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Pulmonary Capillary Blood Flow and Cardiac Output Measurement by Partial Carbon Dioxide Rebreathing in Patients with Acute Respiratory Distress Syndrome Receiving Lung Protective Ventilation

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Background: **Partial carbon dioxide rebreathing noninvasively measures the pulmonary capillary blood flow and estimates the cardiac output with the use of a predicted shunt value. It has been reported that the accuracy of the method is decreased in patients with high pulmonary shunt. The aim of this study was to investigate the agreement between partial rebreathing and thermodilution for the determination of pulmonary capillary blood flow and cardiac output in the setting of acute respiratory distress syndrome.**

Methods: **Twenty consecutive patients with the acute respiratory distress syndrome were enrolled. Ventilator settings include low tidal volume (6 ml · kg^{-1}) and positive end-expiratory pressure + 2 cm H_2O higher than the lower inflection point if present or 10 cm H_2O if not. Seven pairs of cardiac output and pulmonary capillary blood flows were recorded every 20 min over a 2-h period. The authors determined bias, SD, limit of agreement (95% confidence interval) and percentage error.**

Results: **Bias and agreement for cardiac output measurement were 0.8 ± 1.2 l · min^{-1} (–2.1 to 3.7 l · min^{-1}), and percentage error was 36%. Bias and agreement for pulmonary capillary blood flow measurement were –0.1 ± 0.8 l · min^{-1} (–2.1 to 1.9 l · min^{-1}), and percentage error was 35%. Dead space, arteriovenous oxygen content difference, mean pulmonary arterial pressure, and baseline cardiac output were independently associated with differences between methods.**

Conclusions: **In patients with the acute respiratory distress syndrome, partial rebreathing cannot yet replace thermodilution for measuring pulmonary capillary blood flow or cardiac output. However, accuracy of the method is close to the boundary of clinical relevance.**

ACUTE respiratory distress syndrome (ARDS) is one of the most common diseases in intensive care units and is associated with high mortality.[1] The primary goal of supportive therapies is to counteract the severe mismatching of ventilation and perfusion that result from the initial lung injury, but the lung is frequently associated with other organ failures. During ARDS, conditions such as mechanical ventilation, hypovolemia, and sepsis promote the occurrence of acute circulatory failure, a complex situation in which the determination of cardiac output may be useful.[2] The standard for determining cardiac output is the thermodilution principle performed in a clinical setting with a pulmonary artery catheter.[3,4] Furthermore, the pulmonary artery catheter allows the measurement of the pulmonary shunt fraction throughout the sampling of mixed venous blood gas in the pulmonary circulation.[5] Therefore, it indirectly gives the pulmonary capillary blood flow, defined as the part of cardiac output that perfuses the nonshunted ventilated area. However, the insertion of a pulmonary artery catheter remains an invasive procedure, and its utility is still debated.[6] In this context, it may be of particular interest to implement an alternative and noninvasive technology to determine cardiac output: partial carbon dioxide rebreathing.[7,8]

The partial carbon dioxide rebreathing method applies the Fick principle to carbon dioxide; that is, flow is proportional to the elimination rate by the lung (V_{CO_2}) and to the difference between mixed venous (Cv_{CO_2}) and arterial (Ca_{CO_2}) blood content.[9] To avoid the invasive measurement of blood gases, a brief period of carbon dioxide reinhalation (rebreathing period) is compared with normal condition (nonrebreathing period). Pulmonary capillary blood flow can be calculated as the change in V_{CO_2} between the nonrebreathing and the rebreathing periods divided by the change in Cv_{CO_2} minus Ca_{CO_2}.[10] To further clarify the equation, the change in Cv_{CO_2} is considered insignificant, and Ca_{CO_2} is approximated by the end-tidal partial pressure of carbon dioxide (P_{ETCO_2}).[11] Therefore, pulmonary capillary blood flow can be estimated by the variation in V_{CO_2} and P_{ETCO_2} during the two rebreathing conditions.[12] The $NICO_2$ monitor (Novametrix Medical System, Wallingford, CT) provides breath-by-breath analysis of volumetric capnography and measures pulmonary capillary blood flow automatically. Cardiac output is estimated in a second step according to pulmonary capillary blood flow and a predicted shunt value.[13]

The accuracy of the partial rebreathing method, as compared with thermodilution, has been established mainly in the operating room and in surgical critically ill patients.[14–19] A number of factors have been identified as potential sources of errors, including the respiratory

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rate and the breathing pattern.[20,21] However, few studies have been conducted in patients with acute lung injury, and some data suggest that the accuracy of the method is reduced in patients with high shunt fraction.[18,22] To our knowledge, no data are available in ARDS patients ventilated with a lung protective approach, which constitutes the current standard of delivering mechanical ventilation.

The objective of this study was to investigate, in this specific population, the agreement between partial carbon dioxide rebreathing and continuous thermodilution for the determination of pulmonary capillary blood flow and cardiac output, and to identify the factors that contribute to differences. The results of this article have been presented in an abstract form at the European Society of Intensive Care Medicine 21st Annual Congress (2008), in Lisbon, Portugal.[23]

Materials and Methods

Patients

The protocol was approved by our local ethics committee (Marseille University Hospital, Marseille, France), and informed consent was obtained from next of kin. This study was performed in a 12-bed medical intensive care unit in a university teaching hospital. We prospectively enrolled twenty consecutive mechanically ventilated patients meeting the American-European Consensus Conference criteria of ARDS.[24] Exclusion criteria were age under 18 yr, pregnancy, a history of chronic respiratory failure, hemodynamic instability defined by rapid change in mean arterial pressure, renal replacement therapy, bronchopleural fistula, almitrine infusion, and inhaled nitric oxide.

Settings

All patients received volume-controlled mechanical ventilation in a semirecumbent position (Evita XL; Dräger Medical, Lübeck, Germany). Inspiratory gases were automatically heated and fully humidified with a MR 850 device (Fisher & Paykel, Auckland, New Zealand). An endotracheal aspiration was performed before the investigation by using a closed-suction system (Steri-cath® 16-French; Portex, Keene, NH). Pulmonary aspiration was not repeated during the study period. A recruitment maneuver was performed after suctioning (40 cm H_2O for 30 s) to standardize the lung volume history. Respiratory settings included a tidal volume of 6 ml · kg^{-1} of predicted body weight with a 0.4-s end-inspiratory pause. Respiratory rate was adjusted to complete expiratory lung washout and to maintain $Paco_2$ at 35–55 Torr and pH greater than 7.25. After completion of a quasi-static pressure volume curve by using the Evita XL tool, the positive end-expiratory pressure level was set at + 2 cm H_2O higher than the low inflection point when present or at 10 cm H_2O if not. Continuous infusion of midazolam, sufentanil, and ketamine if needed, was adjusted to provide a Ramsay scale score of 6 without spontaneous breathing efforts.[25] Mean arterial pressure was recorded through a 20-gauge radial artery cannula (Plastimed 4 French; Saint Leu la Fôret, France) and maintained constant higher than 70 mmHg. Fluid requirement and the need for vasopressor were assessed before entering the study.

Hemodynamic Measurements.

Thermodilution. Cardiac output was measured by continuous thermodilution using a 7.5-French pulmonary artery catheter (Vigilance II Monitor; Edwards, Irvine, CA). The pulmonary artery catheter was introduced *via* the right internal jugular vein into the pulmonary artery by using the pressure signal obtained at the distal port. The proximal pressure port displays the right atrial pressure. The correct position of the pulmonary artery catheter was confirmed if the pulmonary artery occlusion pressure remained below the diastolic pulmonary pressure and if the distal tip of the catheter was located in the proximal pulmonary artery on the chest radiography. A 10-cm thermal filament continuously delivered heat into the bloodstream according to a pseudorandom binary sequence.[26] The change in blood temperature was detected by a thermistor and correlated with the input sequence to produce a thermodilution washout curve.[27] Cardiac output corresponds to the area under the curve. In critically ill patients, continuous thermodilution provides good agreement with intermittent bolus thermodilution or with dye dilution method.[28–32] We thus considered for the purpose of this study that the continuous thermodilution method is the reference. The monitor was set in the trend mode, updating cardiac output values every minute. We considered the average value of the last 3 min for statistical analyses. Central venous pressure and pulmonary artery occlusion pressure were recorded in the semirecumbent position by using the midaxillary line as zero reference. Arterial and mixed venous blood gases were analyzed immediately after drawing blood with a RapidPoint® 405 instrument (Bayer Health Care, Sudbury, United Kingdom). After inclusion, the inspired oxygen fraction was increased to 100% during 15 min to determine the true pulmonary shunt fraction according to the Berggren equation[5]:

$$Q_S/Q_T\ (\%) = (C_{c'}O_2 - C_aO_2)/(C_{c'}O_2 - C_vO_2)$$

where Q_S is the pulmonary shunt blood flow, Q_T is the total pulmonary blood flow, $C_{c'}O_2$ is end-capillary oxygen content ($C_{c'}O_2$ = hemoglobin · 1.34 + P_AO_2 · 0.0033), C_aO_2 is arterial oxygen content (Cao_2 = hemoglobin · Sao_2 · 1.34 + Pao_2 · 0.0033), and C_vO_2 is mixed venous oxygen content (Cvo_2 = hemoglobin · SvO_2 · 1.34 + Pvo_2 · 0.0033). We assumed that the end-capillary oxygen saturation at an inspired oxygen fraction of 1 was 100%. Although breathing 100% oxygen for a short period may induce alveolar collapse

by denitrogenation, it has been reported that a sufficiently high positive end-expiratory pressure level impairs the formation of atelectasis and thus prevents the increase in pulmonary shunt.[33,34] Respiratory settings were kept constant throughout the investigation, and the protocol duration was short; therefore, we assumed that the pulmonary shunt fraction remained constant, and we considered the initial shunt fraction for all other measurements. Thereafter, inspired oxygen fraction was resumed at baseline level. Pulmonary capillary blood flow measured by thermodilution was calculated as cardiac output minus shunt.

Partial Carbon Dioxide Rebreathing. The $NICO_2$ monitor version 3.0 is a fully automated device placed between the Y piece of the ventilator and the endotracheal tube. It includes a calibrated mainstream infrared carbon dioxide sensor, a differential pressure flow sensor, and a pneumatically controlled loop acting as an adjustable rebreathing bag (from 150 to 400 ml). Complete function and procedure of the $NICO_2$ monitor have been described elsewhere.[11,13] Briefly, the additional dead space obtained during the rebreathing period raises P_{ETCO_2} slightly (typically by 3–5 mmHg) and lowers V_{CO_2}. This rebreathing period is activated for 35 s before resuming basal condition for 60 s. Finally, a stabilization period of 85 s completes the NICO cycle, which is cyclically repeated every 3 min. Pulmonary capillary blood flow measured by partial carbon dioxide rebreathing corresponds to the difference between nonrebreathing and rebreathing periods such that:

$PCBF_{REB}$ ($ml \cdot min^{-1}$) = $-\Delta V_{CO_2}/S.\Delta P_{ETCO_2}$, where S is the slope of the carbon dioxide dissociation curve from hemoglobin.[35] Cardiac output is then calculated by adding a noninvasive estimation of the shunt. For this purpose, the $NICO_2$ software plotted the manually entered F_{IO_2}, Pa_{O_2} (or Sp_{O_2}), and hemoglobin values on Nunn's iso-shunt line.[36] To compare the estimation of shunt by $NICO_2$ with the true shunt (Q_S/Q_T), we used the following formula:

$$Shunt_{REB}\ (\%) = [1 - (PCBF_{REB}/CO_{REB}] \cdot 100$$

We also determined the dead space fraction (V_D/V_T) according to a breath-by-breath analysis of volumetric capnography. Pa_{CO_2} was manually entered into the $NICO_2$ monitor, which continuously displayed the V_D/V_T and other volumetric indices.

Protocol

After a 2-h period of hemodynamic stability (*i.e.*, mean arterial pressure constant higher than 70 mmHg), we performed seven pairs of measurements of cardiac output and pulmonary capillary blood flow, repeated every 20 min over a 2-h period. Finally, 140 pairs of simultaneous measurements by thermodilution and partial carbon dioxide rebreathing were available. No other interventions were allowed during the study period.

Statistical Analysis

Distribution of the data were determined by using a Kolmogorov-Smirnoff test. Data are expressed as mean ± SD or median ± interquartile range (25–75%) according to normality. We used analysis of variance on ranks for repeated measurements (RM ANOVA) to determine significant changes in hemodynamic variables through the study period. Correlation between methods for the determination of cardiac output and pulmonary capillary blood flow was calculated by using a Spearman Rank Order test (r^2) because of the nonparametric distribution of data. Agreement was determined according to the method described by Bland and Altman for repeated measurements where the true value varies.[37] We calculated bias (mean difference), precision (SD of the difference), and limit of agreement (95% confidence interval [CI]) for cardiac output and pulmonary capillary blood flow. For this purpose, we used the R statistical software (The R Project for Statistical Computing, Vienna, Austria).[38] We also determined the percentage error of agreement (2 · SD/mean of the reference method).[39]

Finally, we performed a linear mixed model analysis to identify variables associated with difference in the measurement of cardiac output and pulmonary capillary blood flow between methods.[40] The following variables were introduced in the two models: shock (as defined by the presence of norepinephrine), dead space, arteriovenous oxygen content difference (Dav_{O_2}), mean pulmonary arterial pressure, baseline cardiac output, and total positive end-expiratory pressure. The estimated fixed effect of each parameter was quantified with the use of estimated value and SE. The dependant variables were the difference in cardiac output measurement for the first model and the difference in pulmonary capillary blood flow measurement for the second model. Significance level was set at $P < 0.05$. All statistical analyses were performed with SPSS 15 (SPSS Software, Chicago, IL).

Results

Characteristics of the patients at inclusion are presented in table 1. Sixteen patients (80%) received norepinephrine, and none received dobutamine. Respiratory, hemodynamic, and NICO-related parameters at inclusion are presented in table 2. No significant changes in metabolic, respiratory, and hemodynamic parameters (heart rate, mean arterial pressure, central venous pressure, pulmonary artery occlusion pressure, cardiac output, and pulmonary capillary blood flow) were observed during the study period (analysis of variance for repeated measurements).

Cardiac Output

Cardiac output values ranged from 3.2 to 11.1 $l \cdot min^{-1}$ with thermodilution and from 2.7 to 11.3 l ·

Table 1. Characteristics of the Study Population (20 Patients)

Variables	
Male, n (%)	15 (75)
Age, years, median (IQR)	71 (56–77)
SAPS II on ICU admission, median (IQR)	41 (33–49)
SOFA on inclusion, median (IQR)	9 (8–11)
Shock on inclusion, n (%)	16 (80)
Type of admission	
Medical, n (%)	14 (70)
Surgical, n (%)	6 (30)
Lung injury score, mean ± SD	2.4 ± 0.4
Type of ARDS	
Pulmonary, n (%)	12 (60)
Nonpulmonary, n (%)	8 (40)
Cause of ARDS	
Pneumonia, n (%)	7 (35)
Aspiration, n (%)	5 (25)
Sepsis, n (%)	4 (20)
Pancreatitis, n (%)	3 (15)
Mediastinitis, n (%)	1 (5)
Duration of MV prior inclusion, days, median (IQR)	3 (2–6)
Duration of ARDS prior inclusion, days, median (IQR)	0 (0–1)
Duration of MV, days, median (IQR)	20 (16–27)
Length of ICU stay, days, median (IQR)	26 (18–31)
ICU mortality, n (%)	12 (60)

ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range (25–75%); MV = mechanical ventilation; SAPS II = simplified acute physiologic score; SOFA = sequential organ failure assessment.

Table 2. Respiratory, Hemodynamic, and NICO-related Parameters in the Study Population at Inclusion

Variables, Units	
Respiratory parameters	
V_T, ml · kg^{-1} PBW	6.3 ± 0.4
Vt_{exp}, ml · kg^{-1}	411 ± 73
RR, c · min^{-1}	22 ± 3
V_M, l · min^{-1}	9 ± 1
Pplat, cm H_2O	23 ± 3
$PEEP_{tot}$, cm H_2O	10 ± 1
pH_a	7.32 ± 0.1
$Paco_2$, mmHg	44 ± 5
Pao_2/Fio_2, mmHg	174 ± 31
Q_S/Q_T, %	30 ± 6
Hemodynamic parameters	
HR, bpm	86 ± 20
MAP, mmHg	75 ± 6
mPAP, mmHg	27 ± 4
CVP, mmHg	9 ± 3
PAOP, mmHg	11 ± 3
CO_{TD}, l · min^{-1}	6.8 ± 1.6
SV_{TD}, ml	81 ± 16
$Davo_2$, ml · dl^{-1}	3.3 ± 0.6
Tao_2, ml · min^{-1}	860 ± 209
E_Ro_2, %	26 ± 5
Vo_2, ml · min^{-1}	218 ± 45
NICO-related parameters	
Vco_2, ml · min^{-1}	178 ± 42
V_D/V_T, %	59 ± 8
$V_{D\ AIRWAY}$, ml	190 ± 37
$V_{D\ ALV}$, ml	38 ± 25
$V_{T\ ALV}$, ml	203 ± 65
$V_{M\ ALV}$, ml	4.4 ± 1.1
PEF, l · min^{-1}	45 ± 9
CO_{NICO}, l · min^{-1}	5.8 ± 1.9
SV_{NICO}, ml	68 ± 21
$PCBF_{NICO}$, l · min^{-1}	4.7 ± 1.6

Data are expressed as mean ± standard deviation.

CO_{NICO} = cardiac output obtained by NICO; CO_{TD} = cardiac output obtained by thermodilution; CVP = central venous pressure; $Davo_2$ = arteriovenous oxygen content difference; E_Ro_2 = oxygen extraction ratio; HR = heart rate; MAP = mean arterial pressure; mPAP = mean pulmonary arterial pressure; $Paco_2$ = arterial carbon dioxide tension; Pao_2/Fio_2 = arterial oxygen tension to inspired oxygen fraction ratio; PAOP = pulmonary artery occlusion pressure; PBW = predicted body weight; $PCBF_{NICO}$ = pulmonary capillary blood flow obtained by NICO; $PEEP_{tot}$ = total positive end expiratory pressure; PEF = peak expiratory flow; pH_a = arterial pH; Pplat = plateau pressure; Q_S/Q_T = venous admixture; RR = respiratory rate; SV_{NICO} = stroke volume obtained by NICO; SV_{TD} = stroke volume obtained by thermodilution; $T_{aa}o_2$ = oxygen delivery; Vco_2 = carbon dioxide production; $V_{D\ AIRWAY}$ = anatomical dead space (airway and instrumentation); V_{DALY} = alveolar dead space; V_D/V_T = total dead space to tidal volume ratio; V_M = minute ventilation; Vo_2 = oxygen consumption; V_T = tidal volume; $V_{T\ ALV}$ = alveolar tidal volume; $V_{T\ exp}$ = expiratory tidal volume; $V_{M\ ALV}$ = alveolar minute ventilation.

min^{-1} with partial carbon dioxide rebreathing. Mean cardiac output values were 6.7 ± 1.9 l · min^{-1} with thermodilution and 5.8 ± 1.7 l · min^{-1} with partial carbon dioxide rebreathing. The correlation coefficient between methods was $r^2 = 0.42$ ($P < 0.001$, fig. 1). Bias was 0.8 ± 1.2 l · min^{-1}, and limit of agreement ranged from −2.1 to 3.7 l · min^{-1} (fig. 2). Percentage error was 36%. In linear mixed analysis, dead space, $Davo_2$, and baseline cardiac output were independently associated with difference between methods (table 3).

Pulmonary Capillary Blood Flow. Pulmonary capillary blood flow values ranged from 2 to 8.5 l · min^{-1} with thermodilution and from 2.2 to 9.9 l · min^{-1} with partial carbon dioxide rebreathing. Mean pulmonary capillary blood flow values were 4.6 ± 1.3 l · min^{-1} with thermodilution and 4.8 ± 1.4 l · min^{-1} with partial carbon dioxide rebreathing. The correlation coefficient between methods was $r^2 = 0.45$ ($P < 0.001$, fig. 3). Bias was −0.1 ± 0.8 l · min^{-1}, and limit of agreement ranged from −2.2 to 1.9 l · min^{-1} (fig. 4). Percentage error was 35%. In linear mixed analysis, dead space and mean pulmonary arterial pressure were independently associated with difference between methods (table 4).

Pulmonary Shunt. Pulmonary shunt (Q_S/Q_T at FIO_2 1) values ranged from 22 to 40% with thermodilution and from 6 to 28% with partial carbon dioxide rebreathing. Mean shunt values were 30 ± 6% with thermodilution and 18 ± 6% with partial carbon dioxide rebreathing. The correlation coefficient between methods was $r^2 = 0.17$ ($P = 0.046$). Bias and limit of agreement were, respectively, 12 ± 6% and −0.5 to 24%.

Discussion

The main findings of this study are that, in a population of ARDS patients receiving lung protective ventilation, (1) partial carbon dioxide rebreathing cannot replace thermodilution for the measurement of cardiac output or

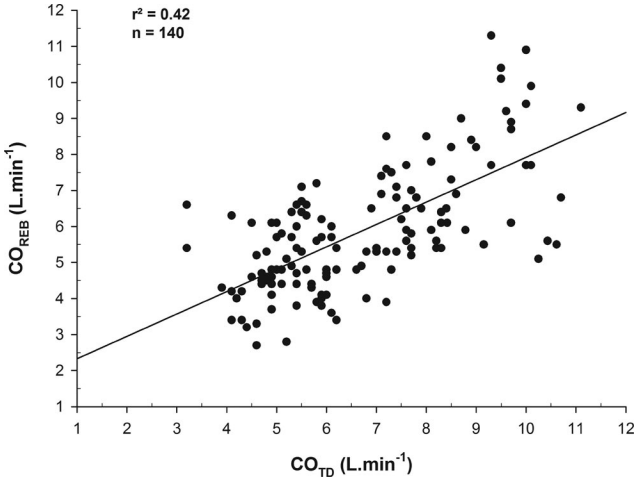

Fig. 1. Linear regression plot of the cardiac output values measured by thermodilution (CO_{TD}) and by partial carbon dioxide rebreathing (CO_{REB}). *Solid line* represents the regression line. $P < 0.001$ for significance of the Spearman rank order correlation.

pulmonary capillary blood flow because it slightly overpasses the boundary of clinical relevance, and (2) the main factors that contribute to differences between methods were the mean pulmonary arterial pressure, the dead space fraction, the arteriovenous oxygen content difference, and the baseline cardiac output.

In the current study, the partial carbon dioxide rebreathing method underestimated cardiac output. Most previous studies have reported similar results.[15,17,18] Because the partial carbon dioxide rebreathing method is underlaid by a number of assumptions, several factors may have contributed to this difference.[41]

The change in P_{ETCO_2} during rebreathing is supposed to mirror the change in Ca_{CO_2}. However, the relation between P_{ETCO_2} and Ca_{CO_2} is not a straight line but curvilinear, convex at higher values. Thus, depending on the nonrebreathing P_{ETCO_2} value, the change in Ca_{CO_2} will differ. For instance, a high P_{ETCO_2} will be associated with a lower change in Ca_{CO_2}.

The difference between P_{ETCO_2} and Pa_{CO_2} should remain constant during the rebreathing and the nonrebreathing periods.[11,13] Basically, this difference depends on the magnitude of dead space, which is largely increased in ARDS patients.[42] In the setting of high dead space fraction, alveolar ventilation is reduced and the time required for equilibrium after a rebreathing period is longer. Thus the difference between P_{ETCO_2} and Pa_{CO_2} will not remain constant. It must been underlined that the low tidal ventilation employed in this study may have also increased dead space.[21]

The change in mixed venous carbon dioxide content during rebreathing is supposed to be negligible. This assumption is supported by the large carbon dioxide storage capacity of the body.[11,13] Odenstedt *et al.* reported a slight increase in Pv_{CO_2} (2.5 ± 0.3%) during the rebreathing period.[17] In this study, we did not record Pv_{CO_2}, but we would expect at least similar variation. Nillson *et al.* stated

Table 3. Estimated Values of the Fixed Effect with Corresponding *P* Values on the Difference in Cardiac Output Measurement between Thermodilution and Partial Carbon Dioxide Rebreathing

Variables	Estimated Value	Standard Error	*P* Value
Shock	0.39	0.27	0.145
Dead space, %	4.48	1.62	0.006
Dav_{O_2}, ml · dl^{-1}	−0.60	0.18	0.001
mPAP, mmHg	0.05	0.03	0.132
Baseline CO, l · min^{-1}	0.20	0.06	0.001
$PEEP_{tot}$, cm H_2O	−0.03	0.09	0.681

CO = cardiac output; Dav_{O_2} = arteriovenous oxygen content difference; mPAP = mean pulmonary arterial pressure; $PEEP_{tot}$ = total positive end expiratory pressure.

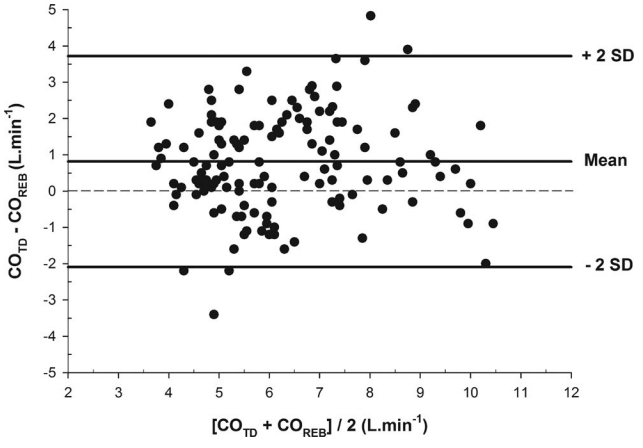

Fig. 2. Scatterplot of the difference and average of the cardiac output values measured by thermodilution (CO_{TD}) and by partial carbon dioxide rebreathing (CO_{REB}). *Solid line* represents the mean, the upper 95% confidence interval line (+2 SD), and the lower 95% confidence interval line (–2 SD).

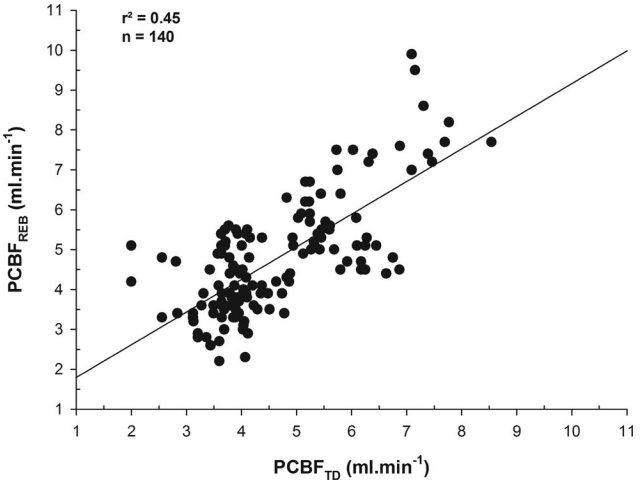

Fig. 3. Linear regression plot of the pulmonary capillary blood flow values measured by thermodilution ($PCBF_{TD}$) and by partial carbon dioxide rebreathing ($PCBF_{REB}$). *Solid line* represents the regression line. $P < 0.001$ for significance of the Spearman rank order correlation.

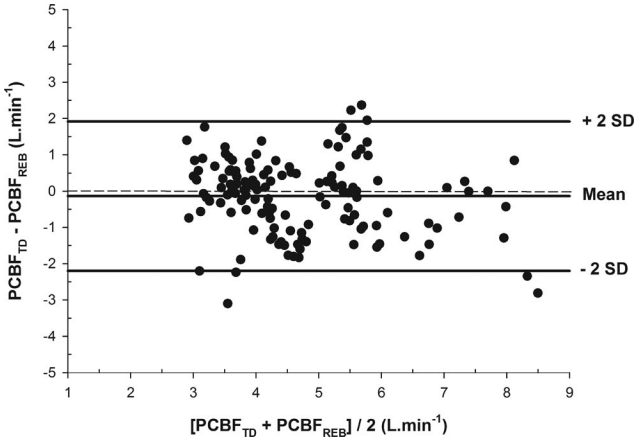

Fig. 4. Scatterplot of the difference and average of the pulmonary capillary blood flow values measured by thermodilution ($PCBF_{TD}$) and by partial carbon dioxide rebreathing ($PCBF_{TD}$). *Solid line* represents the mean, the upper 95% confidence interval line (+2 SD), and the lower 95% confidence interval line (–2 SD).

that the range of $Pvco_2$ variation is not large enough to influence cardiac output's measurement.[16]

Finally, our data show a large and systematic underestimation of pulmonary shunt by using the partial rebreathing method as compared with venous admixture. Similar underestimation has been reported already in critically ill patients.[17] One of the sources of error in the shunt's estimation may be in the computation of arterioenous oxygen content difference. The $NICO_2$ software uses a constant value at 5 ml · dl^{-1}, which is largely above the range observed in the ARDS population. In the current study, the mean $Davo_2$ was 3.3 ± 0.6 ml · dl^{-1}. Hence, we are not surprised to identify $Davo_2$ as a factor contributing to inaccuracy in the measurement of cardiac output. The lower the $Davo_2$, the larger the error in measurement. Nevertheless, the contribution of shunt in the underestimation of cardiac output is weak, as confirmed by the poor weight of its estimated value in the linear mixed model. For instance, supposing a cardiac output value of 5 l · min^{-1}, a shunt value of 20%, and an error in the estimation of shunt of 10%, the change in the cardiac output measurement will be about 0.5 l · min^{-1}.

Table 4. Estimated Values of the Fixed Effect with Corresponding *P* Values on the Difference in Pulmonary Capillary Blood Flow between Thermodilution and Partial Carbon Dioxide Rebreathing

Variables	Estimated Value	Standard Error	*P* Value
Shock	0.34	0.21	0.111
Dead space, %	4.25	1.27	0.001
$Davo_2$, ml · dl^{-1}	−0.06	0.14	0.657
mPAP, mmHg	0.05	0.02	0.040
Baseline CO, l · min^{-1}	0.05	0.04	0.259
$PEEP_{tot}$, cm H_2O	−0.02	0.07	0.690

CO = cardiac output; $Davo_2$ = arteriovenous oxygen content difference; mPAP = mean pulmonary arterial pressure; $PEEP_{tot}$ = total positive end expiratory pressure.

Because an increase in pulmonary shunt and dead space fraction is a common finding during ARDS,[43] De Abreu *et al.* have investigated their respective effect on the precision of the method.[44] In an animal model, they demonstrated that increasing both shunt and dead space induces error in the estimation of $Caco_2$. They also demonstrated that during high cardiac output conditions, the higher $Pvco_2$ values tend to overestimate $Petco_2$ during rebreathing. By using computer models of emphysema and pulmonary embolism, Yem *et al.* have identified four sources of systematic error: ventilation-perfusion imbalance, alveolar-proximal airway Pco_2 gradient, venous blood recirculation, and duration of the rebreathing period.[45] In the current study, we demonstrated in a clinical setting that dead space, $Davo_2$, and baseline cardiac output have a significant impact on the accuracy of the cardiac output determination by partial rebreathing. According to the estimated values of parameters entered in our linear mixed model, dead space seems to be the most important source of error.

Contrasting with the results on cardiac output, the measurement of pulmonary capillary blood flow is somewhat overestimated by the partial rebreathing method, but agreement with thermodilution is closer. Bear in mind that the partial carbon dioxide rebreathing algorithm has been elaborated to measure pulmonary capillary blood flow and not cardiac output. As a result, it is important to note that the accuracy of the algorithm is correct in most measurements. In the current study, we found that the accuracy of the method is reduced in the setting of high dead space fraction and/or a high mean pulmonary artery pressure; both are associated with the severity of the disease. Nevertheless, the clinical utility of the bedside measurement of pulmonary capillary blood flow in ARDS patients remains poorly investigated.[12] De Abreu *et al.* have suggested a place in the titration of positive end-expiratory pressure, challenging the hypothesis that excessive positive end-expiratory pressure level will be associated with a worse pulmonary capillary blood flow.[46] Whether pulmonary capillary blood flow should be considered as a resuscitation endpoint remains to be investigated.

From a clinical point of view, one major question is whether the measurement of cardiac output or pulmonary capillary blood flow by partial rebreathing is sufficiently close to the "true value" such that it would provide helpful assistance to the physician. For this purpose, two major criteria have been proposed to address the clinical relevance of a new method: SD of bias less than 1 l · min^{-1} and percentage error of agreement no greater than 30%.[39,47] In our population, percentage error was 36% for cardiac output and 35% for pulmonary capillary blood flow. SD of bias overlapped 1 l · min^{-1} for cardiac output (1.2 l · min^{-1}) but not for pulmonary capillary blood flow (0.8 l · min^{-1}). On the basis of the limit of agreement that we observed, 95% of the pulmo-

nary capillary blood flow values measured by partial rebreathing ranged between -2.2 and $1.9\ l \cdot min^{-1}$ around the true value. In the same way, 95% of the cardiac output values measured by rebreathing ranged between -2.1 and $3.7\ l \cdot min^{-1}$ around the true value. Taken together, these results indicate that pulmonary capillary blood flow and cardiac output measurement by partial rebreathing should not be recommended *stricto sensu* for routine monitoring.

Some limitations must be highlighted in this study. We used continuous and not intermittent thermodilution measurement, but equivalence has already been addressed in critically ill patients, as discussed in the Materials and Methods section. Although the shunt fraction was only measured once at the beginning of the 2-h period, making this a potential limitation of the study, we controlled most of respiratory, hemodynamic, and metabolic variables. We investigated ARDS patient who all received standardized mechanical ventilation with low tidal volume and positive end-expiratory pressure. As a result, this study presents the advantage of testing a new device under homogeneous ventilator settings. However, these results cannot be extrapolated to other settings or breathing patterns. In the same way, our data were recorded under stable hemodynamic conditions of arterial pressure and cardiac output, and most of our patients received norepinephrine; these results may not be extrapolated to other hemodynamic situations. The crude mortality of our population was 60%, but it seems in accordance with the literature regarding the number of organ failure and the characteristics of our patients.

In conclusion, partial carbon dioxide rebreathing is a semicontinuous, noninvasive, and automated method to quantify pulmonary capillary blood flow. In the situation of ARDS patients ventilated with lung protective settings, its accuracy is not sufficient to replace thermodilution for the routine measurement of pulmonary capillary blood flow or cardiac output. The main clinical factors associated with the inaccuracy of the rebreathing method were baseline cardiac output, dead space, and $Dav\bar{o}_2$ for cardiac output measurement; only dead space and mean pulmonary arterial pressure were associated with the inaccuracy of the pulmonary capillary blood flow measurement. Further research will be required to improve the algorithm of partial carbon dioxide rebreathing for ARDS patients.

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