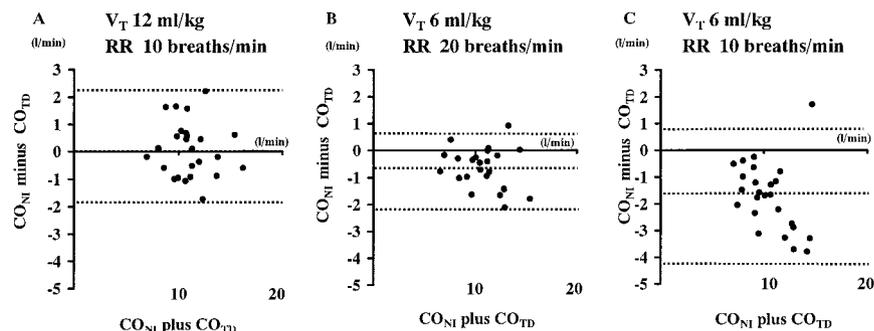
Statistical Analysis

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.⁷ Statistical significance was set at $P < 0.05$.

Results

Patients had respiratory system compliance of 48.4 ± 8.7 ml/cm H₂O and resistance of 9.6 ± 2.8 cm H₂O \cdot s.

Fig. 2. Bias analysis comparing cardiac output measurement results during controlled mechanical ventilation, from partial carbon dioxide rebreathing (CO_{NI}) and thermodilution (CO_{TD}) methods. (A) Large tidal volume (V_T, 12 ml/kg) with respiratory rate (RR) of 10 breaths/min. (B) Small tidal volume (6 ml/kg) with respiratory rate of 20 breaths/min. (C) Small tidal volume (6 ml/kg) with respiratory rate of 10 breaths/min. Dotted lines show bias and limits of agreement between the two methods.



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 \dot{V}_E was identical, there was higher PaCO₂ and V_D/V_T at the ventilatory setting of V_T of 6 ml/kg and respiratory rate of 20 breaths/min than at V_T of 12 ml/kg and respiratory rate of 10 breaths/min. When \dot{V}_E was set to a smaller value (V_T of 6 ml/kg and respiratory rate of 10 breaths/min), PaCO₂ and P_{ET}CO₂ were significantly higher, and CO_{NI} and $\dot{V}CO_2$ were significantly lower, compared with the other two settings that provided twice as much \dot{V}_E . The values of CO_{TD}, a ratio of Pao₂ to Fio₂, and \dot{Q}_s/\dot{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 \dot{V}_E was high, regardless of the V_T (figs. 1 and 2). However, when \dot{V}_E was set at half, CO_{NI} underestimated CO ($y = 0.70x$; 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 V_T 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

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

Ventilatory Setting	SIMV/PSV (n = 25)		PSV/Long Loop (n = 25)		PSV/Short Loop (n = 25)	
	Normal breathing	CO ₂ rebreathing	Normal breathing	CO ₂ rebreathing	Normal breathing	CO ₂ rebreathing
\dot{V}_E , l · min ⁻¹ · kg ⁻¹	0.11 ± 0.02	0.14 ± 0.03*	0.11 ± 0.02	0.16 ± 0.03*	0.11 ± 0.03	0.13 ± 0.03*‡
V _T , ml/kg	6.9 ± 2.5	8.5 ± 3.1*	9.3 ± 2.3†	11.2 ± 2.3*†	9.4 ± 2.2†	10.4 ± 2.2†
RR, breaths/min	12.3 ± 3.1	15.8 ± 3.5*	12.4 ± 3.3	16.1 ± 3.5*	12.3 ± 2.8	13.5 ± 3.2‡
pH	7.38 ± 0.03		7.38 ± 0.03		7.38 ± 0.03	
Paco ₂ , mmHg	44.2 ± 4.1		44.1 ± 4.6		44.2 ± 3.8	
P/F	286 ± 101		289 ± 99		279 ± 97	
CO _{TD} , l/min	5.96 ± 1.33		6.32 ± 1.59		6.07 ± 1.42	
CO _{NI} , l/min	6.14 ± 1.46		7.12 ± 1.95		7.27 ± 2.24	
\dot{V}_{CO_2} , ml · min ⁻¹ · kg ⁻¹	3.0 ± 1.0		3.6 ± 1.1		3.2 ± 0.8	
PETCO ₂ , mmHg	44.5 ± 4.1		43.8 ± 5.2		44.1 ± 4.2	
V _D /V _T	0.42 ± 0.18		0.35 ± 0.13		0.37 ± 0.13	
Q _S /Q _T	0.08 ± 0.05		0.09 ± 0.05		0.08 ± 0.05	

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

CO_{NI} = cardiac output with carbon dioxide rebreathing; CO_{TD} = cardiac output with thermodilution; Paco₂ = arterial carbon dioxide tension; PETCO₂ = 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 H₂O) with the rebreathing loop adjusted for V_T of 12 ml/kg; PSV/Short Loop = PSV (10 cm H₂O) with the rebreathing loop fully retracted; Q_S/Q_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 H₂O); \dot{V}_{CO_2} = carbon dioxide production; V_D/V_T = dead-space fraction; \dot{V}_E = minute ventilation; V_T = tidal volume (recorded during PSV).

showed similar \dot{V}_E (mean value of 0.11 l · min⁻¹ · 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, \dot{V}_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, \dot{V}_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 \dot{V}_E (+17%), V_T (+10%), and respiratory rate (+10%). There were no significant differences at the three ventilatory settings in blood gas analysis data, \dot{V}_{CO_2} , PETCO₂, V_D/V_T, and Q_S/Q_T.

The results of Bland-Altman analysis and regression analysis when spontaneous breaths were present are summarized in table 5 and figures 3 and 4. During SIMV-PSV mode, the correlation between the CO_{NI} and CO_{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_{NI} overestimated CO_{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 \dot{V}_E led to less accuracy of CO_{NI}. (2) When spontaneous breathing effort was present, CO_{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_{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_{NI} correlates well with CO_{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_{NI}, and

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

Ventilatory Setting	SIMV/PSV (n = 25)	PSV/long loop (n = 25)	PSV/short loop (n = 25)
Bias, l/min	0.18	0.80	1.20
Precision, l/min	1.41	1.26	1.80
Limits of agreement, l/min	-2.64 to +3.00	-1.72 to +3.32	-2.40 to +4.80
Slope of linear regression	1.01	1.12	1.19
Correlation coefficient, R	0.23	0.75	0.58

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

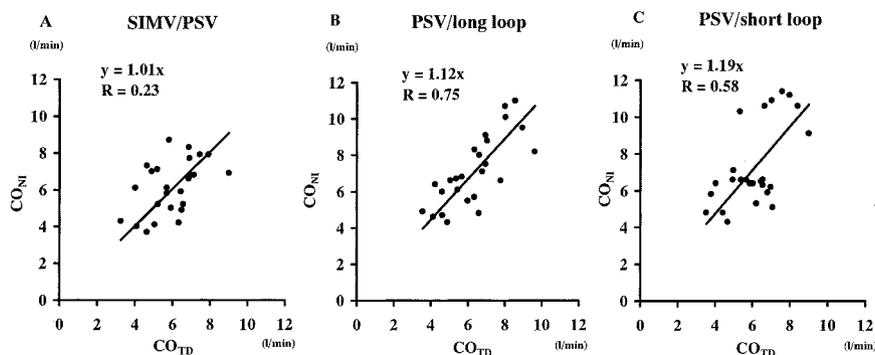


Fig. 3. Agreement between cardiac output measurements obtained by carbon dioxide rebreathing (CO_{NI}) and those obtained by thermodilution technique (CO_{TD}) when spontaneous breathing is present. (A) Synchronized intermittent mandatory ventilation (SIMV, respiratory rate of 5 breaths/min) plus pressure support ventilation (PSV, 6 cm H₂O). (B) Pressure support ventilation (10 cm H₂O). (C) Pressure support ventilation (10 cm H₂O) with the shortest rebreathing loop. Equations and result curves for linear regression analysis are also shown. In A and B, the rebreathing loop was size adjusted according to the manufacturer's instructions recommended for tidal volume of 12 ml/kg. In C, the loop was fully retracted.

the reason for this discrepancy remained to be clarified. We designed the first part of this study to investigate whether V_T or \dot{V}_E is the dominant factor for the accuracy of CO_{NI} . For V_T , when \dot{V}_E of volume-controlled ventilation was set to maintain normocapnia, a correlation between CO_{NI} and CO_{TD} was clinically acceptable ($|\text{bias}| < 1$ l/min, precision ≤ 1 l/min), whether V_T 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 V_T setting, 13% for small V_T setting) because acceptable range is reported to be less than 20%.⁸ By contrast, when \dot{V}_E was reduced to half, CO_{NI} underestimated CO_{TD} with worse precision (1.27 l/min) and percentage error (29%). These findings clearly indicate that \dot{V}_E is more important than V_T for CO_{NI} accuracy. The NICO₂ system, by using the following equation, assumes that $C\bar{v}CO_2$ is constant during the measurement period:

$$(-\Delta\dot{V}CO_2) = CO \times (\Delta Caco_2 - \Delta C\bar{v}CO_2)$$

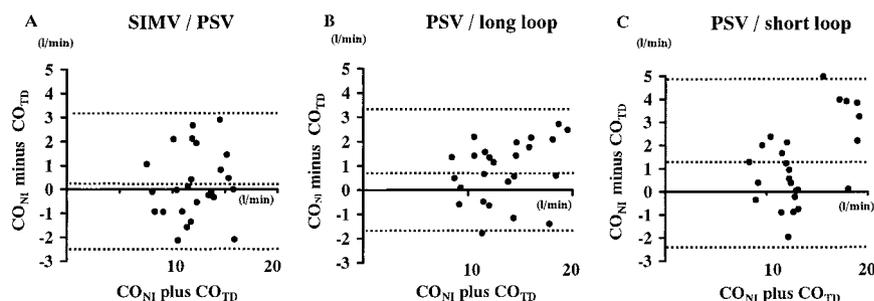
$C\bar{v}CO_2$ may increase during carbon dioxide rebreathing, however, when V_D/V_T is large and alveolar ventilation is low. When using the above equation, the neglecting of $\Delta C\bar{v}CO_2$ could lead to an underestimation of CO. At the end of the 50-s rebreathing period in the NICO₂ system, mixed venous Pco_2 was reported to increase by 0.53 mmHg (median) or by 2.5% (average) from the

initial value.^{9,10} Even at identical \dot{V}_E , we observed that CO_{NI} underestimated CO at a high respiratory rate (20 breaths/min) and small V_T , compared to ventilation at a low respiratory rate (10 breaths/min) and large V_T (table 3). We speculate that increased V_D/V_T and decreased alveolar \dot{V}_E at high respiratory rate leads to this inaccuracy and that a change in V_T can also affect CO_{NI} accuracy by this mechanism. It is clear that controlled mechanical ventilation with constant \dot{V}_E and constant V_T 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,¹¹⁻¹³ and modified algorithms were used.^{11,12} Meanwhile, using a system different from the NICO₂, Gama de Abreu *et al.*¹⁴ have reported that the intraindividual variability of CO measured by partial

Fig. 4. Bias analysis comparing cardiac output measurement results, when spontaneous breathing is present, from partial carbon dioxide rebreathing (CO_{NI}) and thermodilution (CO_{TD}) methods. (A) Synchronized intermittent mandatory ventilation (SIMV, respiratory rate of 5 breaths/min) plus pressure support ventilation (PSV, 6 cm H₂O). (B) Pressure support ventilation (10 cm H₂O). (C) Pressure support ventilation (10 cm H₂O) with the shortest rebreathing loop. Dotted lines show bias and limits of agreement between the two methods.



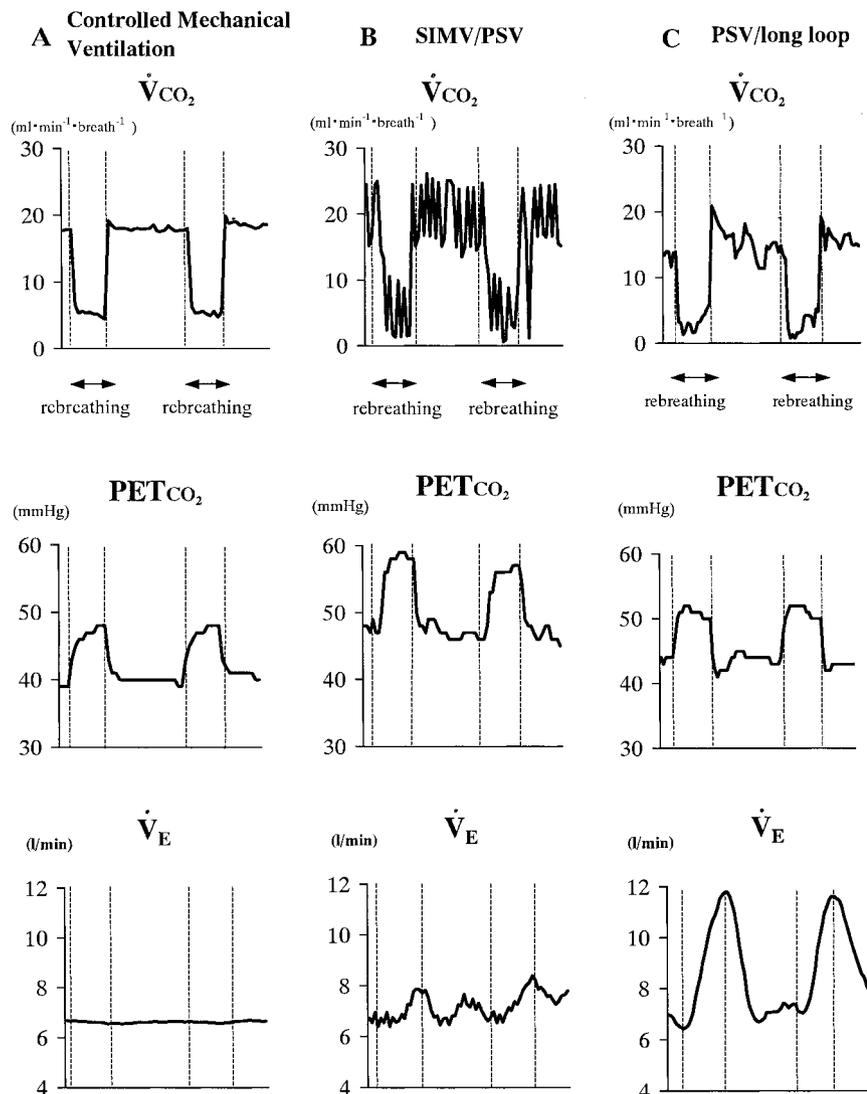


Fig. 5. Representative traces of carbon dioxide production (\dot{V}_{CO_2}), end-tidal carbon dioxide partial pressure (PET_{CO_2}), and minute ventilation (\dot{V}_E) from a 62-yr-old patient who underwent mitral valve plasty for mitral regurgitation. Two cycles of partial carbon dioxide rebreathing are demonstrated. (A) Controlled mechanical ventilation: respiratory rate of 10 breaths/min and tidal volume of 12 ml/kg. (B) Synchronized intermittent mandatory ventilation (SIMV, respiratory rate of 5 breaths/min) plus pressure support ventilation (PSV, 6 cm H₂O). (C) Pressure support ventilation (10 cm H₂O). The rebreathing loop was size adjusted according to the manufacturer's instructions recommended for set tidal volume of 12 ml/kg in all ventilatory settings.

carbon dioxide rebreathing technique was significantly larger during irregular spontaneous breathing than when respiratory rate and V_T 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 $C\bar{v}CO_2$ 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, V_T changes

breath by breath, which may affect accurate measurement of \dot{V}_{CO_2} or PET_{CO_2} .

Figure 5 shows representative \dot{V}_{CO_2} and PET_{CO_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 PET_{CO_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 V_T between mandatory breaths (830 ml) and spontaneous breaths (540–620 ml). In the NICO₂ system, values for \dot{V}_{CO_2} and PET_{CO_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 PET_{CO_2} , during SIMV-PSV, the presence of marked breath-by-breath changes in \dot{V}_{CO_2} and PET_{CO_2} may affect CO_{NI} accuracy. During PSV, breath-by-breath changes in \dot{V}_{CO_2} or PET_{CO_2} are smaller than during

SIMV-PSV. Even so, neither \dot{V}_{CO_2} nor P_{ETCO_2} produced a steady plateau during normal breathing or rebreathing periods, probably because \dot{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 NICO₂ system. In fact, a correlation between CO_{NI} and CO_{TD} was better even during PSV in the previous study⁴ 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 \dot{V}_{E} . The increase in \dot{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 \dot{V}_{E} is changed, more time may be required to attain stable conditions and more accurate CO_{NI} , which impairs clinical usefulness of NICO₂ 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 \dot{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 NICO₂ system under various hemodynamic conditions.

In conclusion, the change in \dot{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.

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