Central Venous Oxygen Saturation as a predictor of extubation failure in mechanically ventilated Chronic Obstructive Pulmonary Disease patients

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Abstract: Objective: To investigate the utility of the central venous saturation ($ScvO_2$) as a predictor of extubation failure in mechanically ventilated Chronic Obstructive Pulmonary Disease (COPD) patients. **Methods:** In this prospective cohort clinical study, 35 mechanically ventilated COPD adult patients were enrolled over a 9 months period. After successful completion of SBT (pressure support $\leq$ 7 cmH_2O) and extubation, the patients were followed for extubation failure (EF) during post-extubation 48 hours period. Arterial and venous blood samples were collected in the 1st minute and 30th minute of the SBT. Haemodynamic parameters, ventilatory parameters, $ScvO_2$ and Oxygen extraction ratio (O_2ER) were also assessed. **Results:** Twenty seven patients (77.2%) attained successful extubation (ES) while eight patients (22.8%) had failed extubation (EF). Univariate logistic regression analysis identified f/V_T and PCO_2 at the 30th minute of the SBT and the difference between $ScvO_2$ at the 1st and 30th minute of the SBT (Δ $ScvO_2$) as predictors of extubation failure. Multivariate regression identified Δ $ScvO_2$ as the only independent variable able to discriminate extubation outcome. The Δ ScvO2 in the EF group was 5.88 ± 1.89 as compared with 3.11 ± 1.63 in ES group (p = 0.002). A reduction in $ScvO_2$ by $\geq$ 4% during the SBT was an independent predictor of reintubation with OR of 2.96 (95% CI= 1.05 – 8.38) with a sensitivity of 87.5% and specificity of 74%. **Conclusions:** Central venous saturation is a good independent predictor of extubation failure and that could be included in weaning protocols of mechanically ventilated COPD patients.

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1. Introduction:

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. Many people suffer from this disease and die prematurely from it or its complications. COPD is the fourth leading cause of death in the world, **(1)** and further increases in its prevalence and mortality can be predicted in the coming decades. **(2)**

Weaning or discontinuation from mechanical ventilation can be particularly difficult and hazardous in patients with COPD. The most influential determinant of mechanical ventilatory dependency in these patients is the balance between the respiratory load and the capacity of the respiratory muscles to cope with this load.**(3)** Weaning patients from the ventilator can be a very difficult and prolonged process and the best method (pressure support or a T-piece trial) remains a matter of debate.**(4-6)**

Tolerance of a spontaneous breathing test (SBT) indicates weaning success, but variably predicts extubation success. After successful SBT, the need for reintubation within the subsequent 24 hrs to 72 hrs occurs in 5% to 30% of patients, depending on the population.**(7)**

The change in central venous saturation ($ScvO_2$) during the SBT was evaluated as a predictor of extubation failure. It is hypothesized that $ScvO_2$ could be a "reliable and convenient tool to rapidly warn about the acute changes in oxygen supply and demand of the patient during weaning.**(8)** The aim of the work was to investigate the utility of the central venous saturation as a predictor of extubation failure in mechanically ventilated Chronic Obstructive Pulmonary Disease patients.

2. Patients and Methods:

The study was carried on 35 adult mechanically ventilated COPD patients, who were admitted to Critical Care Medicine Departments in Alexandria Main University Hospital. Approval of the medical ethics committee of Alexandria faculty of Medicine, and an informed consent from the patient or next of kin were taken before conducting the study.

Inclusion criteria comprise adult COPD patients who are intubated and mechanically ventilated for a period of 48 hours or more. Tracheostomized patients, patients with left ventricular dysfunction, patients died before weaning trial or patients with no central line were excluded from the study.

Data collected:

Enrolled Patients were assessed daily for presence of the readiness-to wean criteria.**(9)** Patients meeting these criteria were weaned in a semi-recumbent position, using a two-step weaning protocol (measurements of predictors followed by a spontaneous breathing trial during 30 mins). Spontaneous breathing trial (SBT) is a trial of spontaneous breathing, carried out on low-level pressure support (PSV $\leqslant$ 7 mmHg).**(10)**

After successful completion of a SBT, patients were extubated, and followed for presence of postextubation respiratory distress during 48 hours. Extubation failure was defined as need of reintubation in 48 hours.**(11)** Noninvasive ventilation may be used to prevent respiratory distress after extubation when needed.

Measurements of haemodynamic (mean blood pressure (MBP) and heart rate) and ventilatory parameters [Minute ventilation, Respiratory frequency (*f*), Tidal volume (V_T), and Frequency–tidal volume ratio (f/V_T)] were recorded at first minute and at 30th minute of SBT. Arterial and venous blood samples were collected immediately before SBT (during MV support) and at 30th min of SBT. Echocardiography to assess left ventricular systolic function was done at the date of admission. Vital signs, demographic data, Acute Physiology and Chronic Health Evaluation (APACHE II) score **(12)** at first 24 hours of ICU stay, days in ICU, MV days were also registered.

The central venous saturation ($ScvO_2$) was sampled by central venous access placed in the internal jugular or subclavian vein (proper site previously confirmed by plain x-ray) and was analyzed along with simultaneous arterial blood sample immediately, using a blood gas analyzer (Osmitech Opti CCA). Arterial blood Oxygen extraction ratio (O_2ER) was calculated as follows: $O_2ER = (SaO_2 - ScvO_2)/SaO_2$.

Outcome measures:

All patients will be followed for the presence of respiratory distress and/or extubation failure during post-extubation 48 hours period. Extubation failure is defined by the need for reintubation in the next 48 hours.

Statistical Analysis:

All data were expressed as mean ± standard deviation for continuous variables and percentages for categorical variables. Collected data were tabulated and analyzed by the following tests Mann Whitney test.**(13)** & Chi- square test.**(14)** Data were analyzed by SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). All hypotheses were constructed two-tailed and $p \leqslant 0.05$ was considered significant. Discrimination of the logistic models was assessed by calculating the area under receiver operating characteristic (ROC) curve. The best cut-off point was chosen as that one which maximizes the Youden index (sensitivity + specificity - 1). Comparing the areas under ROC curves (AUC) was performed using the nonparametric technique described by **DeLong et al.(15).**

3. Results:

Demographic and clinical data:

Thirty five patients included in this study from April 2013 till December 2013 fulfilled the inclusion and exclusion criteria previously mentioned. Twenty seven patients (77.2%) had successful extubation and 8 patients (22.8%) had failed extubation and reintubated during the following 48 hours period.

The mean age of the study population was 56.51 ± 6.05 and 31 patients (88.6%) were male. The mean APACHE II score in the 1st 24 hours of the ICU stay of the study population was 20.66 ± 1.39 The difference in mean age and APACHE II score between both groups was not statistically significant ($p = 0.859$, $p = 0.188$) respectively. Male gender was 23 patients in extubation success group, while the male patients in extubation failure group was eight .The difference in sex between both groups showed no statistical significance ($p = 0.553$). (Table-1)

Mechanical ventilation days was significantly longer in reintubated patients as compared to successfully extubated patients (4.04 ± 1.13 versus 5.63 ± 1.30, $p = 0.004$). Regarding ICU stay, the reintubated patients stayed longer than the successfully extubated patients (8.67 ± 2.04 versus 11.13 ± 1.64, $p = 0.007$). (Table-1).

At the 1st minute of SBT: (Table-2)

Hemodynamic data:

The mean heart rate of the study population was 90.57 ± 19.23. In the extubation success group was 89.81 ± 20.74 while in the extubatuion failure group was 93.13 ± 13.74. The mean of the MBP in the extubation success group was 94.30 ± 13.91 and in the extubation failure group was 84.5 ± 15.37, yet there was no significant difference between the two groups (p= 0.675, $p = 0.135$) respectively.

Arterial blood gases data:

The mean PH of the study population was 7.40 ± 0.02. in the extubation success group was 7.41 ± 0.02 while in the extubation failure group was 7.40 ± 0.02, yet there was no significant difference between the two groups (p= 0.487). Similarly the other parameters of ABG (PCO_2, PO_2, HCO_3, SaO_2) showed no statistically significant difference between the two groups.

$ScvO_2$ and O_2 ER:

There was no statistically significant difference in the $ScvO_2$ between the extubation success and the extubation failure groups . Its mean was 75.93 ± 2.43 in the extubation success group and 76.25 ± 1.83 in the extubation failure group (p= 0.512) and similarly the O2ER showed no statistical difference between the two groups (p= 0.427).

Ventilatory parameters:

The ventilatory parameters (Minute Volume, Frequency (f), Tidal Volume (V_T) and the f/V_T) showed no significant statistical difference between the extubation success group and the extubation failure group.

Table 1. Baseline Demographic & Clinical Data

		All Patients (N = 35)	Extubation Success (N = 27)	Extubation Failure (N = 8)	*p*
Age		56.51 ± 6.05	56.67 ± 6.44	56.00 ± 4.78	0.859
APACHE II		20.66 ± 1.39	20.52 ± 1.48	21.13 ± 0.99	0.188
MV Days		4.40 ± 1.33	4.04 ± 1.13	5.63 ± 1.30	0.004
ICU stay		9.23 ± 2.20	8.67 ± 2.04	11.13 ± 1.64	0.007
SEX	**Female**	4	4	0	0.553
	Male	31	23	8	

Table 2. Patients' data at the 1st minute of SBT

	All Patients *(N = 35)*	Extubation Success *(N = 27)*	Extubation Failure *(N = 8)*	*p*
Hemodynamic data:				
Heart Rate (beat/min)	90.57 ± 19.23	89.81 ± 20.74	93.13 ± 13.74	0.675
MBP (mmHg)	92.06 ± 14.63	94.30 ± 13.91	84.5 ± 15.37	0.135
Arterial Blood Gases:				
PH	7.40 ± 0.02	7.41 ± 0.02	7.40 ± 0.02	0.487
PCO_2 (mmHg)	49.37 ± 2.67	49.19 ± 2.65	50.00 ± 2.83	0.406
PO_2 (mmHg)	72.91 ± 6.55	73.41 ± 7.00	71.25 ± 4.74	0.420
HCO_3 (mMol)	29.83 ± 1.65	29.78 ± 1.60	30.00 ± 1.93	0.857
SaO_2 (%)	93.74 ± 1.54	93.78 ± 1.63	93.63 ± 1.30	0.703
Central Venous Saturation	76.00 ± 2.29	75.93 ± 2.43	76.25 ± 1.83	0.512
O_2 Extraction Ratio	0.19 ± 0.02	0.19 ± 0.03	0.18 ± 0.02	0.427
Ventilatory parameters:				
Minute Volume (L/min)	7.32 ± 1.06	7.26 ± 1.10	7.53 ± 0.99	0.428
Frequency (cycle / min)	16.09 ± 1.65	15.78 ± 1.53	17.13 ± 1.73	0.103
Tidal Volume (L)	0.46 ± 0.06	0.46 ± 0.06	0.44 ± 0.04	0.313
f / V_T	36.03 ± 6.46	35.04 ± 6.51	39.38 ± 5.34	0.066

At 30th minute of SBT: (Table-3)

Hemodynamic data:

Neither the Heart Rate nor the MBP showed any significant statistical difference between the extubation success and the extubation failure groups at 30th min of SBT. (p =0.086, p=0.247) respectively.

Arterial blood gases data:

The mean PH became 7.39 ± 0.03 in the extubation success group and 7.36 ± 0.03 in the extubation failure group at 30th min of SBT with a statistical significant difference between the two groups (p= 0.01). There was also a significant statistical difference regarding the PCO_2 between the two groups at 30th min of SBT (p= 0.047). Other parameters of ABG (PO_2, HCO_3, SaO_2) appeared to be with no significant statistical difference.

Table 3. Patients' data at the 30th minute of SBT

	All Patients (N = 35)	Extubation Success (N = 27)	Extubation Failure (N = 8)	p
Hemodynamic data:				
Heart Rate (beat/min)	98.71 ± 17.20	96.00 ± 17.37	107.88 ± 13.89	0.086
MBP (mmHg)	90.83 ± 11.98	92.48 ± 10.52	85.25 ± 15.49	0.247
Arterial Blood Gases:				
PH	7.38 ± 0.03	7.39 ± 0.03	7.36 ± 0.03	0.010
PCO_2 (mmHg)	52.37 ± 2.69	51.81 ± 2.17	54.25 ± 3.54	0.047
PO_2 (mmHg)	70.34 ± 6.17	70.96 ± 6.42	68.25 ± 5.06	0.260
HCO_3 (mMol)	30.20 ± 1.53	30.11 ± 1.42	30.50 ± 1.93	0.687
SaO_2 (%)	93.09 ± 1.60	93.26 ± 1.61	92.50 ± 1.51	0.172
Central Venous Saturation	72.26 ± 2.87	72.81 ± 2.95	70.38 ± 1.60	0.010
O_2 Extraction Ratio	0.22 ± 0.03	0.22 ± 0.03	0.24 ± 0.02	0.031
Ventilatory parameters:				
Minute Volume (L/min)	7.11 ± 1.08	7.33 ± 1.09	6.36 ± 0.67	0.018
Frequency (cycle / min)	18.54 ± 3.35	17.96 ± 3.35	20.50 ± 2.67	0.040
Tidal Volume (L)	0.40 ± 0.10	0.42 ± 0.09	0.32 ± 0.08	0.010
f / V_T	50.23 ± 21.04	46.78 ± 21.49	61.88 ± 15.29	0.029

$ScvO_2$ and O_2 ER:

The mean Central venous Saturation became 72.81 ± 2.95 in extubation success group and 70.38 ± 1.60 in the extubation failure group at 30th min of SBT with a significant statistical difference between the two groups (p= 0.01). And similarly the mean O_2ER became 0.22 ± 0.03 in the extubation success group and 0.24 ± 0.02 in the extubation failure group with a statistical significant difference (p= 0.031).

Ventilatory parameters:

The mean minute volume at 30th min of SBT became 7.33 ± 1.09 in the extubation success group and 6.36 ± 0.67 in the extubation failure group with a significant statistical difference between the two groups (p= 0.018). Similarly the other ventilator parameters (Frequency (f), Tidal Volume (V_T), f/ V_T) showed significant statistical difference between the two groups at 30th min of SBT.

Difference between $ScvO_2$& O_2ER before and at 30th min of SBT :(Table-4)

Table 4. Difference between Central venous Saturation & Oxygen Extraction Ratio before and at 30th min of SBT

	All Patients (N = 35)	Extubation Success (N = 27)	Extubation Failure (N = 8)	p
Δ $ScvO_2$ (%)	3.74 ± 2.03	3.11 ± 1.63	5.88 ± 1.89	0.002
Δ O_2 ER	0.03 ± 0.02	0.03 ± 0.02	0.05 ± 0.02	0.006

There was a significant statistical difference between the extubation success and the extubation failure groups regarding the difference between the mean ScvO2 before and at 30th min of SBT (p=0.002). And also the difference between the mean O_2ER before and at 30th min of SBT showed a significant statistical difference between the two groups (p= 0.006).

Logistic regression analyses in predicting Extubation failure: (Table-5)

Univariate logistic regression analysis identified f/V_T and PCO_2 at the 30th minute of the SBT and the difference between $ScvO_2$ at the 1st and 30th minute of the SBT (Δ $ScvO_2$) as predictors of extubation failure. Multivariate regression identified Δ $ScvO_2$ as the only independent variable able to discriminate extubation outcome.

Receiver operating characteristic curve was depicted for $\Delta ScvO_2$ and ΔO_2ER in predicting extubation failure (Figures 1&2). Δ $ScvO_2$ showed a good discriminative ability (AUC= 0.861, 95% CI 0.702 - 0.954, $p < 0.001$). The sum of sensitivity and specificity was maximized at a decrease of 4% in $ScvO_2$ (sensitivity = 0.87; specificity = 0.74). Δ O_2ER showed a good discriminative ability (AUC= 0.838, 95% CI 0.674 - 0.940, $p < 0.001$). The sum of sensitivity and specificity was maximized at an increase of 0.037 in O_2ER (sensitivity = 0.87; specificity=0.70).(Figures1and2)

Table 5. Summary of logistic regression analyses in predicting Extubation failure

	Univariate analysis			Multivariate analysis		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***
Δ $ScvO_2$	2.52	1.25 – 5.09	0.01*	2.96	1.05 – 8.38	0.041
***f*/ V_T** (30th min of SBT)	1.04	1.01 – 1.07	0.048*	0.98	0.92 – 1.04	0.435
PCO_2 (30th min of SBT)	1.47	1.01 – 2.13	0.042*	1.20	0.75 – 1.90	0.450

OR= Odds Ratio, CI= Confidence Interval

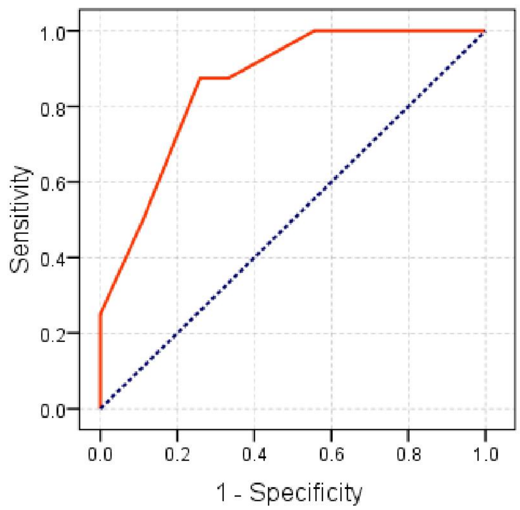

Figure 1. ROC curve of Δ $ScvO_2$ in predicting Extubation failure with AUC = 0.861

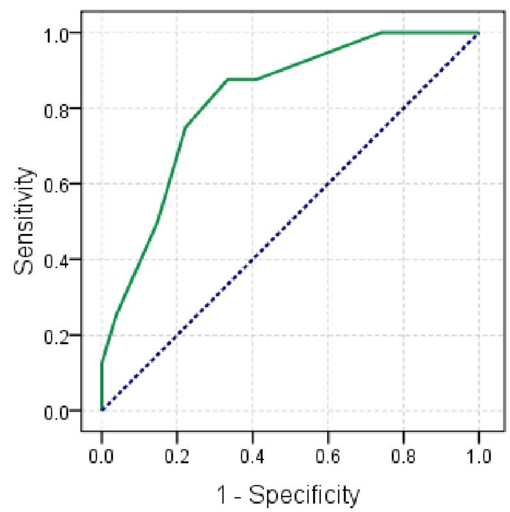

Figure 2. ROC curve of Δ O_2ER in predicting Extubation failure with AUC = 0.838

4. Discussion:

The hemodynamics and mixed venous saturation (SvO_2) in patients during weaning trials had been studied. **(16)** Patients who failed weaning also failed to increase oxygen delivery ($\dot{D}O_2$) to the tissues, in part due to elevated right and left ventricular afterloads.**(16)** Central venous oxygen saturation ($ScvO_2$), although less accurate than SvO_2, has been successfully used as an adequate resuscitation goal in critical illness. (17, 18) Adequate correlation between $ScvO_2$ and SvO_2 had been demonstrated. As such, in the weaning process, measurement of $ScvO_2$ could potentially be a reliable and convenient tool to warn rapidly about acute changes in the oxygen supply and demand of these patients.**(19, 20)**

Several investigators **(9, 21-24)** reported that formalizing weaning steps into a protocol might improve the outcome. However, approximately 25% of patients have EF when followed during 48 hours to 72 hours.(9) Our patients were extubated based on a rigid two step weaning protocol, and the reintubation rate was 22.8%. This rate is matching with previous studies that reported extubation failure rate of 14% to 32%. **(21, 25-27)**

There was no significant difference between patients with successful versus failed extubation as regards baseline clinical characteristics and demographic data (age, sex, admission APACHE II score, and vital signs). In accordance with that, **Teixeira et al.(28)** in a cohort of 51 mechanically ventilated patients reported no statistically significant difference between extubation success and extubation failure group regarding baseline clinical characteristics and demographic data. This is also matching with the study conducted by **Saugel et**

al.(29) in a cohort of 61 mechanically ventilated patients which also showed no significant difference between the two groups as regards the age , sex and vital signs. However, **Savi et al.(30)** in a cohort of 500 mechanically ventilated patients reported a statistically significant difference regarding the age. Different study population and variable etiologies for mechanical ventilation rather than COPD patients only in our study may give explanation for such difference.

There was statistically significant difference between patients with successful versus failed extubation as regards mechanical ventilation days and ICU stay. However **Teixeira et al.(28)** reported no statistically significant difference between extubation success and extubation failure group regarding mechanical ventilation days. Different definitions of MV days between Teixeira et al.(28) and our study may account for the notable difference (MV days only before the SBT versus the whole MV period, respectively).

The present study revealed no statistically significant difference between the extubation success versus the extubation failure group regarding the ABG parameters (PH, PCO_2, PO_2, HCO_3, and SaO_2) at the 1^{st} minute of SBT. In accordance with that **Teixeira et al. (8)** in a cohort of 73 mechanically ventilated patients reported no statistically significant difference between extubation success and extubation failure group regarding the ABG parameters at the 1^{st} minute of SBT.

Regarding the Central venous Saturation and the Oxygen Extraction before SBT, There was no statistically significant difference between the extubation success versus the extubation failure group in this study. This is also matching with a study conducted by **Teixeira et al. (8)** reported the same results.

Regarding the ventilatory parameters measured at the 1st min of SBT (Minute Volume, Frequency (*f*), Tidal Volume (V_T) and the f / V_T) , This study revealed no statistically significant difference between the extubation success versus the extubation failure groups. In accordance with that **Teixeira et al. (8)** reported no statistically significant difference between extubation success and extubation failure group regarding the same ventilator parameters when measured before the SBT.

This study revealed statistically significant difference of the PH and the PCO_2 between the extubation success versus the extubation failure group when measured at 30th min of the SBT. In agreement with that Mokhlesi et al. found that Pre-extubation hypercapnoea ($PCO_2 \geqslant 44$ mmHg) due to an imbalance of respiratory load and capacity was an independent risk factor for extubation failure**.(31)**

On the contrary **Teixeira et al.(8)** reported no statistically significant difference between extubation success and extubation failure group regarding the PH and the PCO_2. And similar observation was noted by **Saugel et al.(29)** also showed no significant difference between the two groups as regards the PH and the PCO_2. A possible explanation for that difference in the results is clear; the present study included only COPD patients with chronic respiratory acidosis who are mechanically ventilated for acute decompensation while the two latter studies included patients with variable causes of mechanical ventilation for example (pneumonia, sepsis, ARDS, trauma, congestive heart failure).

Regarding the rapid shallow breathing index (f/V_T), the present study revealed a statistically significant higher RSBI in the extubation failure success group when measured at 30^{th} min of SBT. The RSBI was first described by **Yang and Tobin (32)** and early studies suggested that it was the most accurate predictor of failure in weaning patients from mechanical ventilation.(33, 34)

In this study multivariate regression identified Δ $ScvO_2$ as the only independent variable able to discriminate extubation outcome. The Δ $ScvO_2$ in the EF group was 5.88 ± 1.89 as compared with 3.11 ± 1.63 in ES group ($p = 0.002$). A reduction in $ScvO_2$ by $\geqslant 4\%$ during the SBT was an independent predictor of reintubation. In accordance with that Teixeira et al.(8) reported that reduction of central venous saturation by >4.5% was an independent predictor of reintubation, with odds ratio of 49.4 (95% confidence interval 12.1 201.5), a sensitivity of 88%, and a specificity of 95%. According to the Fick principle, oxygen uptake (VO_2) depends on $\dot{D}O_2$ and O_2ER**.(17, 35)** In the present study, $\dot{D}O_2$ was not measured, but similar results between groups (EF and ES) had been estimated based on the same hemoglobin level, hemodynamic parameters, and SaO_2 and PaO_2. Therefore, it appears that the drop in $ScvO_2$ could reflect the increase of respiratory muscles VO_2 observed in EF patients during the SBT. (16, 36) $ScvO_2$ reflects increased O_2 extraction due to abnormal lung function (demand) but not due to systolic dysfunction as they were excluded of our study by echocardiography.

Use of mixed venous Oxygen saturation (SvO_2) during the weaning period has been previously studied (17, 23, 24, 37-39). Jubran et al (16) demonstrated that SvO2 decreased in weaning failure patients, probably due to increased respiratory muscles O_2ER. **Noll and Byes (40)** showed correlation of SvO_2, vital signs, and arterial blood gases in 30 consecutive postoperative coronary artery bypass graft cases, but only SpO_2 and respiratory rate correlated with weaning failure. Cason et al (41), in ten postoperative coronary artery bypass graft patients, evaluated SvO_2 and SpO_2 during SBT and showed that weaning failure occurred when SvO_2 was <60%. **Armaganidis and Dhainaut (42)** monitored SvO_2 in postoperative coronary artery bypass graft patients and demonstrated that SvO2 of >60% was the best weaning success predictor studied and depended on O_2ER measurements.The choice of $ScvO_2$ instead of SvO_2 was due to limited use of a pulmonary artery catheter during weaning period, reflecting everyday clinical practice. Pulmonary artery catheterization is costly and has inherent risks. In comparison, $ScvO_2$ is part of the standard care of critically ill patients and is easier and safer. Others investigators **(19, 43)** had demonstrated adequate correlation between $ScvO_2$ and SvO_2. **Rivers et al (18) and Vallet et al.(43)** previously showed that early goal directed therapy based on $ScvO_2$ reduces mortality in patients with severe sepsis and septic shock. Measurement of $ScvO_2$ is a potentially reliable and convenient tool, which could rapidly warn about acute change in the oxygen supply and demand of critically ill patients. Our data showed that, during MV (immediately before SBT), $ScvO_2$ was not different between EF and ES patients, but that $ScvO_2$ reduction during T-tube trial was able to predict EF in 86% of the cases.

Mechanically ventilated COPD patients may pass the SBT successfully, but successful extubation is still unpredicted therefore, we believe that $ScvO_2$ measured before and at 30th min of SBT may be a good and accurate predictor of extubation failure in mechanically ventilated COPD patients.

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