

Central Venous-to-Arterial Pco₂ Difference and Central Venous Oxygen Saturation in the Detection of Extubation Failure in Critically Ill Patients

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Objectives: To evaluate the ability of central venous-to-arterial carbon dioxide pressure difference, central venous oxygen saturation, and the combination of these two parameters to detect extubation failure in critically ill patients.

Design: Multicentric, prospective, observational study.

Setting: Three ICUs.

Patients: All patients who received mechanical ventilation for more than 48 hours and tolerated spontaneous breathing trials with a T-piece for 60 minutes.

Interventions: Extubation after successful spontaneous breathing trials. Extubation failure was defined as the need for mechanical ventilation within 48 hours.

Measurements and Main Results: The oxygen delivery index, oxygen consumption index, central venous oxygen saturation, central venous-to-arterial carbon dioxide pressure difference, and oxygen extraction were measured immediately before spontaneous breathing trials and at 60 minutes after spontaneous breathing trials initiation. Seventy-five patients were enrolled, and extubation failure was noted in 18 (24%) patients. Oxygen consumption index increased significantly during spontaneous breathing trials in the failure group. Oxygen delivery index increased in both success and failure groups. Oxygen extraction increased in the failure group ($p = 0.005$) and decreased in the success group ($p = 0.001$). Cen-

tral venous oxygen saturation decreased in the failure group and increased in the success group ($p = 0.014$). ΔPco_2 value increased in the extubation failure group and decreased in the success group ($p = 0.002$). Changes in ΔPco_2 ($\Delta - \Delta\text{PCO}_2$) and central venous oxygen saturation (ΔScvO_2) during spontaneous breathing trials were independently associated with extubation failure (odds ratio, 1.02; 95% CI, 1.01–1.05; $p = 0.006$, and odds ratio, 0.84; 95% CI, 0.70–0.95; $p = 0.02$, respectively). $\Delta - \Delta\text{PCO}_2$ and central venous oxygen saturation could predict extubation failure with areas under the curve of 0.865 and 0.856, respectively; however, their combined areas under the curve was better at 0.940.

Conclusions: We found that $\Delta - \Delta\text{Pco}_2$ and central venous oxygen saturation, during spontaneous breathing trials, were independent predictors of weaning outcomes. Combination analysis of both parameters enhanced their diagnostic performance and provided excellent predictability in extubation failure detection in critically ill patients. (*Crit Care Med* 2020; XX:00–00)

Key Words: extubation failure; oxygen consumption; oxygen delivery; spontaneous breathing trial; venous-to-arterial co₂ difference; venous oxygen saturation

Weaning and extubation are essential steps for the management of critically ill patients when mechanical ventilation (MV) is no longer required. Extubation failure (EF) occurs in approximately 10–30% (1, 2) of all patients meeting the readiness criteria and have tolerated a spontaneous breathing trial (SBT). EF is associated with prolonged MV, as well as increased morbidity and mortality (2). Therefore, the early identification of critically ill patients who are likely to experience EF is vital for improved outcomes.

Discontinuation of ventilatory support can be challenging for clinicians, mainly because the pathophysiology of weaning failure is complex and not fully understood. EF can result from different factors (respiratory, metabolic, neuromuscular), particularly cardiac factor, and can be caused by the inability of the respiratory muscle pump to tolerate increases in the

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cardiac and respiratory load (1, 3). Weaning from MV is usually associated with an increase in oxygen consumption (Vo_2) linked to the augmented work of breathing (4–7). To meet the metabolic demand of the weaning trial, increases in Vo_2 should be accompanied by increases in cardiac output (CO) and oxygen delivery (Do_2). Venous oxygen saturation reflects the balance between Vo_2 and Do_2 . In published studies, decreases in venous oxygen saturation during SBT were associated with weaning and extubation failure (8, 9); however, this was not observed in all patients with EF (10–13).

When Vo_2 increases, the tissue carbon dioxide (Co_2) production also increases. The mixed venous-to-arterial partial pressure difference of co_2 ($[\text{Pmvco}_2 - \text{Paco}_2]$) reflects the adequacy of CO in clearing out the co_2 produced by tissues (14, 15). Interestingly, $[\text{Pmvco}_2 - \text{Paco}_2]$ can be replaced by the central venous-to-arterial Pco_2 difference (ΔPco_2) in critically ill patients (16, 17), and both of them are good indicators for the assessment of the adequacy between oxygen supply and oxygen demand in chronic heart failure and septic shock patients (18, 19). Therefore, ΔPco_2 could be useful for the evaluation of extubation outcomes. Nevertheless, it has never been tested as a diagnostic tool for EF detection.

We hypothesized that patients with EF would have increased ΔPco_2 values during SBTs. Therefore, the aims of our study were as follows: 1) to evaluate the ability of changes in ΔPco_2 ($\Delta - \Delta\text{Pco}_2$), central venous oxygen saturation (ΔScvo_2), and their combination during SBTs to predict EF and 2) to assess if $\Delta - \Delta\text{Pco}_2$ is an independent predictor of EF.

MATERIALS AND METHODS

This prospective multicenter study was conducted in three general adult ICUs between the end of December 2016 and February 2018. The local Ethics Committees of each center approved the study (number:160402). Informed consent was obtained from all patients or their next of kin. The study was retrospectively registered in the ISRCTN registry (registration number ISRCTN10162509).

Patients

All patients 18 years old or older who received MV for at least 48 hours and satisfied the weaning criteria were eligible for enrollment. The readiness-to-wean criteria we employed have been described previously (1) (**Supplementary-1a**, Supplemental Digital Content 1, <http://links.lww.com/CCM/F555>). Patients also had to have an arterial catheter and a central line with the tip confirmed by radiography as being in the superior vena cava near the entrance or in the right atrium. The exclusion criteria were as follows: 1) having undergone tracheostomy, 2) do-not-reintubate orders, 3) pregnancy, 4) absence of informed consent, 5) SBT failure, and 6) inability to obtain adequate echocardiographic windows.

Weaning Protocol

SBTs were then performed in semirecumbent patients on a T-piece (20) with supplementary humidified oxygen for the achievement of an arterial oxygen saturation value greater

than 90%, as measured by pulse oximetry. The SBT duration was 60 minutes. The criteria used for poor SBT tolerance have been defined previously (20) (**Supplementary-1b**, Supplemental Digital Content 2, <http://links.lww.com/CCM/F556>). The decision to stop SBT was made by the physicians. Patients who failed SBT were reconnected to a ventilator and were not enrolled in the study.

Patients who completed the SBT were extubated and followed-up for 48 hours. The medical team (physician, nurse, and respiratory therapist) involved in the extubation decision was blinded to the ΔPco_2 and Scvo_2 results. EF was diagnosed if the patient was extubated but required MV (invasive or non-invasive) owing to respiratory failure within the following 48 hours. Criteria for poor SBT tolerance and for respiratory failure after extubation have been listed in **Supplementary-1b** (Supplemental Digital Content 2, <http://links.lww.com/CCM/F556>). The management of postextubation respiratory failure was not protocolized and was left to the physician's discretion.

Measurements

Ventilatory and hemodynamic parameters were recorded as the average of the three measurements immediately before SBT (on MV) and at 60 minutes after SBT initiation. Echocardiography assessment was performed by board-certified physicians in echocardiography immediately before SBT and at 60 minutes after its initiation, using a General Electric Vivid3 machine (GE Healthcare, Chalfont St. Giles, Buckinghamshire, United Kingdom). The velocity–time integral (VTI) was recorded by a pulsed wave Doppler on a 5-chamber apical view, and stroke volume (SV), CO, cardiac index, and SV index were calculated as described in **Supplementary-1c** (Supplemental Digital Content 3, <http://links.lww.com/CCM/F557>). Left ventricular systolic function was assessed by the left ventricular ejection fraction, as measured with Simpson's modified rule. Left ventricular diastolic function was evaluated by the measurement of the mitral E and A waves, the mean e' wave of the lateral, medial mitral annulus, and the calculation of the E/e' ratio. The average of five consecutive VTI, SV, CO, E/A, and E/e' measurements were obtained for each step of the study (before and 60 minutes after SBT initiation).

Arterial and central venous blood gas were measured using GEM Premier 4000 (Instrumentation Laboratory Co, Paris, France) immediately before SBT and at 60 minutes after SBT initiation. ΔPco_2 was calculated as the difference between the central venous and arterial carbon dioxide tension. DO_2 index, VO_2 index, and oxygen extraction (O_2E) values were calculated as described in **Supplementary-1d** (Supplemental Digital Content 4, <http://links.lww.com/CCM/F558>).

The plasma aminoterminal-probrain-natriuretic peptide (NT-proBNP) concentration was measured immediately before SBT and at 60 minutes of SBT initiation (**Supplementary-1d**, Supplemental Digital Content 4, <http://links.lww.com/CCM/F558>).

Changes in hemodynamic and oxygenation variables were expressed as relative changes ($([\text{parameter at the end of SBT} - \text{parameter immediately before SBT}]/\text{parameter immediately before SBT}) \times 100$).

Statistical Analyses

The normality of data distribution was assessed using the Shapiro-Wilk test and by visually checking the distribution (histogram) of each variable. Data were expressed as mean \pm SD when they were normally distributed and as median and interquartile range (IQR) when they were nonnormally distributed. Proportions were used as descriptive statistics for categorical variables. Comparisons of values between the extubation success and failure groups were performed using a two-tailed Student's *t* test or Mann-Whitney *U* test, as appropriate. Analyses of discrete data were performed using the chi-square test or Fisher exact test when the numbers were small. Pairwise comparisons between the different study time periods were assessed using a paired Student's *t* test or Wilcoxon test, as appropriate. Linear correlations were tested using Pearson's or Spearman tests, as appropriate.

Receiver operating characteristics (ROC) curves were constructed to evaluate the ability of $\Delta - \Delta\text{PCO}_2$ and ΔScvO_2 to predict EF. The areas under the ROC curves (AUCs) were compared using the nonparametric technique described by DeLong et al (21). Previously, we showed that the upper 95% CI values of the least significant changes (LSC), which are the minimum changes that are needed to be measured by a laboratory analyzer for the recognition of a real measurement change (Supplementary-1e, Supplemental Digital Content 5, <http://links.lww.com/CCM/F559>), for ΔPCO_2 and ScvO_2 were 36.5% and 5.0%, respectively (22). Thus, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR⁺), negative likelihood ratio (LR⁻), and their 95% CIs were calculated for $\Delta - \Delta\text{PCO}_2 > 36.5\%$ and $\Delta\text{ScvO}_2 > 5.0\%$.

Multivariable logistic regression analysis was used to identify significant independent predictors that were associated with EF. Variables that were associated with EF ($p < 0.1$) in the univariate analysis during SBT were entered into the model. Potential problems related to collinearity were evaluated using Spearman or Pearson's correlation coefficient before the analysis was performed. The model's goodness-of-fit was assessed using the Hosmer–Lemeshow test.

Usually, variables are considered to be good clinical tools (with good discriminative property) when the inferior limits of the 95% CI of their AUC are greater than 0.75 (23). For this purpose, considering an EF incidence of 17% (based on the rate in the three participating centers, unpublished data), 72 patients were required for a power of 80% and an alpha risk of 0.05.

Statistical analyses were performed using Software Foundation's R packages for Windows 3.5.1 version. $p < 0.05$ was considered statistically significant. All reported p values were two sided.

RESULTS

Study Population

Of 677 screened patients on MV, 85 were eligible for study entry. Ten patients failed SBT. Thus, the 75 patients who successfully

completed their SBT were enrolled. Of them, 18 patients developed respiratory failure within 48 hours of extubation. Thirteen of 18 were reintubated and five others were treated only with noninvasive ventilation (Supplementary-Fig. 1, Supplemental Digital Content 6, <http://links.lww.com/CCM/F560>).

The main characteristics of the cohort are summarized in Table 1. The primary reason for intubation and MV at ICU admission was acute respiratory failure caused by pneumonia (62.7%).

Comparisons Between the Success and Failure Groups at the Baseline

Chronic obstructive pulmonary disease (COPD) diagnosis and exacerbation were associated with EF (Table 1).

Immediately before SBT, the Vo_2 index and ΔPCO_2 values were significantly lower and the ScvO_2 value was higher in the failure group compared to those in the success group (Table 2).

Comparisons Between the Values at the Start and End of SBT

The cardiac index, heart rate (HR), and respiratory rate (RR) increased significantly after SBT in both groups (Table 2). However, the SV index increased significantly only in the success group (Table 2). Additionally, the magnitude of the increases in the RR and HR was greater in the failure group (Table 3). Sao_2 dropped significantly in the failure group.

ScvO_2 decreased significantly from $74.7 \pm 11.2\%$ to $66.7 \pm 12.0\%$ in the failure group, whereas it increased in the success group (Table 2). ΔPCO_2 showed the opposite course; it increased significantly from 4.0 (2.0 – 5.0) mm Hg to 6.5 (5.2 – 9.7) mm Hg in the failure group and decreased in the success group (Table 2). Do_2 index increased in both groups, while the Vo_2 index increased significantly only in the failure group (Table 2). O_2E changed in the opposite direction; it increased in the failure group and decreased in the success group (Table 2). E/A, E/e', and NT-proBNP values did not change in either group.

Correlations Between the Changes in the Hemodynamic and Oxygenation Variables

Significant correlations were observed between ΔScvO_2 and ΔVo_2 ($r = -0.71$, $p < 0.001$), Δ -cardiac index ($r = 0.31$, $p = 0.009$), $\Delta\text{o}_2\text{E}$ ($r = -0.89$, $p < 0.001$), and $\Delta - \Delta\text{PCO}_2$ ($r = -0.52$, $p < 0.001$).

$\Delta - \Delta\text{PCO}_2$ was found to be correlated with ΔVo_2 (0.28, $p = 0.02$), Δ -cardiac index ($r = -0.38$, $p < 0.001$), and $\Delta\text{o}_2\text{E}$ ($r = 0.50$, $p < 0.001$).

Multivariable Analysis for EF Prediction

Multivariable logistic regression analysis was performed to investigate if $\Delta - \Delta\text{PCO}_2$ and ΔScvO_2 were independently associated with extubation outcomes. In the univariate analysis (Tables 3), seven variables were associated with EF ($p < 0.1$). However, for the reasons of the collinearity between ΔScvO_2 , ΔVo_2 , and $\Delta\text{o}_2\text{E}$, five variables (ΔScvO_2 , $\Delta - \Delta\text{PCO}_2$, ΔRR , ΔHR , and ΔSao_2) were finally entered into the multivariable

TABLE 1. Baseline Characteristics of the Study Population

Variables	All Patients (n = 75)	Success (n = 57)	Failure (n = 18)	p
Age, yr	68 ± 11	69 ± 11	65 ± 11	0.27
Weight, kg	79 (67–99)	75 (65–91)	87 (71–102)	0.14
BMI, kg/m ²	26.4 (23.1–33.5)	26 (23.0–31.5)	29.4 (27.8–36.7)	0.052
BMI > 30 kg/m ² , n (%)	27 (36)	20 (35.1)	7 (38.9)	0.78
Admission SAPS II	60 ± 17	62 ± 17	55 ± 17	0.25
Male, n (%)	56 (74.7)	41 (71.9)	15 (83.3)	0.51
Diabetes, n (%)	24 (32.0)	20 (35.1)	4 (22.2)	0.39
Hypertension, n (%)	46 (61.3)	32 (56.1)	14 (77.8)	0.17
COPD, n (%)	21 (28)	11 (19.3)	10 (55.6)	0.007
CHF, n (%)	30 (40)	21 (36.8)	9 (50.0)	0.47
Pneumonia, n (%)	42 (62.7)	35 (61.4)	12 (66.7)	0.90
COPD exacerbation, n (%)	6 (8.0)	2 (3.5)	4 (22.2)	0.027
Acute pulmonary edema, n (%)	10 (13.3)	9 (15.8)	1 (5.6)	0.43
Stroke, n (%)	6 (8.0)	4 (7.0)	2 (11.1)	0.62
Other, n (%)	9 (12.0)	8 (14.0)	1 (5.6)	0.68
Hemoglobin, g/dL	9.9 (9.1–10.7)	10.0 (9.2–10.7)	9.8 (8.9–11.0)	0.95
Time to SBT, d	6.0 (4.0–9.0)	6.0 (4.0–9.0)	6.5 (4.2–10.0)	0.68
Ventilatory settings at weaning trial				
PEEP, cmH ₂ O	6 (6–7)	6 (6–7)	6 (6–8)	0.19
Inspiratory pressure, cmH ₂ O	10 (8–12)	10 (8–12)	11 (8–12)	0.79
Fio ₂ , %	30 (25–30)	30 (25–30)	30 (25–30)	0.11
Tidal volume, mL/kg	8.0 (7.0–8.2)	8.0 (7.0–8.3)	7.7 (7.0–8.0)	0.82
Respiratory rate/tidal volume, min/L	37 (26–48)	37 (26–50)	30 (24–47)	0.34

BMI = body mass index; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; Fio₂ = inspired oxygen fraction; PEEP = positive end expiratory pressure; SAPS II = Simplified Acute Physiologic Score II; SBT = spontaneous breathing trial.

Data are expressed as mean ± sd, median (25–75 interquartile range), or count.

logistic model (Table 4). Of these, Δ Scvo₂ and $\Delta - \Delta$ Pco₂ were independently associated with EF. The Hosmer-Lemeshow test results were not statistically significant ($p = 0.39$), indicating the model's goodness of fit. $\Delta - \Delta$ PCO₂ was also independently associated with EF after adjustment for COPD presence (Supplementary-Table 1, Supplemental Digital Content 7, <http://links.lww.com/CCM/F561>).

Ability of $\Delta - \Delta$ Pco₂ and Δ Scvo₂ to predict extubation outcomes

The ability of $\Delta - \Delta$ Pco₂ and Δ Scvo₂ to predict extubation outcomes was very good, with AUCs of 0.865 (95% CI, 0.767–0.933) and 0.856 (95% CI, 0.756–0.926), respectively (Figure 1).

The best cutoff value (according to the Youden index (23)) for Δ Scvo₂ was -3.2% (sensitivity = 83%; 95% CI, 59–96%; specificity = 74%; 95% CI, 60–84%), which was lower than its LSC (5%) (22). Taking into account the repeatability (LSC), the best cutoff

value was less than or equal to -5.4% (sensitivity = 67%; 95% CI, 41–87%; specificity = 86%; 95% CI, 74–94%; PPV = 60%; 95% CI, 36–81%; NPV = 89%; 95% CI, 78–96%; LR⁺ = 4.7; 95% CI, 2.3–9.8; and LR⁻ = 0.4; 95% CI, 0.2–0.8).

The best cutoff value (according to the Youden index) for $\Delta - \Delta$ Pco₂ was greater than or equal to 40% (sensitivity = 67%; 95% CI, 41–87%; specificity = 93%; 95% CI, 83–98%; PPV = 75%; 95% CI, 48–93%; NPV = 90%; 95% CI, 79–96%; LR⁺ = 9.5, 95% CI, 3.5–25.8; and LR⁻ = 0.4, 95% CI, 0.2–0.7).

The AUCs of Δ Scvo₂ and $\Delta - \Delta$ Pco₂ were not significantly different ($p = 0.88$). The combination of Δ Scvo₂ and $\Delta - \Delta$ PCO₂ led to improved EF detection, with an AUC (0.940; 95% CI, 0.859–0.981) that was significantly better than that observed for Δ Scvo₂ ($p = 0.04$) and $\Delta - \Delta$ PCO₂ ($p = 0.03$) (Fig. 1).

The combination of $\Delta - \Delta$ PCO₂ $\geq 40\%$ and Δ Scvo₂ $\leq -5.4\%$ could predict EF with a sensitivity of 56% (95% CI, 31–78%),

TABLE 2. Hemodynamic, Respiratory, and Tissue Oxygenation Parameters During Mechanical Ventilation (MV) (Immediately Before SBT) and at 60 Minutes of SBT in the Success and Failure Groups

Variables	Success (n = 57)		Failure (n = 18)	
	Immediately Before SBT	60 Minutes SBT	Immediately Before SBT	60 Minutes SBT
Heart rate, beats/min	86 ± 14	89 ± 17 ^a	86 ± 14	94 ± 12 ^a
Systolic arterial pressure, mm Hg	134 ± 17	134 ± 16	131 ± 17	135 ± 16
Cardiac index, L/min/m ²	2.9 (2.0–4.0)	3.6 (2.6–4.8) ^a	2.8 (2.4–3.7)	3.2 (2.5–4.7) ^a
Stroke volume index, mL/m ²	33.3 (24.6–48.1)	42.3 (30.6–52.0) ^a	33.3 (27.4–41.7)	37.6 (28.0–52.9)
Arterial pH	7.47 ± 0.05	7.47 ± 0.04	7.45 ± 0.06	7.47 ± 0.06
Bicarbonate, mmol/L	26.5 (24.4–28.8)	26.5 (24.4–28.4)	29.0 (26.6–32.6) ^b	28.0 (26.6–32.4)
Arterial oxygen saturation, %	97 (95–99)	97 (95–98)	97 (94–97)	94 (90–97) ^{ab}
Pao ₂ /Fio ₂ , mm Hg	300 (251–347)	289 (250–425)	280 (242–306)	238 (210–311) ^b
Paco ₂ , mm Hg	35 (31–39)	36 (32–39)	38 (36–47) ^b	37 (36–43)
Respiratory rate, breath/min	22 ± 6	25 ± 5 ^a	22 ± 5	26 ± 6 ^a
Scvo ₂ , %	67.7 ± 8.5	70.3 ± 9.1 ^a	74.7 ± 11.2 ^b	66.7 ± 12.0 ^a
Pcvco ₂ , mm Hg	42 (39–46)	42 (38–46)	42 (40–51)	45 (42–55) ^b
DO ₂ , mL/min/m ²	373 (259–535)	449 (350–603) ^a	344 (280–511)	379 (314–601) ^a
Vo ₂ , mL/min/m ²	104 (83–135)	112 (88–136)	85 (57–95) ^b	115 (82–147) ^a
O ₂ E, %	31 ± 9	27 ± 9 ^a	22 ± 12 ^b	29 ± 12 ^a
ΔPco ₂ , mm Hg	7.0 (5.0–9.0)	6.0 (4.0–7.1) ^a	4.0 (2.0–5.0) ^b	6.5 (5.2–9.7) ^{ab}
LVEF, %	52 ± 11	50 ± 11	53 ± 9	52 ± 10
E/A	0.9 (0.8–1.2)	0.9 (0.7–1.2)	0.9 (0.7–1.4)	0.8 (0.8–1.4)
E/e′	9.9 ± 4.7	9.8 ± 4.9	9.1 ± 2.0	10.0 ± 2.7
NT-proBNP, pg/mL	2,695 (1,444–7,560)	2,766 (1,446–7,568)	2,105 (555–5,507)	1,943 (299–4,026)

SBT = spontaneous breathing trial; Pao₂ = arterial oxygen partial pressure; Fio₂ = inspired oxygen fraction; Paco₂ = arterial carbon dioxide partial pressure; Scvo₂ = central venous oxygen saturation; Pcvco₂ = central venous carbon dioxide partial pressure; Do₂ = oxygen delivery; Vo₂ = oxygen consumption; O₂E = oxygen extraction; ΔPco₂ = difference between central venous and arterial carbon dioxide partial pressures; LVEF = left ventricular ejection fraction; NT-proBNP = amino terminal pro-brain natriuretic peptide.

Data are expressed as mean ± SD or as median (interquartile range, 25–75).

^ap < 0.05 comparisons between during MV vs 60 min SBT.

^bp < 0.05 comparisons between success vs failure.

a specificity of 96 (95% CI, 88–100%), an NPV of 87% (95% CI, 80–92%), a PPV of 83% (95% CI, 55–95%), an LR⁺ of 15.8 (95% CI, 3.8–65.7), and an LR⁻ of 0.46 (95% CI, 0.27–0.77).

DISCUSSION

The main findings of our study can be summarized as follows (1): the abilities of ΔScvo₂ and Δ – ΔPco₂ to predict EF were similar and significantly good (2); combination analysis of these two parameters led to enhanced EF detection. Indeed, Δ – ΔPco₂ ≥ 40% and ΔScvo₂ ≤ –5.4% during SBTs accurately predicted EF (3); Δ – ΔPco₂ and ΔScvo₂ were independent predictors of EF.

The transition from MV to spontaneous ventilation leads to increases in the Vo₂ of respiratory muscles related to the

increased work of breathing (4–7). There should be an obligatory increase in CO and Do₂ to match the increased Vo₂ demand. Venous oxygen saturation is used as a marker of adequacy between Do₂ and Vo₂. In a previous study, the mixed venous oxygen saturation (Svo₂) decreased progressively in patients with SBT failure, but not in those with SBT success (8). The Svo₂ decrease was attributed to an O₂E increase, probably by the respiratory muscles; the O₂E decreased and CO increased in patients with weaning success (8). Teixeira et al (9) demonstrated that changes in the Scvo₂ between MV and the end of SBT were independently associated with EF in patients with weaning difficulty. A decrease greater than 4.5% in the Scvo₂ predicted EF with very good PPV and NPV (9), similar to our results. We found that ΔScvo₂ was an independent factor of EF in patients with good SBT tolerance (Table 4).

TABLE 3. Changes in Hemodynamic, Tissue Oxygenation, and Respiratory Parameters Between the End of SBT and Immediately Before SBT

Variables	Success (n = 57)	Failure (n = 18)	p
- P _{co₂} , %	-14.3 (-33.3 to 2.7)	130.0 (1.4 to 200.0)	< 0.001
Scv _{o₂} , %	0.9 (-3.4 to 8.7)	-8.7 (-13.7 to -4.3)	< 0.001
CI, %	13.6 (7.1 to 28.2)	12.7 (0.2 to 16.6)	0.37
V _{o₂} , %	7.2 (-9.3 to 22.9)	29.4 (14.8 to 62.8)	0.001
D _{o₂} , %	14.5 (5.3 to 25.6)	12.7 (0.2 to 15.2)	0.17
O ₂ E, %	-8.7 (-23.2 to 5.8)	23.8 (7.8 to 36.0)	< 0.001
RR, %	10.5 (3.0 to 17.4)	25.0 (7.7 to 32.4)	0.06
HR, %	3.6 (0.0 to 5.7)	8.4 (2.4 to 10.5)	0.009
SaO ₂ , %	-0.6 (-2.2 to 1.0)	-1.7 (-5.6 to 0.0)	0.08

SBT = spontaneous breathing trial; P_{co₂} = difference between central venous and arterial carbon dioxide partial pressures; Scv_{o₂} = central venous oxygen saturation; CI = cardiac index; V_{o₂} = oxygen consumption; QE = oxygen extraction; D_{o₂} = oxygen delivery; RR = respiratory rate; HR = heart rate; SaO₂ = arterial oxygen saturation.

All changes in parameters are expressed as relative changes. Data are expressed as mean or as median (interquartile range, 25–75).

TABLE 4. Multivariate Logistic Regression Analysis for Extubation Predictors

Variables	Odds Ratio (95% CI)	p
- P _{co₂} , %	1.02 (1.01–1.05)	0.006
Scv _{o₂} , %	0.84 (0.70–0.95)	0.02
Sa _{o₂} , %	0.92 (0.71–1.23)	0.57
RR, %	0.96 (0.89–1.02)	0.25
HR, %	1.09 (0.97–1.25)	0.16

P_{co₂} = difference between central venous and arterial carbon dioxide partial pressures; Scv_{o₂} = central venous oxygen saturation; RR = respiratory rate; HR = heart rate; Sa_{o₂} = arterial oxygen saturation.

All changes in parameters are expressed as relative changes between the end of SBT and immediately before SBT.

Additionally, a reduction of 5.4% or greater in the Scv_{o₂} was associated with a very good NPV but only a moderate PPV in EF prediction. The reduction in the Scv_{o₂} in the failure group can be explained by the increase in the V_{o₂} response to the higher energy requirement by the respiratory muscles not being matched by an adequate increase in the CO and D_{o₂}.

Indeed, we found a strong negative correlation between Scv_{o₂} and V_{o₂}. However, our findings are not in agreement with those of some previous studies (10–13). The inconsistencies between our findings and those of previous studies may stem from several factors. First, the study populations were dissimilar. Second, in our study patients were mechanically ventilated for at least 48 hours, whereas in the other studies, they were ventilated for less than 24 hours (10, 12, 13).

According to the Fick equation applied to the determinants of P_{co₂} are tissue CO₂ production and CO (15, 24, (19). Thus, we hypothesized that P_{co₂}, as an index of the V_{o₂}/CO ratio, could be a useful marker for the assessment of venous blood flow for the removal of the CO₂ produced by

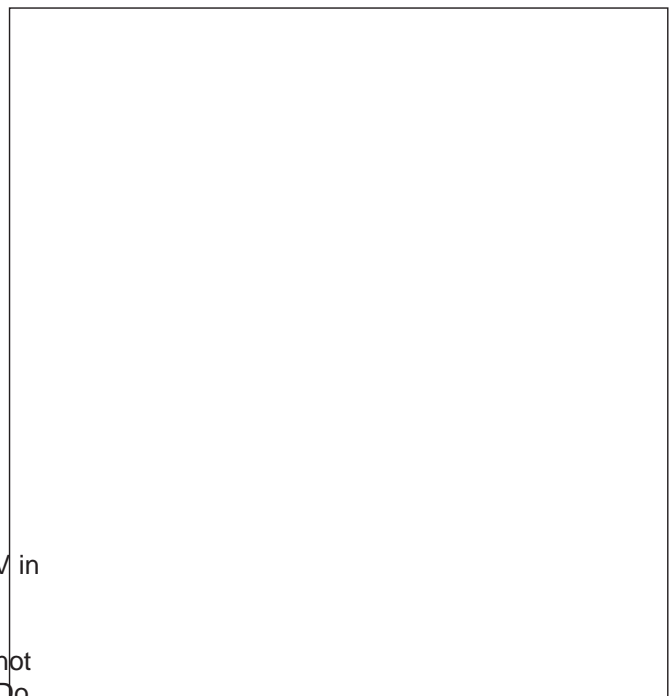


Figure 1. Receiver operating characteristic (ROC) curves showing the ability of the changes in P_{co₂} (- P_{co₂}) (black curve), Scv_{o₂} (Scv_{o₂}) (green curve), and their combinations (red curve) between immediately before the spontaneous breathing trial (SBT) and at the end of SBT to predict the weaning failure. AUC = areas under the ROC curves.

the peripheral tissues (26–28). Dobutamine may increase V_{o₂} and V_{co₂} values through its potential thermogenic effects related to its 1-adrenergic properties (29). We showed that P_{co₂} could be used to distinguish the hemodynamic from the metabolic effects of dobutamine in septic shock patients (25). P_{co₂}, as an index of the V_{o₂}/CO ratio, could be a useful marker for the assessment of the adequacy between CO and V_{o₂} during the weaning trial.

and could be able to predict extubation outcomes in critically ill patients. We found that P_{CO_2} was an independent predictor of EF, even after adjustment for $ScvO_2$ and COPD (Supplementary-Table 1, Supplemental Digital Content 7, <http://links.lww.com/CCM/F561>). Furthermore, P_{CO_2} 40% predicted EF with a very good NPV but with a moderate PPV. However, the combination of P_{CO_2} and $ScvO_2$ showed better EF predictability (AUC = 0.940) than did P_{CO_2} and $ScvO_2$ individually. Additionally, P_{CO_2} 40% and $ScvO_2$ -5.4%, after a successful SBT, could predict EF with very good NPV and PPV and an excellent LR⁺ (16).

Our results are of clinical importance and add significant data to the existing literature. Our study is the first multicenter study to show that P_{CO_2} is a useful marker for the reliable prediction of extubation outcomes. Furthermore, for patients with central venous and arterial catheters during an SBT, the tracking of both P_{CO_2} and $ScvO_2$ showed excellent predictability, better than that associated with each parameter separately. This combined value has the potential to assist clinicians with extubation decisions and the identification of patients at a high EF risk who may need to be extubated to noninvasive ventilation or high-flow nasal oxygen (30). Moreover, the metabolic approach (P_{CO_2} and $ScvO_2$) appears to be better than the echocardiographic one (E/A and E/e'), which failed to predict EF.

Our study presents some limitations. First, Pa_{CO_2} was calculated from $ScvO_2$ and not from SvO_2 neither was it measured by indirect calorimetry, limiting its accuracy. However, we were interested in the changes in the Pa_{CO_2} observed during SBT, rather than its absolute value. Second, the increase in Pa_{CO_2} at the end of the SBT in the EF group could be explained by the Haldane effect (31). Although the Pa_{CO_2} decreased significantly in the failure group, it is unlikely that this change could have affected the P_{CO_2} content relationship, because it was not strong. Indeed, changes in P_{CO_2} may not parallel changes in c_{pCO_2} content differences under conditions of very low SvO_2 (< 30%) (32), which was not the case in our patients. Third, we included patients who had passed their first SBTs; thus, our findings should be confirmed in difficult-to-wean patients. However, 68% of our population had COPD and congestive heart failure (Table 1) and could be considered as having a high EF risk (30). Additionally, it may be helpful to compare, in a future work, the predictability of P_{CO_2} and $ScvO_2$ in terms of the traditional weaning parameters. Fourth, we did not fully address the causes of EF. However, the absence of changes in the B -line and NT-proBNP values during SBT suggests that weaning-induced pulmonary edema did not cause EF. Nevertheless, this cannot be ruled out because we did not check for the development of B-lines using lung ultrasound (33). Fifth, the SBTs were performed on a 1-hour T-piece; thus, our findings may not be generalizable to other SBT modalities (34).

CONCLUSIONS

P_{CO_2} and $ScvO_2$ during SBTs were independent predictors of extubation outcomes. Combination analysis of

both parameters led to enhanced diagnostic performance and showed excellent predictability for EF detection. The combination of P_{CO_2} 40% and $ScvO_2$ -5.4% at the end of a tolerated SBT was accurate in EF detection.

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Drs. Mallat, Baghdadi, and Mohammad UM designed the study. Drs. Mallat, Baghdadi, Mohammad, Lemyze, Temime, Tronchon, and Thevenin collected data. Dr. Mallat conducted statistical analyses. Drs. Mallat and Fischer participated in manuscript writing and reviewing. All authors read and approved the final manuscript.

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