

Effect of Ventilatory Settings on Accuracy of Cardiac Output Measurement Using Partial CO_2 Rebreathing

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Background: **Recently, a new device has been developed to measure cardiac output noninvasively using partial carbon dioxide (CO_2) rebreathing. Because this technique uses CO_2 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 (V_T) of 12 ml/kg; (2) volume-controlled ventilation with V_T of 6 ml/kg; (3) pressure-controlled ventilation with V_T of 12 ml/kg; (4) pressure-controlled ventilation with V_T 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 with V_T set at 12 ml/kg. After establishing steady-state conditions (15 min), they measured cardiac output using CO_2 rebreathing and thermodilution *via* a pulmonary artery catheter. Finally, they repeated the measurements during pressure support ventilation, when the patients had restored spontaneous breathing. The correlation between two methods was evaluated with linear regression and Bland-Altman analysis.**

Results: **When V_T was set at 12 ml/kg, cardiac output with the CO_2 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 V_T of 6 ml/kg, the CO_2 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 CO_2 rebreathing technique overestimated cardiac output.**

Conclusions: **Although cardiac output was underreported at small V_T values, cardiac output measured by the CO_2 rebreathing technique correlates fairly with that measured by the thermodilution method.**

ALTHOUGH there is controversy over the cost benefit of pulmonary artery catheterization,[1,2] cardiac output (CO) is commonly monitored when treating critically ill patients. Recently, a new device, the $NICO_2$ system (Novametrix Medical Systems Inc., Wallingford, CT), has been developed to measure CO noninvasively using partial carbon dioxide (CO_2) rebreathing.[3,4] This device uses periodic partial CO_2 rebreathing to create a CO_2 disturbance, which is then used in a differential Fick CO_2 equation to calculate CO.[3]

There have been few studies to investigate how well the results obtained by CO_2 rebreathing correlate with those obtained by the conventional thermodilution technique.[5–7] Furthermore, it remains to be clarified which ventilatory or hemodynamic parameters affect the measured values when the CO_2 rebreathing technique is used. Because noninvasive CO measurement depends on CO_2 rebreathing and assumes constant dead space and mixed venous CO_2 content through the CO_2 rebreathing procedure,[3,4] 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 (V_T), ventilatory mode, inspired oxygen fraction (FIO_2), and positive end-expiratory pressure (PEEP) on the accuracy of the measurement. The $NICO_2$ 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.

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 in the intensive care unit; and (3) no leakage around the endotracheal tube. We excluded candidates who (1) had central nervous system disorders; (2) might be adversely affected by induced hypercapnia (risk of severe pulmonary hypertension or increased intracranial pressure); or (3) demonstrated severe tricuspid regurgitation on intraoperative examination of transesophageal echocardiography, which interferes with the accuracy of thermodilution CO measurement. 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 pa-

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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

tients. After waiting 1–3 h for hemodynamics to stabilize after surgery, we started the measurements.

Measurements

We measured CO using two methods. Values for CO derived from a thermodilution technique (CO_{TD}) 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,[8] 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_{NI}) was performed with a $NICO_2$ system (software version 3.1, fast mode). This procedure has been presented in detail elsewhere.[3,4] Briefly, on a breath-by-breath basis, CO_2 production ($\dot{V}CO_2$) is calculated from the flow and CO_2 concentration at the airway opening. Then, to establish the relation between $\dot{V}CO_2$ and CO, the Fick principle is applied as follows:

$$\dot{V}CO_2 = CO \times (C\bar{v}CO_2 - CaCO_2), \qquad (1)$$

where $C\bar{v}CO_2$ and $CaCO_2$ represent the CO_2 content in mixed venous and arterial blood, respectively. In the $NICO_2$ system, CO_2 rebreathing is performed for 50 s every 3 min using a disposable sensor (Novametrix Medical Systems). A brief period of CO_2 rebreathing caused a change in $PaCO_2$ and a change in $\dot{V}CO_2$ but little or no change in $C\bar{v}CO_2$ in anesthetized dogs,[3] probably because the quantity of CO_2 stores in the body is large, and new equilibrium levels are attained after 20–30 min.[9] Assuming that CO and $C\bar{v}CO_2$ remain constant during the CO_2 rebreathing procedure, the following equation can be substituted for the previous one:

$$\Delta\dot{V}CO_2 = CO \times (-\Delta CaCO_2), \qquad (2)$$

where $\Delta\dot{V}CO_2$ is the change in $\dot{V}CO_2$ between normal breathing and CO_2 rebreathing, and $\Delta CaCO_2$ is the change in arterial CO_2 content. Assuming here that dead space fraction (V_D/V_T) remains constant during the CO_2 rebreathing and that $\Delta CaCO_2$ is proportional to changes in arterial carbon dioxide pressure ($PaCO_2$) and end-tidal CO_2 pressure ($PETCO_2$), the following equation can be plotted:

$$CO = \Delta\dot{V}CO_2/S \times \Delta PETCO_2, \qquad (3)$$

where $\Delta PETCO_2$ is the change in $PETCO_2$ between normal breathing and CO_2 rebreathing, and S is the slope of the CO_2 dissociation curve from hemoglobin. The constant S can be expressed as a function of hemoglobin concentration and $PaCO_2$ as follows[3]:

$$S = (1.34 \times [Hb] + 18.34)/(1 + 0.193 \times PaCO_2)$$
$$[ml\ CO_2 \cdot l^{-1}\ blood \cdot mmHg^{-1}], \qquad (4)$$

where [Hb] is hemoglobin concentration.

Before the start of the study protocol, the $NICO_2$ system was calibrated for zero CO_2 by opening the system to the atmosphere, according to the manufacturer's instructions. We entered the results of arterial oxygen pressure (PaO_2), $PaCO_2$, FIO_2 (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_2 and FIO_2), alveolar dead space ($PaCO_2$), and the slope of the CO_2 dissociation curve (hemoglobin).[3,4]

Study Protocol

We used Bird 8400*STi* 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_T of 10 ml/kg; decelerating flow pattern; respiratory rate of 10–12 breaths/min; and inspiratory time of 1.0 s. The FIO_2 was adjusted by attending physicians to maintain a PaO_2 greater than 100 mmHg. Baseline PEEP was set at 4 cm H_2O in 23 patients; because of hypoxemia, the remaining 2 patients needed PEEP of 6 and 8 cm H_2O, respectively. With the patients maintained in the supine position, sedated with continuous intravenous injection of propofol (2–3 $mg \cdot kg^{-1} \cdot h^{-1}$), 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_T, we chose VCV with inspired V_T of 12 or 6 ml/kg and pressure-controlled ventilation (PCV) with the same V_T settings. The FIO_2 and respiratory rate were fixed identical to baseline. The PEEP was also fixed identical to the baseline measurement (4 cm H_2O in 23 patients, 6 cm H_2O in 1, and 8 cm H_2O in 1). The inspiratory time was set to 1.0 s for both VCV and PCV. The level of pressure control was adjusted

Table 2. Ventilatory Settings

Ventilatory mode	VCV	VCV	PCV	PCV	VCV	VCV	VCV	VCV	PSV
Inspired tidal volume (ml/kg)	12	6	12	6	12	12	12	12	8.8
F_{IO_2}	0.5	0.5	0.5	0.5	1.0	0.5	0.5	0.5	0.5
PEEP*	4	4	4	4	4	15	4	4	4
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 (F_{IO_2}) and positive end-expiratory pressure (PEEP).

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

* In two patients, PEEP of 6 and 8 cm H_2O 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.

to obtain the same V_T during VCV. The rebreathing loop was sized according to the manufacturer's instructions recommended for a set V_T of 12 ml/kg. To examine the effects of F_{IO_2}, we increased the F_{IO_2} to 1.0 with VCV and 12 ml/kg V_T. To examine the effects of high PEEP, we increased PEEP to 12–15 cm H_2O with VCV and 12 ml/kg V_T, depending on the patient's hemodynamic stability. The order of these six conditions was randomized. Then, to examine the effects of varying the length of the rebreathing loop, in 17 patients, measurements were performed with the loop maximally expanded (400 ml) or fully retracted (150 ml) while VCV and 12 ml/kg V_T were used. After the measurements were completed, vecuronium infusion was stopped. When the patient recovered stable spontaneous breathing, we switched the ventilatory mode to continuous positive airway pressure of 4 cm H_2O plus pressure-support ventilation (PSV) of 10 cm H_2O.

After establishing steady-state conditions (approximately 15 min) at each setting, we measured both CO_{NI} and CO_{TD}. We limited ourselves perform only nine measurements (one measurement for each ventilatory setting) per patient. Arterial blood samples were analyzed with a calibrated blood gas analyzer (ABL 505; Radiometer, Copenhagen, Denmark). Hemodynamic data were also recorded. V_D/V_T and venous admixture fraction

Table 3. Respiratory and Hemodynamic Parameters at Each Ventilatory Setting

Ventilatory Setting	VCV Large V_T	VCV Small V_T	PCV Large V_T	PCV Small V_T	VCV F_{IO_2} 1.0	VCV High PEEP	VCV Long Loop	VCV Short Loop	PSV
V_T (ml/kg)	13.0 ± 0.6	6.9 ± 0.9*	13.2 ± 0.8	6.9 ± 0.9*	12.9 ± 0.7	13.2 ± 0.7	13.1 ± 0.8	13.1 ± 0.8	8.8 ± 2.6†
$\dot{V}_E$ ($l \cdot min^{-1} \cdot kg^{-1}$)	0.13 ± 0.01	0.07 ± 0.02*	0.13 ± 0.01	0.07 ± 0.02*	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.13 ± 0.01	0.14 ± 0.04
PIP (cm H_2O)	27.5 ± 5.8	17.0 ± 3.5	27.0 ± 6.4	16.4 ± 3.9	27.2 ± 5.8	36.6 ± 7.1	26.9 ± 7.1	26.9 ± 7.0	15.2 ± 2.7
PEEP (cm H_2O)	4.2 ± 0.9	4.2 ± 0.9	4.2 ± 0.9	4.2 ± 0.9	4.2 ± 0.9	14.0 ± 1.7	4.4 ± 1.1	4.4 ± 1.1	4.1 ± 0.4
pH	7.45 ± 0.04	7.32 ± 0.04*	7.44 ± 0.05	7.31 ± 0.03*	7.42 ± 0.04	7.44 ± 0.05	7.42 ± 0.05	7.45 ± 0.04	7.39 ± 0.05
Pa_{CO_2} (mmHg)	37.7 ± 5.4	55.2 ± 6.8*	39.2 ± 6.4	56.1 ± 6.4*	40.4 ± 6.4	38.8 ± 7.5	40.5 ± 7.8	36.6 ± 7.1	43.6 ± 5.9
P/F	292 ± 87	239 ± 69	299 ± 88	238 ± 58	376 ± 87‡	357 ± 113‡	324 ± 95	330 ± 94	275 ± 87
Lactate (mM)	2.0 ± 1.2	1.9 ± 1.2	2.1 ± 1.2	1.9 ± 1.1	1.9 ± 1.1	2.0 ± 1.0	2.0 ± 0.9	2.1 ± 1.0	2.1 ± 1.2
CO_{TD} (l/min)	5.24 ± 1.45	5.69 ± 1.58	5.23 ± 1.56	5.87 ± 1.79	5.10 ± 1.50	4.46 ± 1.45	5.34 ± 1.67	5.19 ± 1.33	5.43 ± 1.40
CO_{NI} (l/min)	5.41 ± 1.36	4.02 ± 1.00§	5.60 ± 1.40	4.23 ± 1.36‖	5.30 ± 1.45	4.82 ± 1.24	5.81 ± 1.58	6.49 ± 1.58	5.95 ± 1.38
$\dot{V}_{CO_2}$ ($ml \cdot min^{-1} \cdot kg^{-1}$)	3.0 ± 0.3	2.0 ± 0.4*	3.1 ± 0.5	2.2 ± 0.5*	3.1 ± 0.4	3.0 ± 0.4	3.2 ± 0.5	3.0 ± 0.5	3.2 ± 0.9
PET_{CO_2} (mmHg)	34.5 ± 3.8	49.9 ± 6.8*	35.4 ± 4.9	50.4 ± 6.1*	35.7 ± 4.7	34.7 ± 4.9	36.7 ± 5.3	34.6 ± 4.8	42.4 ± 7.4#
V_D/V_T	0.43 ± 0.09	0.50 ± 0.10**	0.43 ± 0.10	0.45 ± 0.13	0.45 ± 0.09	0.43 ± 0.09	0.43 ± 0.11	0.41 ± 0.12	0.53 ± 0.17
$\dot{Q}_S/\dot{Q}_T$	0.05 ± 0.03	0.10 ± 0.07	0.06 ± 0.04	0.10 ± 0.04	0.03 ± 0.03	0.04 ± 0.03	0.05 ± 0.04	0.06 ± 0.03	0.07 ± 0.05
HR (beats/min)	92 ± 7	95 ± 9	93 ± 8	95 ± 9	94 ± 8	92 ± 9	92 ± 9	91 ± 8	94 ± 8
BP (mmHg)	79 ± 9	77 ± 10	77 ± 10	77 ± 12	79 ± 11	74 ± 11	76 ± 8	77 ± 9	79 ± 11
PA (mmHg)	19.3 ± 5.6	25.3 ± 7.8	18.6 ± 5.5	24.6 ± 5.8	19.0 ± 6.1	21.3 ± 5.5	20.2 ± 6.6	19.6 ± 6.0	20.1 ± 5.7
CVP (mmHg)	7.9 ± 2.5	9.6 ± 3.5	7.5 ± 2.7	9.4 ± 3.3	7.6 ± 2.6	10.4 ± 2.4††	7.6 ± 2.9	7.7 ± 2.3	8.6 ± 3.0
PCWP (mmHg)	9.8 ± 2.2	11.5 ± 3.9	9.6 ± 2.5	11.8 ± 2.8	10.1 ± 2.5	11.8 ± 2.1	10.2 ± 2.8	10.0 ± 2.5	10.4 ± 3.8
PVR ($dyn \cdot s \cdot cm^{-5}$)	158 ± 89	212 ± 120	153 ± 100	194 ± 111	149 ± 93	185 ± 105	167 ± 108	161 ± 102	157 ± 84
SVR ($dyn \cdot s \cdot cm^{-5}$)	1,162 ± 372	997 ± 243	1,145 ± 379	974 ± 216	1,191 ± 315	1,237 ± 405	1,106 ± 335	1,126 ± 302	1,101 ± 320
$S\bar{v}_{O_2}$ (%)	72 ± 7	73 ± 7	73 ± 7	73 ± 7	79 ± 6‡‡	70 ± 8	73 ± 7	72 ± 6	72 ± 7

* $P < 0.05$ *versus* volume-controlled ventilation (VCV)–large tidal volume (V_T), pressure-controlled ventilation (PCV)–large V_T, fraction of inspired oxygen (F_{IO_2}) 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 V_T, PCV–small V_T, and PSV. § $P < 0.05$ *versus* VCV–large V_T, PCV–large V_T, F_{IO_2} 1.0, long loop, short loop, and PSV. ‖ $P < 0.05$ *versus* PCV–large V_T, long loop, short loop, and PSV. # $P < 0.05$ *versus* VCV–large V_T, VCV–small V_T, PCV–large V_T, PCV–small V_T, F_{IO_2} 1.0, high PEEP, and short loop. ** $P < 0.05$ *versus* VCV–large V_T and short loop. †† $P < 0.05$ *versus* PCV–large V_T and F_{IO_2} 1.0. ‡‡ $P < 0.05$ *versus* VCV–large V_T, PCV–large V_T, high PEEP, and PSV.

$\dot{V}_E$ = minute ventilation; PIP = peak inspiratory pressure; Pa_{CO_2} = arterial carbon dioxide tension; P/F = ratio of arterial oxygen tension to F_{IO_2}; CO_{TD} = cardiac output with thermodilution; CO_{NI} = cardiac output with carbon dioxide rebreathing; $\dot{V}_{CO_2}$ = carbon dioxide production; PET_{CO_2} = end-tidal carbon dioxide pressure; V_D/V_T = dead-space fraction; $\dot{Q}_S/\dot{Q}_T$ = 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; $S\bar{v}_{O_2}$ = mixed venous oxygen saturation.

Table 4. Results of Bland-Altman Analysis and Regression Analysis

Ventilatory Setting	VCV Large V_T	VCV Small V_T	PCV Large V_T	PCV Small V_T	VCV F_{IO_2} 1.0	VCV High PEEP	VCV Long Loop	VCV Short Loop	PSV
Bias (l/min)	0.18	−1.67	0.37	−1.64	0.19	0.37	0.48	1.30	0.52
Precision (l/min)	1.04	1.06	1.17	1.19	1.12	0.81	1.27	1.15	1.02
Limits of agreement (l/min)	−1.90 to +2.26	−3.79 to +0.45	−1.97 to +2.71	−4.02 to +0.74	−2.05 to +2.43	−1.25 to +1.99	−2.06 to +3.02	−1.00 to +3.60	−1.52 to +2.56
Slope of linear regression	1.01	0.69	1.04	0.71	1.01	1.05	1.05	1.23	1.07
Correlation coefficient (R)	0.63	0.66	0.50	0.72	0.62	0.72	0.54	0.61	0.63

VCV = volume-controlled ventilation; PCV = pressure-controlled ventilation; PSV = pressure-support ventilation; V_T = tidal volume; F_{IO_2} = fraction of inspired oxygen; PEEP = positive end-expiratory pressure.

($\dot{Q}_S/\dot{Q}_T$) were calculated using the following equations[10,11]:

$$V_D/V_T = 1 - (0.863 \cdot \dot{V}CO_2)/(\dot{V}_E \cdot PaCO_2) \quad (5)$$

and

$$\dot{Q}_S/\dot{Q}_T = (Cc'O_2 - CaO_2)/(Cc'O_2 - C\bar{v}O_2), \quad (6)$$

where $\dot{V}_E$ is minute ventilation, $Cc'O_2$ is oxygen content at the pulmonary capillary, CaO_2 is arterial oxygen content, and $C\bar{v}O_2$ 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:

$$\dot{Q}_S/\dot{Q}_T = (1 - SaO_2)/(1 - S\bar{v}O_2), \quad (7)$$

where SaO_2 and $S\bar{v}O_2$ 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.[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_{IO_2}, V_T, V_E, PEEP, peak inspiratory pressure, pH, PaO_2, $PaCO_2$, $PETCO_2$, $\dot{V}CO_2$, and $S\bar{v}O_2$. 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 $\dot{V}CO_2$, 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.

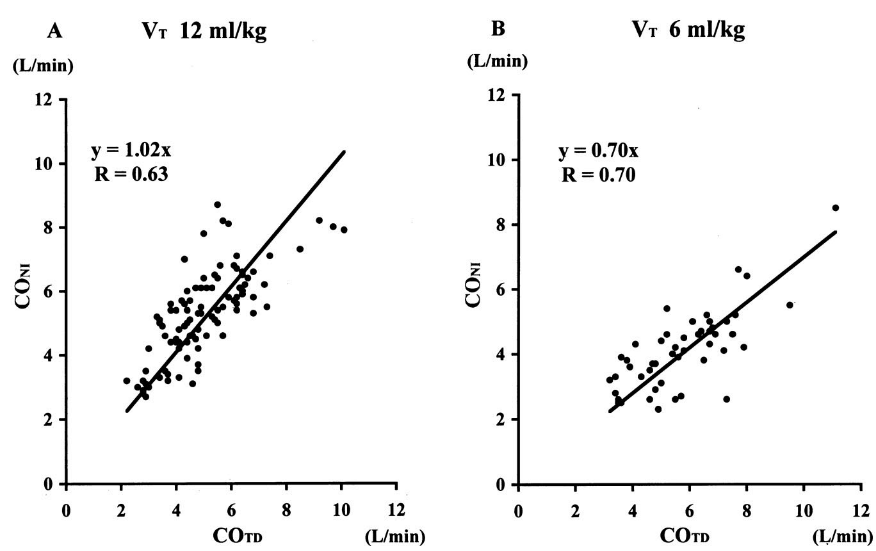

Fig. 1. Agreement between cardiac output measurements obtained by carbon dioxide rebreathing (CO_{NI}) and those obtained by thermodilution technique (CO_{TD}). (*A*) Large tidal volumes (V_T, 12 ml/kg) during both volume-controlled ventilation and pressure-controlled ventilation. (*B*) Same modes, but with small tidal volumes (6 ml/kg). Equations and result curves for linear regression analysis are also shown.

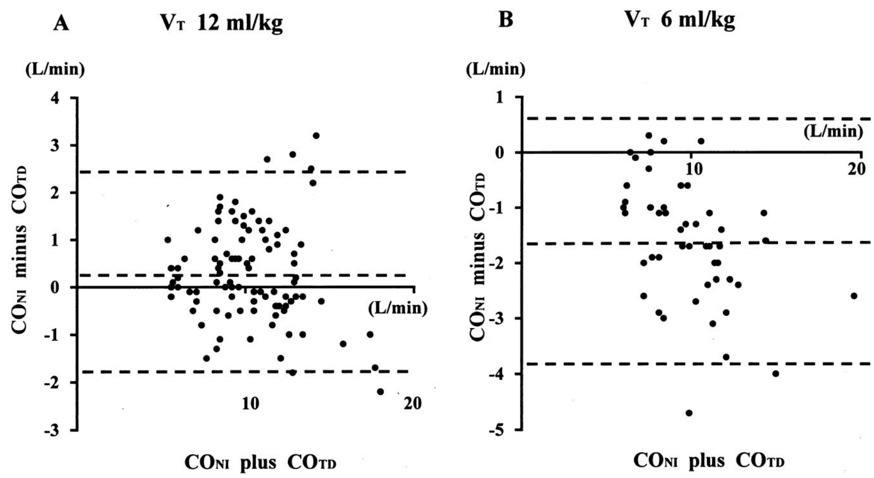

Fig. 2. Bias analysis between cardiac output measurements obtained by carbon dioxide rebreathing (CO_{NI}) and one those obtained by thermodilution technique (CO_{TD}). (*A*) Large tidal volumes (V_T; 12 ml/kg) during both volume-controlled ventilation and pressure-controlled ventilation. (*B*) Same modes, but with small tidal volumes (6 ml/kg). Dotted lines show bias and limits of agreement between the two methods.

Levels of pressure control were 24 ± 7 (16–36) cm H_2O with inspired V_T of 12 ml/kg and 13 ± 4 (8–22) cm H_2O with V_T of 6 ml/kg. As a result, there was no difference in peak inspiratory pressure for VCV and PCV at either V_T setting (table 3).

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

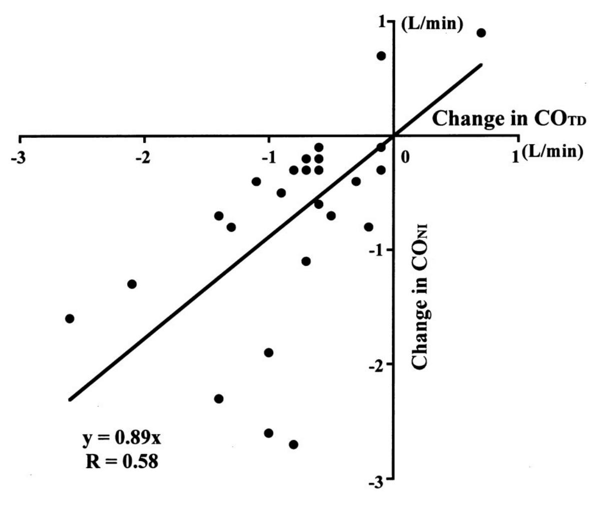

Fig. 3. Relation between changes in cardiac output measurements obtained by thermodilution technique and those obtained by carbon dioxide rebreathing when positive end-expiratory pressure was increased. Ventilatory settings are volume-controlled and 12 ml/kg tidal volume. When positive end-expiratory pressure was increased from 4.2 to 14.0 cm H_2O in average, cardiac output measurements obtained both by thermodilution technique and by carbon dioxide rebreathing decreased in almost all patients. Each point corresponds to a different patient. Note that both values moved in identical directions in all patients but one. Equations and result curves for linear regression analysis are also shown.

When V_T was 12 ml/kg, a fair correlation was observed between CO_{NI} and CO_{TD} (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 F_{IO_2} or high PEEP (table 4). By contrast, when V_T 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 CO_{TD} and those in CO_{NI} when PEEP was increased during VCV and 12-ml/kg V_T. When average PEEP was increased from 4.2 to 14.0 cm H_2O, both CO_{TD} and CO_{NI} decreased. Both values moved in identical directions in all patients but one. The value of CVP increased from 7.9 ± 2.5 to 10.4 ± 2.4 mmHg at higher PEEP, and pulmonary capillary wedge pressure also increased from 9.8 ± 2.2 to 11.8 ± 2.1 mmHg (table 3).

Discussion

The main findings of this study are as follows. (1) During mechanical ventilation with large constant V_T or during PSV, CO measurements obtained by CO_2 rebreathing technique correlate with those obtained by thermodilution method. (2) When minute ventilation is large, the accuracy of the CO_2 rebreathing technique is not affected by a selection of VCV, PCV, spontaneous breathing (PSV), PEEP, or F_{IO_2}. (3) When V_T and minute ventilation are reduced, the CO_2 rebreathing technique underreports CO. (4) CO measurements are accurate when the rebreathing loop is maximally expanded but is overestimated when the loop is fully retracted.

Clinical Implications

Using partial CO_2 rebreathing, CO can be measured noninvasively.[3,4] However, there have been few clinical reports, on the accuracy of this technique.[5-7] 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 V_T setting and with constant minute ventilation, CO measurements obtained from this technology correlate fairly with those from the thermodilution method. When inspired V_T 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 $l \cdot min^{-1} \cdot kg^{-1}$, the linear regression slopes for CO_{NI} and CO_{TD} 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 F_{IO_2}. Correlation of results from CO_{NI} and CO_{TD} was also satisfactory during PSV (table 4). These observations suggest that this CO_2 rebreathing technique is reliable both with large constant V_T 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 V_T. In contrast, when the rebreathing loop was set too short for a given V_T, CO_{NI} measurements had greater values than those obtained by CO_{TD} (table 4). This may be due to the small changes in PET_{CO_2} that occur with the shortest loop during CO_2 rebreathing, when a slight amount of noise would likely generate large errors.

To our surprise, when V_T was small (6 ml/kg), CO_{NI} measurements showed consistently lower values than those produced by CO_{TD}, resulting in a linear regression slope of 0.70 and a negative value of bias (figs. 1 and 2). Low V_T (6 ml/kg) is currently recommended for ventilator management in acute respiratory failure,[14] so attention needs to be drawn to the lack of reliable measurement using CO_{NI} at the low V_T 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 V_T, when V_T 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 CO_{NI} measurements less accurate (table 4). This finding suggests that the combination of long loop and small V_T are unlikely to impair the accuracy of CO_{NI}.

Second, at small V_T settings, PET_{CO_2} increased to almost 60 mmHg in several patients. The software (version 3.1) that we used suspends rebreathing when the baseline PET_{CO_2} is greater than 65 mmHg or PET_{CO_2} is greater than 80 mmHg during CO_2 rebreathing. It could be that the linearity between Ca_{CO_2} and PET_{CO_2} is less accurate when PET_{CO_2} is extremely high.

Finally, the assumed constancy of mixed venous CO_2 content may be false for some time after V_T and minute ventilation are changed. The measured values of $\dot{V}_{CO_2}$ were smaller at low V_T than at high V_T (table 3). Although we waited for 15 min, this may not have been enough time for CO_2 stores to reach a steady state, which is 100 times larger than oxygen stores.[9] In addition, the time course of the increase in Pa_{CO_2} after abrupt decrease of ventilation is much slower than the rate of decrease after abrupt increase of ventilation.[9] These facts suggest that CO_2 stores and mixed venous CO_2 content may continue to change even after Pa_{CO_2} and PET_{CO_2} seem to have reached plateau values. If this is the case, the accuracy of the CO_2 rebreathing technique may be compromised when there are abrupt changes in minute ventilation and $\dot{V}_{CO_2}$. Further study is needed to find out exactly what happens after these sudden changes and whether these mechanisms affect the accuracy of the CO_2 rebreathing technique.

Limitations

The current study has several limitations. First, the patients in our study were sedated and paralyzed initially, resulting in constant V_T and stable $\dot{V}_{CO_2}$. Even during PSV, they breathed quietly with small variation in V_T. Therefore, our results may not be directly extrapolated to populations of patients whose V_T and $\dot{V}_{CO_2}$ are changing.[6] Secondly, our patients had relatively normal lung mechanics (respiratory system compliance, 45.4 ± 12.8 ml/cm H_2O; resistance, 11.2 ± 4.1 cm $H_2O \cdot s \cdot l^{-1}$), 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 $NICO_2$ technique: *e.g.*, constant V_D/V_T, constant CO, and constant mixed venous CO_2 content during the CO_2 rebreathing procedure. Finally, it remains to be clarified whether the impaired accuracy of CO_{NI} with small V_T results from small V_T itself or from reduced minute ventilation. During PSV, when V_T was smaller (8.8 ± 2.6 ml/kg) but minute ventilation was similar to that at the high V_T settings, CO_{NI} and CO_{TD} values correlated fairly ($y = 1.07x$); we speculate that if normocapnia is sustained by adjusting the respiratory rate, the accuracy of the CO_{NI} technique can be maintained at small V_T.

In conclusion, noninvasive measurement of CO using CO_2 rebreathing is reliable with a bias of less than 0.5 l/min and a precision of 1 l/min when the tidal volume is large and constant, regardless of ventilatory modes. However, at small tidal volume, the rebreathing system underreports CO, compared with the conventional thermodilution technique.

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