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Evaluation of a new device for noninvasive measurement of nonshunted pulmonary capillary blood flow in patients with acute lung injury

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A patent on the device for noninvasive measurement of nonshunted pulmonary capillary blood flow has been issued to Drs. Gama de Abreu and Albrecht in the United States and is still pending in other countries. MedServ, Leipzig, Germany, has been granted the license with nonexclusive rights to produce this equipment. This work was supported by departmental funds

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Abstract *Objectives:* To evaluate the performance of a new device for noninvasive measurement of nonshunted pulmonary capillary blood flow (PCBF) by partial CO_2 rebreathing. *Design and setting:* Prospective clinical trial in an intensive care unit of a university hospital. *Patients and participants:* Twenty mechanically ventilated patients with acute lung injury. *Interventions:* Variations in PEEP of ±3 cmH_2O. *Measurements and results:* Initially PCBF was measured invasively as cardiac output minus venous admixture $(\dot{Q}_{VA}/\dot{Q}_t)$ flow, and by partial CO_2 rebreathing at baseline PEEP ($PEEP_b$). The PEEP was then reduced by 3 cmH_2O (to $PEEP_{b-3}$) and measurements were repeated after 30 min. PEEP was then increased by 6 cmH_2O (to $PEEP_{b+3}$), and measurements were repeated after 10, 20, and 30 min. The overall correlation coefficient between noninvasive and invasive PCBF measurements at $PEEP_b$ was high (r=0.97), with close agreement between methods being observed (0.1±0.6 l/min, bias and precision, respectively). Accordingly, both the correlation coefficient and agreement between methods for changes in PCBF from $PEEP_{b-3}$ to $PEEP_{b+3}$ levels were satisfactory (r=0.71; 0.2±0.5 l/min, bias and precision). The new device was able to detect the correct PCBF trend in 17 of 20 patients investigated and in all patients who showed invasive PCBF changes equal to or greater than 0.3 l/min (n=12). Noninvasive PCBF changes were stable as early as 10 min after variation in PEEP, as compared to 30 min values. *Conclusions:* The new device appears to be clinically useful for the monitoring of PCBF in patients suffering from acute lung injury. Our results suggest that titration of PEEP aimed at improving PCBF can be performed with the new device.

Keywords Nonshunted pulmonary capillary blood flow · Noninvasive · CO_2 rebreathing · Automated · Positive end-expiratory pressure

Introduction

We recently demonstrated that the nonshunted pulmonary capillary blood flow (PCBF) can be noninvasively measured by short periods of partial CO_2 rebreathing and suggested that this technique could prove useful for guiding adjustments of positive end-expiratory pressure (PEEP) in mechanically ventilated patients [1]. Nevertheless, our previous work did not include modulations of the respiratory pattern, which may affect PCBF significantly, for instance, the variation in PEEP. Also, the experimental setup used in our previous work [1] was not automated, and switching of valves to obtain rebreathing maneuvers had to be performed manually. In addition, the identification of measurement artifacts had to be made by a physician experienced in the method. With these technical limitations in mind, a fully automated device was developed which permits the monitoring of

PCBF without intervention with the medical personnel and is capable of identifying measurement artifacts by means of gas exchange stability criteria (David Monitor, MedServ, Leipzig, Germany).

The use of PEEP in mechanically ventilated patients is usually associated with an improvement in arterial oxygenation, but, unfortunately, also with an impairment of lung perfusion. Evidence has accumulated that PEEP can stabilize recruited alveoli [2, 3, 4, 5], preventing cycling closure and reopening of atelectasis [6, 7] and improving ventilation/perfusion matching. However, such beneficial effects may be outweighed by the reduction in the venous return and the impairment of the right ventricle function, phenomena which are commonly observed during the use of PEEP [8, 9, 10]. As a consequence, the total pulmonary perfusion may decrease, resulting in a diminished blood flow through well ventilated lung zones, i.e., a reduced PCBF. Hence monitoring of PCBF under those conditions may be clinically useful, particularly if it can be accomplished noninvasively and automatically.

The aim of this work was to evaluate the performance of the new device for noninvasive measurement of PCBF in mechanically ventilated patients suffering from acute lung injury during fine titration of PEEP.

Materials and methods

Partial CO_2 rebreathing maneuvers

Partial CO_2 rebreathing maneuvers were performed using the David Monitor, which consists of a rebreathing device and a microprocessed control unit. The rebreathing device is connected between the endotracheal tube of the patient and the Y-piece of the mechanical ventilator. It contains a hot-wire sensor for measurement of airflow (EKU Elektronik, Leiningen, Germany), a mainstream infrared CO_2 sensor for measurement of CO_2 (Capnostat, Novametrix, Wallingford, Conn., USA), and an electromagnetic valve that can switch between a 30-ml and a 200-ml deadspace (nonrebreathing and rebreathing deadspace, respectively). In the control unit the flow and CO_2 signals, which are synchronized to each other, and have no important phase shift, are digitized at 48 Hz and processed to calculate breath-by-breath CO_2 elimination ($\dot{V}CO_2$) and end-tidal CO_2 pressure ($P_{ET}CO_2$). Also, the con-trol unit commands the electromagnetic valve to switch from the nonrebreathing to the rebreathing deadspace for 30 s. During this period ($\dot{V}CO_2$) is reduced, and $P_{ET}CO_2$ rises until the valve is switched back to the nonrebreathing deadspace. Finally, PCBF is calculated according to the differential form of the Fick principle presented in Eq. 1, which was deduced and described in detail in our previous work [1]:

$$PCBF = -\frac{\Delta \dot{V}CO_2}{f(\Delta P_{ET}CO_2)} \tag{1}$$

where ($\dot{V}CO_2$) and $\Delta P_{ET}CO_2$ represent the ($\dot{V}CO_2$) and $P_{ET}CO_2$ differences between the nonrebreathing and the rebreathing periods, respectively. Briefly, nonrebreathing ($\dot{V}CO_2$) and $P_{ET}CO_2$ are calculated as the mean values of each respective variable during 60 s of ventilation with the minimal apparatus deadspace. Rebreathing ($\dot{V}CO_2$) and $P_{ET}CO_2$ are calculated as the mean values of the respective variables within 15 and 30 s after the electromagnetic valve was switched, and the patient was ventilated through the additional 200 ml deadspace, as described in the work by Gama de Abreu et al. [1]. Finally, f represents the equation proposed by McHardy [11] to convert $P_{ET}CO_2$ difference into end-capillary CO_2 content ($CcCO_2$) difference, as shown in Eq. 2:

$$\begin{aligned} CcCO_2(R) - CcCO_2(NR) = {} & 11.02 \times (P_{ET}CO_2(R)^{0.396}) \\ & - (P_{ET}CO_2(NR)^{0.396}) \\ & - 0.015 \times (15 - HB) \\ & \times (P_{ET}CO_2(R) \\ & - (P_{ET}CO_2(NR)) \end{aligned} \tag{2}$$

where Hb is hemoglobin concentration in g/dl.

The David Monitor considers the measurements to be artifact free if: (a) ($\dot{V}CO_2$) remains stable during the whole measurement period (<20% variation between two consecutive breaths, except to values immediately before and after switching of the rebreathing valve); (b) ($\dot{V}CO_2$) values during the rebreathing period are at least 20% lower than during the nonrebreathing period; (c) ($\dot{V}CO_2$)values do not show a trend towards increase or decrease during the nonrebreathing period; and (d) $P_{ET}CO_2$ rises >2 mmHg during rebreathing. These criteria were derived from the observation of steady state gas exchange conditions obtained with a gas exchange model at the bench.

Protocol for measurements

The study protocol was approved by the Ethics Committee for Human Research of the University Clinic Carl Gustav Carus, Technical University of Dresden. Informed consent for performing the measurements was obtained from a next of kin. A supervising physician not involved in the study was present during all measurements.

Twenty mechanically ventilated patients between the ages of 17 and 86 years and suffering from ALI [12] (Lung Injury Score 2.25±0.5, range 1.25–3.25) were investigated. Patients' general characteristics are presented in Table 1. Criteria for excluding patients from the study were: (a) head injury without intracranial pressure monitoring and (b) presence of a bronchopleural fistula. Criteria for interrupting the study were: (a) arterial oxygen saturation less than 90%, (b) cardiac index less than 2.0 l min^{-1} m^{-2}, (c) peak airway pressure of 45 cmH_2O or higher, and (d) intracranial pressure of 15 mmHg or higher in patients with head injury.

Patients were sedated with a combination of an opioid (e.g., 0.1–0.2 mg fentanyl or 10–40 µg sufentanil per hour) and a hypnotic drug (e.g., 10–20 mg midazolam or 3–4 mg/kg propofol per hour) with boluses being given as necessary to achieve adequate depth of sedation. Patients were naso- or orotracheally intubated, and their lungs were ventilated using the pressure-controlled modus. The initial ventilator settings were defined by the supervising physician according to the general guidelines of the Clinic of Anesthesiology at the University Clinic Carl Gustav Carus for patients with ALI. Briefly, these guidelines can be summarized as follows: (a) pressure-controlled ventilation is preferred, minimal PEEP value is 5 cmH_2O, FIO_2 is adjusted to maintain arterial oxygen saturation higher than 92%; (b) I:E ratio or inverse ratio ventilation should be set to achieve auto-PEEP near 2 cmH_2O, and PEEP should be titrated to maintain FIO_2 at less than 0.6; (c) peak pressures must be minimized avoiding values greater than 35 cmH_2O and maintaining tidal volumes in the range of 6–10 ml/kg ideal body weight; (d) respiratory frequency should be titrated to achieve pH higher than 7.25 using the concept of permissive hypercapnia at lower tidal volumes, however not greater than 25 breaths/min. Decisions regarding deviation from the general guidelines are taken by the medical staff.

Hemodynamic monitoring was performed by means of an arterial catheter placed in the right or left radial or femoral artery and also by an 8-F, 110-cm-long pulmonary artery catheter with fiber-

Table 1 Patient characteristics; infusion rates of vasoactive agents are given in milligrams per kilogram per minute and were held constant throughout measurements (*LIS* Lung Injury Score according to [12], *PEEP* positive end-expiratory pressure, *A* adrenaline, *NA* noradrenaline, *Dop* dopamine, *Dob* dobutamine)

Patient no.	Age (years)	Sex	Primary diagnosis	LIS	$PEEP_b$ (cmH_2O)	Vasoactive drugs
1	79	M	Sepsis	2.5	10	NA (0.07)+Dob (2)
2	71	M	Sepsis	1.75	5	NA (0.05)
3	68	M	Pneumonia	2.0	5	Dop (5)
4	86	M	Pneumonia	2.0	7	Dop (6)
5	64	M	Acute pancreatitis	2.0	8	Dop (3)
6	41	F	Pneumonia	3.25	14	A (0.02) + Dob (2)
7	66	M	Pneumonia	3.25	11	Dop (5)
8	25	M	Burn	1.25	5	NA (0.02)
9	38	F	Acute pancreatitis	2.25	7	A (0.02) + Dob (2)
10	57	M	Sepsis	2.25	7	NA (0.06) + Dop (5)
11	17	M	Lung contusion	1.75	5	Dop (5)
12	66	F	Sepsis	2.25	10	NA (0.02)
13	72	F	Head injury	2.0	6	NA (0.07) + Dop (5)
14	76	M	Multiple trauma	2.5	10	Dop (4)
15	86	M	Pneumonia	2.0	5	Dop (3)
16	83	F	Aspiration of gastric contents	3.0	10	NA (0.02) + Dob (3)
17	66	F	Heart insufficiency, sepsis	1.75	5	NA (0.02) + Dob (4)
18	74	M	Acute pancreatitis	2.25	13	NA (0.01) + Dob (3)
19	59	M	Aspiration of gastric contents	2.75	9	NA (0.4)
20	57	M	Pneumonia	2.75	10	NA (0.06) + Dop (2)

optic oximetry placed through the right innominate vein or the right internal jugular vein (Abbott, Irving, Calif., USA). Prior to measurements the volume status of patients was manipulated to maintain the pulmonary artery occlusion pressure in the upper normal range (13–15 mmHg). Catecholamines were also administrated as necessary, depending on the underlying disease and the hemodynamic status. Cardiac output was measured by the thermodilution technique using the CMS Monitor (Agilent Technologies, Böblingen, Germany). Cardiac output values were averaged from four consecutive measurements with 10 ml 0.9% iced saline solution equally distributed over the entire respiratory cycle, since this procedure has been demonstrated to deliver more accurate results [13]. Blood samples obtained from the peripheral and pulmonary arteries were immediately assayed or kept in ice until analysis by the ABL 620 blood gas analyzer (Radiometer, Copenhagen, Denmark).

Initially, cardiac output by thermodilution, arterial and mixed venous blood gas sampling, and duplicate partial CO_2 rebreathing maneuvers, were performed with the baseline PEEP value set at the mechanical ventilator by the controlling physician ($PEEP_b$, Table 1). $PEEP_b$ was then reduced by 3 cmH_2O (to $PEEP_{b-3}$). After 30 min stabilization the hemodynamic, blood gas, and partial CO_2 rebreathing measurements were repeated. PEEP was then increased by 6 cmH_2O, to 3 cmH_2O above $PEEP_b$ ($PEEP_{b+3}$), and measurements were repeated at 10, 20, and 30 min thereafter. To improve the accuracy partial CO_2 rebreathing measurements at $PEEP_b$ and 30 min after the variation in PEEP were performed in duplicate, and values of measurements free of artifact were averaged. The other settings of the mechanical ventilator, including FIO_2 and hemodynamic support (Table 1), were kept constant throughout measurements. Finally, the results were reported to the supervising physician, who decided to set the PEEP back to baseline levels or to adjust it to a new level.

Calculated variables

Oxygen blood gas contents and $(\dot{Q}_{VA}/\dot{Q}_t)$ were calculated according to standard formulas presented in the literature [14]. For comparison with the noninvasive method PCBF was also calculated invasively as cardiac output minus venous admixture flow, as shown in Eq. 3:

$$PCBF = \dot{Q}_t \times \left(1 - \dot{Q}_{VA}/\dot{Q}_t\right) \quad (3)$$

Statistical analysis

The strength of correlation between noninvasive and invasive values of PCBF obtained at $PEEP_b$ was determined by Pearson's correlation coefficient. Agreement between measurements was determined by calculating bias (mean difference in values) and precision (standard deviation of the difference in values), according to the method of Altman and Bland [15]. To evaluate the stability of PCBF values over time within subgroups of patients who showed an increase or decrease in PCBF according to a post hoc subdivision, paired Student's *t* tests with Bonferroni's correction were used. A p level less than 0.05 was considered significant in all tests.

Results

Comparison between invasive and noninvasive measurements of pulmonary capillary blood flow

The entire protocol was performed in all of the patients who entered the study (n=20), and none of the interrupting criteria was achieved. The overall correlation coefficient between invasive and noninvasive PCBF values was r=0.97 (p<0.001; Fig. 1, left). Bias and precision calculations showed a slight tendency for the partial CO_2 rebreathing technique to overestimate the invasive method (0.1±0.6 l/min; Fig. 1, right). The correlation coeffi-

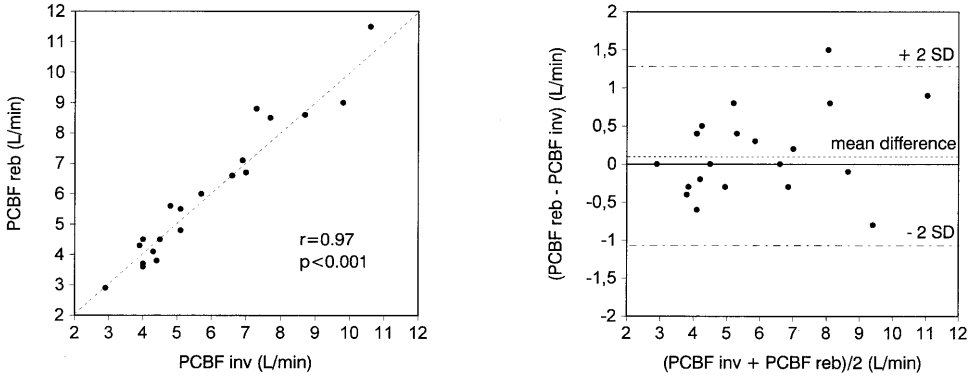

Fig. 1 *Left* Scatterplot of nonshunted pulmonary capillary blood flow measured by partial CO_2 rebreathing (*PCBFreb*) against nonshunted pulmonary capillary blood flow by thermodilution combined to blood gas analysis at baseline PEEP value (*PCBFinv*, determined as cardiac output minus venous admixture, see text; *n*=20). *Dashed line* Identity. *Right* Difference between and plotted against the average of the two techniques; *inner dashed line* mean difference (0.1 l/min); *outer dashed lines* 95% confidence limits (±2 SD; SD=0.6 l/min) of the difference between methods

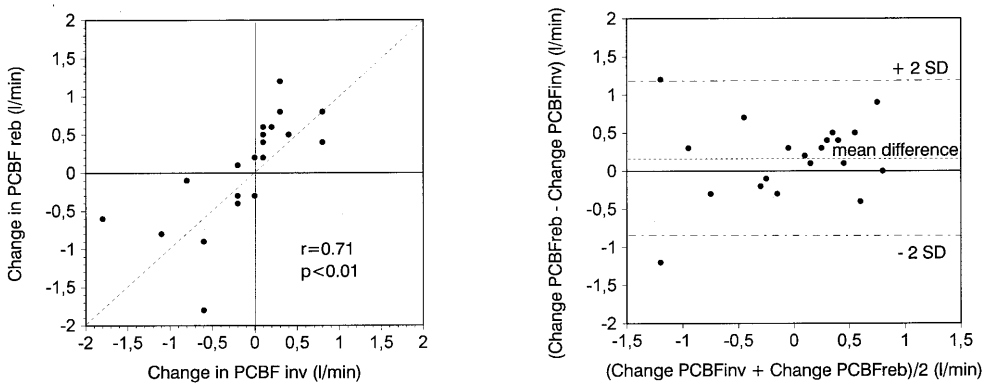

Fig. 2 *Left* Scatterplot of changes in nonshunted pulmonary capillary blood flow by partial CO_2 rebreathing (*Change PCBFreb*) against changes in nonshunted pulmonary capillary blood flow by thermodilution combined to blood gas analysis (*Change PCBFinv*), which resulted from the variation in PEEP from $PEEP_{b-3}$ to $PEEP_{b+3}$ levels (see text); *dashed line:* identity line. *Right* Difference between and plotted against the average of the two techniques; *inner dashed line* mean difference (0.2 l/min); *outer dashed lines* 95% confidence limits (±2 SD; SD=0.5 l/min) of the difference between methods. The noninvasive method correctly determined the trend of PCBF in 17 of 20 patients and in all patients with invasive PCBF changes of at least 0.3 l/min (*n*=12)

cient between changes in PCBF measured by partial CO_2 rebreathing and by the invasive method as a consequence of varying PEEP from $PEEP_{b-3}$ to $PEEP_{b+3}$ levels was r=0.71 (p<0.01; Fig. 2, right). Bias and precision calculations for changes in PCBF were 0.2±0.5 l/min (Fig. 2, left), with the noninvasive method identifying a correct trend of PCBF in 17 of the 20 patients and in all patients who showed invasive PCBF changes of at least 0.3 l/min (*n*=12).

Time needed for pulmonary capillary blood flow by partial CO_2 rebreathing to achieve a new steady state

As a result of varying PEEP from the lower to the higher level ($PEEP_{b-3}$ and $PEEP_{b+3}$, respectively), 12 patients showed an increase in PCBF and 8 a decrease (Fig. 3). In those with a PCBF increase the values at 10 and 20 min did not differ significantly from values determined at

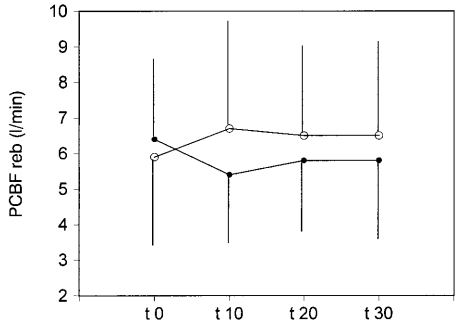

Fig. 3 Nonshunted pulmonary capillary blood flow by partial CO_2 rebreathing (*PCBFreb*) measured at the baseline PEEP value minus 3 cmH_2O (*t0*) and 10, 20, and 30 min (*t10*, *t20*, and *t30*, respectively) after increasing PEEP to the baseline value plus 3 cmH_2O (see text). *Solid circles* Patients with a decrease in PCBFreb (*n*=8); *open circles* patients with an increase in PCBF (*n*=12). Values at *t10* and *t20* were not significantly different from values at *t30* within subgroups. No statistical tests were performed to assess differences between subgroups (post hoc subdivision)

30 min (p=0.06 and p=0.27, respectively; Fig. 3). Similarly, in those with a PCBF decrease the values determined after 10 and 20 min did not differ significantly from values after 30 min (p=0.64 and p=0.19, respectively; Fig. 3).

Discussion

The accuracy of ($\dot{V}CO_2$) and $P_{ET}CO_2$ measurements is crucial in determining PCBF by the partial CO_2 rebreathing technique. Findings by one of the authors (M.G.A.) on the bench show that David Monitor measurements of ($\dot{V}CO_2$) and $P_{ET}CO_2$ are within ±5% of the reference for a wide range of values [16], which is highly acceptable for clinical purposes.

One of the major goals of mechanical ventilation is to provide support for pulmonary gas exchange with minimal impairment of hemodynamics. Therefore it may be beneficial to optimize the respiratory pattern according to the variable which results from these two factors, namely PCBF. According to our results, the David Monitor measures PCBF with satisfactory accuracy and precision when duplicate measurements free of artifact are obtained, even during fine titration of PEEP. Measurements obtained with the new device are more reliable than those obtained with the nonautomated system used in our previous work [1] (r=0.97 vs. r=0.88; 0.1±0.6 vs. 0.3±0.8 l/min – bias ±precision, respectively; no statistical tests performed). This finding adds significantly to our knowledge concerning the clinical value of the partial CO_2 rebreathing that has accumulated as the result of previous studies [17, 18, 19, 20].

According to our data, PCBF measured with the new device tends to achieve a new stable level as early as 10 min after variation in PEEP compared with values determined at 30 min. This finding is in agreement with the report by Patel and Singer [21], who showed that gas exchange and hemodynamics of mechanically ventilated patients tend to achieve a new steady state within 10–15 min after alterations in the respiratory pattern. The practical consequence of this observation is that adjustments of the respiratory pattern aimed at improving PCBF can be performed as rapidly as every 10 min with the new noninvasive device.

Although the titration of PEEP according to PCBF may be beneficial, it was beyond the scope of this work to determine the impact of a mechanical ventilator strategy aimed at maximizing PCBF values on patient outcome. Theoretically, there should be an optimal combination of total pulmonary blood flow and gas exchange that leads to higher PCBF values. This combination does not necessarily represent the best gas exchange or the best pulmonary perfusion, but rather an optimal interaction between these factors. This issue deserves further investigation in clinical studies.

An issue of concern in our study is the magnitude of PCBF changes caused by relatively small variations in PEEP. Due to the importance for the clinical practice we considered it more appropriate to perform the analysis using step variations in PEEP which are more commonly employed in the clinical routine instead of maximizing the relationship between signal (magnitude of PCBF change) and noise (precision of the method) by means of wider PEEP variations. Although the investigation was performed in a lower PEEP variation range, the noninvasive method was able to detect PCBF trends satisfactorily. Another possible issue of concern is the use of only positive PEEP variation maneuvers for the evaluation of a method which can be affected by changes in PEEP in either direction. However, the variation in PEEP does not affect the partial CO_2 rebreathing method itself, but rather the variables determining PCBF, namely total pulmonary blood flow and gas exchange capability of the lungs. Therefore a protocol including the reduction in PEEP would probably not lead to different conclusions. Also important is the fact that our protocol did not include variation in the respiratory mode (e.g., pressure- vs. volume-controlled ventilation), flow pattern characteristics, or inspiratory to expiratory time ratios, which represent important steps during adjustments of the mechanical ventilation in patients suffering from ALI. Nevertheless, the extrapolation of our findings for such kind of adjustments seems to be reasonable since the physiological mechanisms underlying the effects on PCBF are the same.

The interpretation of our findings must bear in mind that the measurements were performed in patients suffering from ALI. The presence of small airway diseases, gas trapping, and low ventilation/perfusion ratio areas may all lead to an impairment of CO_2 exchange during the rebreathing period, which can adversely affect the performance of this noninvasive technique. Further studies are necessary to clarify this issue.

Finally, our results and the clinical utility of the new device cannot be extrapolated to patients who do not have respiratory patterns completely controlled by the mechanical ventilator. As demonstrated recently [22], irregularities in the respiratory pattern, such as those resulting from spontaneous ventilation superposed to controlled ventilation, adversely affect the performance of this technique.

In conclusion, the David Monitor is a new device based on the partial CO_2 rebreathing technique, which measures PCBF automatically and noninvasively in patients with ALI. Since PCBF values are practically stable as early as 10 min after the variation in PEEP, this device may be useful for guiding adjustments of the respiratory pattern in such patients. The clinical impact of a mechanical ventilator strategy guided by PCBF values needs further clinical investigation.

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