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Use of Central Venous to-Arterial Carbon Dioxide Pressure Difference in Detection of Extubation Failure in Critically Ill Patients

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ABSTRACT

Objective: To evaluate the ability of central venous-to-arterial carbon dioxide pressure difference, to detect extubation failure in critically ill patients.

Study design: Prospective observational study

Materials and methods: 64 critically ill patients who received mechanical ventilation for more than 48 hours and passed spontaneous breath trials (SBT) with pressure support ventilation for 60 minutes were enrolled for the study. Arterial blood gas and central venous blood gas analysis was performed immediately before SBT and 60 minutes after SBT and venoarterial carbon dioxide pressure difference (ΔPCO_2) was calculated. Extubation was performed after successful SBT. Extubation failure was defined as reintubation within 48 hours of extubation.

Results: Extubation failure was noted in 16 patients. ΔPCO_2 value increased in the extubation failure group and decreased in the success group (p <0.001). Changes in ΔPCO_2 ($\Delta - \Delta PCO_2$) during spontaneous breathing trials was independently associated with extubation failure (p <0.001). The mean number of ICU days was greater in the failure group [6.96±2.82] compared to the success group [5.00±1.22] (p=0.009). The average number of days spent on a ventilator was considerably more in the failure group [3.98±2.24] compared to the success group [3.01±1.14] (p=0.025).

Conclusion: We found that ΔPCO_2 and $\Delta - \Delta PCO_2$ during spontaneous breathing trials, were good predictors of weaning outcomes and they can be used to predict extubation failure and thereby reduce extubation failure rate.

Keywords: extubation failure, spontaneous breathing trial, venous to arterial CO_2 difference, weaning

Introduction

Weaning from mechanical ventilation and extubation are necessary milestones in the treatment process for critically intubated patients receiving mechanical ventilation (1). The extubation process is an important component of respiratory care in patients who receive mechanical ventilation. Post-extubation respiratory failure (PERF) is not a rare phenomenon and is associated with significant morbidity and mortality (2). Failure of extubation is defined as the requirement for reintubation or non-invasive mechanical ventilation within forty-eight hours of the initial extubation (3). Extubation failure (EF) happens in roughly 10–30% of all patients who meet the readiness requirements and have tolerated a spontaneous breathing trial (SBT) (4). It may be the consequence of several causes (respiratory, metabolic, neuromuscular), most notably a cardiac factor, and may be brought on by an inability of the respiratory muscle pump to accept increases in the cardiac and respiratory load (4). The presence of EF is linked to a prolonged MV, in addition to increased morbidity and death. Therefore, the early identification of critically ill patients who are prone to EF is essential for improving treatment results (5). The success or failure of extubation can be predicted based on many different characteristics, and these variables have been assessed. The difference in PCO_2 levels between the central veins and the arteries is one of the variables (4). The mixed venous-to-arterial partial pressure difference of carbon dioxide ($PmvCO_2 - PaCO_2$) is a measurement that reveals how effective carbon monoxide is at expelling the carbon dioxide that is created by tissues (5). It is interesting to note that in critically ill patients, ($PmvCO_2 - PaCO_2$)

can be replaced by the central venous-to-arterial PCO_2 difference (ΔPCO_2), and both of these variables are good indicators for the assessment of the adequacy between oxygen supply and oxygen demand in patients with chronic heart failure and septic shock (6). As a result, the ΔPCO_2 could be an important factor to consider when evaluating the results of the extubation. In the presence of normal tissue perfusion conditions, delta PCO_2 (ΔPCO_2) is reasonably steady and is less than 6 mmHg (5).

The present study was designed to analyze the effect of central venous-to-arterial carbon dioxide pressure difference in detection of extubation failure in critically ill patients.

Materials and Methods

This study was performed in the medical adult ICU of Era's Lucknow Medical College and Hospital between August 2021 and December 2022. The Institution Ethical Committee (registration number– ECR/717/Int. /UP/2015/RR-21) approved the research protocol. The patients were enrolled in the study after informed consent from them or their next kin. The trial was registered with Clinical trial registry of India (CTRI number– CTRI/2022/09/045275). The primary objective of the study was to evaluate the ability of central venous-to arterial carbon dioxide pressure difference to detect extubation failure in critically ill patients. Secondary objectives were to evaluate and assess effect of central venous-to arterial PCO_2 difference on length of ICU stays and mean days on ventilator.

Critically ill patients admitted to the Intensive Care Unit (ICU) of Era's Lucknow Medical College and Hospital who received mechanical ventilation for at least 48 hours, age 18 years or above and patients with central venous line were included in the study. Patients who didn't give consent, moribund patients, pregnant patients, weaning failure patients, and malpositioned central venous catheter, tracheostomised patients and patients with do-not-reintubate order were excluded from the study.

Sample size

Sample size is calculated based on the Odds ratio of changes in ΔPCO_2 for the risk of extubation failure using the formula, where, p1=1/(1+OR), p2=OR/(1+OR). Taking OR=1.02, the Odds ratio of changes in ΔPCO_2 for the risk of extubation failure (1), e=0.5(p1/ p2), the risk ratio considered to be clinically significant, type I error, α=5% (level of significance), type II error β=10% for setting power of study 90%. Considering data loss factor=10%, the total sample size is calculated to be n=64.

$$n=\frac{\left(z_\alpha+z_\beta\right)^2}{\left[\ln(1-e)\right]^2}\left[\frac{1-p_1}{p_1}+\frac{1-p_2}{p_2}\right]$$

Methodology

A total of 75 patients were screened for enrolment of whom two didn't meet the inclusion criteria and 5 declined to participate in the study. Totally 68 patients who met the inclusion criteria were randomized into two groups. Weaning criteria were used. [appendix 1 (7)]. Arterial Blood Gas (ABG) and central Venous Blood Gas (VBG) samples were drawn immediately before the Spontaneous Breath Trial (SBT). After satisfying weaning criteria, SBT with Pressure Support Ventilation (PSV) was performed in the patients while maintaining SpO_2 >90% as measured by pulse oximetry. Arterial blood gas and central VBG samples were drawn and partial pressure of carbon dioxide (PCO_2) was measured after 60 minutes of SBT. Patients who failed SBT (n=4) were excluded while those who passed SBT (n=64) were extubated and followed up. Criteria for passing SBT include respiratory pattern, adequate gas exchange, haemodynamic stability and patient comfort (7). Extubation failure was considered if patient needed reintubation or noninvasive ventilation (NIV) support within 48 hours of extubation. The value of ΔPCO_2 was compared in the failure group and success group. Intensive care unit length of stay, mean days on ventilator and 28 day hospital mortality was also recorded.

Statistical analysis

Data were entered in Microsoft Excel and analyzed using statistical software IBM Statistical Package for Social Sciences (SPSS) program version 26 (SPSS Inc., Chicago, IL, USA). The normality of data was checked using Kolmogorov-Smirnov and Shapiro-Wilk tests before the statistical analysis was performed. Descriptive statistics summarized patient demographics and baseline characteristics. The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous variables were presented in number/frequency and were analyzed using Chi-square. To compare the means between the two groups, analysis by Student t-test was used. Correlation Analysis was done using Spearman r correlation. At 95% confidence interval, a p-value of <0.05 or 0.001 was considered as statistically significant.

Results

This prospective, observational study was carried out at the Critical Care Unit, Department of Anaesthesiology, xxxx. After obtaining ethical clearance and informed consent, 64 patients who received mechanical ventilation for at least 48 hours were enrolled as per inclusion-exclusion criteria. Based on the outcomes, all the patients were divided into two groups, i. e., the success (n=48) and failure (n=16) groups.

Reintubation was required in 10 patients (63%) and NIV support in 6 patients (37%) in the failure group.

The baseline characteristics are shown in Table 1. The mean age of all the enrolled patients was 45.69±17.71. The average age of success and failure groups was 43.50±17.46 and 52.25±16.82 respectively, the difference was statistically non– significant. The success group had 28 females and 20 males while the failure group had 6 females and 10 males, groups were similar according to gender distribution. The percentage of individuals with co-morbidities (diabetes mellitus, hypertension, chronic lung disease, heart failure) was higher in the failure group (81.25%) compared to the success group (62.50%). Heart failure was present in 17 patients (35%) in the success group and 7 patients (43%) in the failure group. Comorbidities were similar in both groups. (X=1.914, p=0.169).

Table 1. Baseline characteristics

	Success group (n=48)	Failure group (n=16)	Total (n=64)	p
Age (years)	43.50±17.46	52.25±16.82	45.69±17.71	0.084
Female (%)	28 (58.33%)	6 (37.50%)	34 (53.13%)	0.148
Male (%)	20 (41.67%)	10 (62.50%)	30(46.88%)	
Co-morbidities (%)	62.5%	81.25%	67%	0.169

Table 2. Haemodynamic parameters before and after SBT of enrolled patients

	Success			Failure		
	Before SBT	60 min after SBT		Before SBT	60 min after SBT	
	Mean ± SD	Mean ± SD	p	Mean ± SD	Mean±SD	p
SBP (mmHg)	132.67±18.59	133.13±18.81	0.932	131.05±12.51	138.25±13.36	0.054
DBP (mm Hg)	78.98±7.75	79.42±11.70	0.864	74.13±12.45	83.50±6.76	0.005
HR (beats/min)	94.19±15.70	101.25±11.76	0.104	91.75±10.84	101.38±5.85	0.001
RR (breaths/min)	20.58±1.81	21.96±2.88	0.027	20.13±1.90	21.50±3.12	0.039
SPO_2 (%)	99±0.00	99±0.01	p>0.999	100±0.00	99±0.01	p<0.000

SBP: Systolic blood pressure **DBP:** diastolic blood pressure, **HR:** heart rate, **RR:** respiratory rate, **SPO_2:** Periferal oxygen saturation.

Table 3. ABG and VBG before and after SBT of enrolled patients

	Success		p	Failure		
	Before SBT	60 min after SBT		Before SBT	60 min after SBT	
ABG	Mean ± SD	Mean ± SD	p	Mean ± SD	Mean ± SD	p
pH	7.37±0.07	7.42±0.07	0.016	7.37±0.08	7.33±0.12	0.134
pCO_2 (mmHg)	35.84±3.11	36.15±2.89	0.606	38.97±2.88	37.14±3.04	0.002
HCO_3 (mmol/L)	25.69±4.03	25.88±4.61	0.875	26.18±7.53	25.04±6.98	0.595
pH	7.35±0.07	7.39±0.06	0.045	7.33±0.07	7.30±0.13	0.243
pCO_2 (mmHg)	42.46±3.65	42.15±3.25	0.654	41.84±3.04	43.89±3.29	0.001
HCO_3- (mmol/L)	24.69±4.32	25.31±4.62	0.626	25.18±6.42	26.59±5.87	0.440
ΔpCO_2 (mmHg)	7.13±0.54	6.12±0.36	p<0.001	2.87±0.16	6.75±0.25	p<0.001

ABG: Arterial blood gas, **VBG:** Venous blood gas.

The mean systolic blood pressure (SBP) increased after 60 min of SBT in both success and failure groups, and a non-significant difference was found. The mean diastolic blood pressure (DBP) also increased after 60 min of SBT in both success and failure groups, and it was higher in failure group. The mean heart rate (HR) and respiratory rate (RR) were observed to be elevated in both groups after 60 mins of SBT. The HR, RR and SPO_2 significantly differed in the failure group before and after SBT (Table 2).

ABG showed an increase in pH, PCO_2 and HCO_3- levels after SBT in the success group whereas, in the failure group pH, PCO_2 and HCO_3- measurements were decreased.

Furthermore, only pH (p=0.016) in success group and PCO_2 (p=0.002) in failure group showed statistically significant difference before and after SBT (Table 3). In VBG, pH and HCO_3 was increased while PCO_2 was decreased after SBT in success group whereas, in failure group the PCO_2 and HCO_3 were increased and pH was decreased. Venoarterial PCO_2 difference was found to be decreased in the success group [7.13±0.54 to 6.12±0.36], while it was increased in the failure group [2.87±0.16 to 6.75±0.25]. It showed a significant difference (p<0.001) before and after SBT in both success and failure group (Table 3).

The mean change in venoarterial pCO_2 gradient was higher in the failure group [135.19±56.25] than in the success group [-14.16± -33.33], and this difference was statistically significant (p<0.001). Arterial blood gas showed a high amount of mean HCO_3 level change in the success group [0.74± -14.39] compared to the failure group [-4.35± -7.30]. The Venous Blood Gas showed a higher mean value of pCO_2 in the failure group [-6.08±112.63] than in the success group [-4.22± -28.22]. The mean respiratory rate change was higher in the failure group [6.81±64.21] than in the success group [6.71±59.12]. Overall, significant difference was observed only in mean Δ-ΔpCO_2 (p<0.001) (Table 4).

The mean days in ICU was higher in the failure group (6.96±2.82) than the success group (5.00±1.22) and the difference was statistically significant (p=0.009). A significant difference was observed in the mean ventilator days which was higher in the failure group (3.98±2.24) than in the success group (3.01±1.14) (p=0.025) (Table 5). The mean days from intubation to extubation was 3 days and it was similar in the two groups. In 28th day survival analyses, as the days increased the probability of survival decreased in failure with a median survival of 11.00 days (<0.001) (Table 6, Figure 1).

Table 4. Change in variables of enrolled patients between the end of SBT and before SBT

Change in variable		Success Mean ± SD	Failure Mean ± SD	p
Δ-ΔPCO_2		-14.16±-33.33	135.19±56.25	<0.001
ABG	ΔpH%	0.68±0.00	-0.54±50.00	0.864
	ΔpCO_2%	-7.05±-9.98	8.79±100.68	0.279
	ΔHCO_3-%	0.74±-14.39	-4.35±-7.30	0.181
VBG	ΔpH%	0.54±-14.29	-0.41±85.71	0.940
	ΔpCO_2%	-4.22±-28.22	-6.08±112.63	0.915
	ΔHCO_3-%	2.51±6.94	5.60±85.71	0.802
	ΔHR%	7.50±-25.10	10.50±-46.03	0.742
	ΔRR%	6.71±59.12	6.81±64.21	0.995

Table 5. Outcome of enrolled patients

	Success	Failure	Total	p
Mean days in ICU (Mean±SD)	5.00±1.22	6.96±2.82	6.47±2.66	0.009
Mean days on ventilator (Mean±SD)	3.01±1.14	3.98±2.24	3.23±1.76	0.025

Table 6. Survival analysis of the enrolled patients among the groups.

Survival Analysis [Log-rank (Mantel-Cox) test]	Failure group	Success group
# deaths/events	18	0
Median Survival	11.00	--
Chi square	88.06	
df	1	
p	<0.0001*	

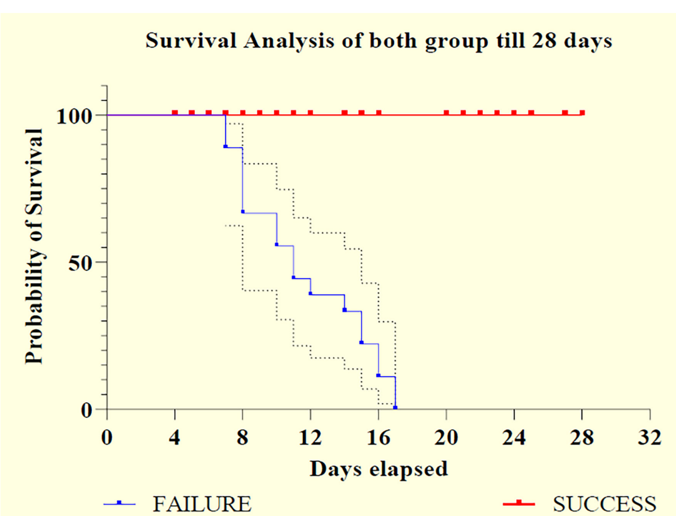

Figure 1. Graphical representation of survival analysis of the enrolled patients among the groups.

Discussion

Mean age of patients were 45.69±17.71 years, with no gender disparities. While comorbidities were more frequent in the failure group (81.25% vs. 62.50%), it wasn't statistically significant (p=0.169). Systolic and diastolic blood pressure increased post-60-minute SBT in both groups, with significant diastolic changes in the failure group. Heart rate, respiratory rate, and blood oxygen levels differed significantly in the failure group before and after SBT. Arterial blood gas revealed pH, PCO_2, and HCO_3 shifts in both groups post-SBT, with significant differences in pH (p=0.016) in the success group and PCO_2 (p=0.002) in the failure group. Venous blood gas showed pH (p=0.045) differences in the success group and PCO_2 (p=0.001) in the failure group pre– and post-SBT. Venoarterial PCO_2 difference changed significantly in both groups (p<0.001). The failure group had a longer ICU stay [6.96±2.82 days, p=0.009] and longer ventilator requirement [3.98±2.24 days, p=0.0254]. Survival analysis displayed a decreasing survival probability in the failure group (p<0.001). The primary findings of the current study can be defined as ΔPCO_2 could be usefull as a valuable indicator for extubation success. ΔPCO_2 is an indicator in determining extubation suitability and individuals at increased risk of extubation failure which leads to potentially necessitating a transition to NIV or high flow nasal oxygen therapy.

Several studies have shown that weaning protocols reduce the overall time of ventilation, the duration of weaning, and the length of stay in the intensive care unit (ICU) without influencing mortality or adverse events. (8–10) Extubation is an essential aspect of respiratory treatment for patients receiving mechanical ventilation (MV) and PERF, is a common consequence associated with an elevated risk of morbidity and mortality (11). Hence a structured weaning and extubation protocol should be followed to minimize extubation failure, however, no definitive extubation process standard can be followed.

In recent years PCO_2 gap (ΔPCO_2) has emerged as a resuscitation end point primarily due to CO_2 being more soluble than oxygen (O_2) in blood. (12) PCO_2 gap is the difference between partial pressure of carbon dioxide in arterial and venous blood. It depends on the CO_2 production in tissues and is inversely related to cardiac output. The venous PCO_2 gap depends on circulatory flow and arterial PCO_2 gap depends on pulmonary gas exchange. Hence, a decreased flow will increase the difference between these two variables. The cut-off PCO_2 gap value in various studies that implies an inadequate cardiac output is >6 mmHg. (6,13,14) ΔPCO_2 may be a significant component to consider when evaluating the extubation efficacy. During transition from mechanical ventilation to spontaneous ventilation there is an increase in oxygen consumption of the respiratory muscles caused by the spontaneous breathing. As stated, the PCO_2 gap depends on the cardiac output and tissues CO_2 production. The adequacy of venous blood flow in the process of washing out the CO_2 created in the peripheric tissue has been indicated by PCO_2 gap. However, clinical studies have not validated it as a diagnostic tool for detecting EF (1). The major objective of the present study was to analyze the effect of central venous-to-arterial carbon dioxide pressure difference on the detection of extubation failure in critically ill patients.

In the present study, 64 patients who underwent mechanical ventilation for at least 48 hours were included. All the patients were separated into two groups, success (n=48) and failure (n=16), based on the outcomes. The mean age of all patients was 45.69±17.71 years; however, the mean age of patients in the failure group was greater than that of patients in the success group. In contrast, Mallat J et al. (1) found a mean age of 68±11 years for the recruited patients (n=75), with the success group having a higher mean age [69±11] than the failure group [65±11]. Male predominance was observed in both the successful (71.9%) and unsuccessful (83.3%) groups. In our study, female dominance was detected in the success group (58.33%), but male dominance was observed in the failure group (62.50%) although the difference was insignificant.In the current study, the mean SBP increased in both the success and failure groups after 60 minutes of SBT, with no significant difference between the two groups. After 60 minutes of SBT, the mean DBP increased in both the success and failure groups. However, a significant difference was noted in the failure group. After 60 minutes of SBT, the mean HR and RR were raised in both groups. The HR, RR, and SPO_2 in the failure group were substantially different before and after SBT.

A substantial difference between the two groups was noted before and after SBT. pH was also significantly higher in the success group following SBT, but no significant difference was observed in the failure group. In the successful group, ΔPCO_2 reduced from 7.13±0.54 to 6.12±0.36, but it increased in the failure group from 2.87±0.16 to 6.75±0.25.

A high PCO_2 gap was associated with higher lactate levels, lower cardiac output and central venous oxygen saturation ($ScvO_2$) and was significantly correlated with mortality. The latter was, however, restricted to medical and surgical patients, with no association found for cardiac surgery patients. Three recent retrospective studies (15–17) reported a negative impact of the high postoperative PCO_2 gap on major complications and mortality after cardiac surgery, although with limited diagnostic performance (18).

In the study by Mallat J. et al., (1) both groups showed increased cardiac index, heart rate (HR), and respiratory rate (RR) after SBT. However, only the success group saw a significant increase in the SV index while the failure group had more pronounced HR and RR increases. The failure group exhibited a substantial ΔPCO_2 increase, while the success group had a decline in ΔPCO_2 (1), mirroring our study's findings. In contrast, Nassar B et al., (18) showed that all evaluated hemodynamic measures were comparable between the two groups at baseline. In both groups, VE (volume expansion) dramatically increased arterial pressures, CVP, and intrathoracic blood volume, while decreasing haemoglobin. Cardiac and stroke volume index only increased significantly in the success group following VE, whereas HR and extravascular lung water remained unchanged. At baseline, arterial and venous pH were not substantially different between the success and failure groups, and they did not vary significantly after VE.

The mean Δ-ΔPCO_2 gradient in the failure group was greater [135.19±56.25] than in the success group [-14.16± -33.33]. Success group ABG exhibited a greater amount of mean change HCO_3 than the failure group. The mean ΔPCO_2 concentration in the VBG was lower in the failure group than in the success group. In the failure group, the average change in heart rate and respiratory rate was greater than in the success group. Except for Δ-ΔPCO_2, no significant changes in variable change were observed. Similarly, Mallat J et al., (1) found a substantially greater Δ– ΔPCO_2 in the failure group than in the success group. The change in heart rate and respiratory rate was likewise greater in the failure group than in the success group 8.4 and, 25.0, respectively; however, only the Δ-ΔPCO_2 change was statistically significant.

In the present study, patients were mechanically ventilated for at least 48 hours. Mallat J et al.[1], in their study had also mechanically ventilated the patients for at least 48 hours. However, in the other studies, patients were mechanically ventilated for fewer than 24 hours (19–21). The mean number of ICU days was greater in the failure group [6.96±2.82] compared to the success group [5.00±1.22]. The average number of days spent on a ventilator was considerably more in the failure group [3.98±2.24] compared to the success group [3.01±1.14]. According to Abdalazeem ES et al., (22) the mean duration of mechanical ventilation was longer in the group with a high ΔPCO_2 (7.2±5.1 days) than in the group with a normal ΔPCO_2 (6.7±4.3 days), although the difference was not statistically significant. In addition, ICU stays were longer when ΔPCO_2 was elevated compared to when it was normal (23).

In th 28^{th} day survival analyses of the patients in both groups, the chance of survival decreased as the number of days increased in the failure group, which had a median survival of 11.00 days. Nevertheless, a statistically significant difference ($p<0.001$) was found between the two groups. Al Duhailib et al., (24) performed a systematic review and meta-analysis with 21 studies to assess the association between a high CO_2 gap and mortality in critically ill patients. It was shown that a high PCO_2 gap can be a strong predictor of mortality in cardiogenic shock. The 28^{th} day or in-hospital mortality was increased in surgical and medical population. Similarly, the 28^{th} day ICU mortality in different studies was significantly higher in the high ΔPCO_2 group ($p=0.042$) compared to the normal group (69 vs 28.6%) (6). Mallat et al., (25) observed comparable outcomes, with 75% death within 28 days in the high ΔPCO_2 group compared to 42% in the normal group ($p=0.003$). Another study found that the high ΔPCO_2 group had a greater mortality rate than the normal group (29% versus 21%).

The present study shows that ΔPCO_2 is a valuable marker for accurately predicting extubation failure. It has the potential to help doctors make extubation decisions and identify patients with a high EF risk who may require non-invasive ventilation or high-flow nasal oxygen (26).

Our study had certain limitations. Firstly, as this is a single-centre study, the findings may not apply to the broader population. Secondly, we selected central venous samples instead of mixed venous samples to evaluate oxygen and CO_2-derived variables, reducing its precision. However, we were more focused on the changes in these variables brought about by the fluid challenge than on overall absolute levels. Thirdly, we adopted PSV as the mode of SBT, thus this study may not be consistent with other modes of SBT. Lastly, our study was not adequately powered for subgroup analysis; therefore, our findings must be confirmed in a subsequent study with a larger number of participants.

Conclusion

According to the present study, central venous-to-arterial PCO_2 difference is an excellent predictor of extubation failure in critically ill patients. Δ–ΔPCO_2 during SBT was an independent predictor of extubation outcomes. It enhances diagnostic performance and high predictability for EF detection in critically ill patients. However, to confirm Δ–ΔPCO_2 during SBTs as an independent predictor, additional large, prospective studies are required.

AUTHOR CONTRIBUTIONS:

Concept: MM, MD; **Design:** MD, RKT; **Supervision:** RKT, MD; **Data Collection and/or Processing:** MV; **Analysis and/or Interpretation**: MV, MD; **Literature Search:** MV; **Writing Manuscript**: MV, MD; **Critical Review:** RKT, Md, MM.

Ethics Committee Approval: Era's Lucknow Medical College and Hospital protocol registration number: ECR/717/Int./UP/2015/RR-21)

Informed Consent: Informed Consent was taken from patient or next kin to patient

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Appendix 1

Weaning criteria were (7):

(1) The resolution or improvement of the underlying cause of respiratory failure for which the patient was intubated.

(2) Hemodynamic stability, defined as heart rate (HR) <140/min and systolic blood pressure between 90 and 160 mmHg with no or minimal doses of vasopressors.

(3) Stable respiratory status, defined as oxygen saturation >90% with fraction of inspired oxygen (FiO2) ≤0.4 and positive end expiratory– pressure (PEEP) ≤8 cmH_2O, respiratory rate (RR) ≤35/min, spontaneous tidal volume (Vt) >5 mL/kg, ratio of RR/Vt <105/min per liter, and no significant respiratory acidosis.

(4) Adequate mental status (Glasgow Coma Scale score >13); and
(5) Adequate cough.