Original article

Utility of arterial to end-tidal carbon dioxide difference [P(a – ET)CO_2] as a weaning index

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Abstract

Introduction: Quantification of physiological dead space (V_{Dphys}) provides important insight into the efficiency of ventilation and its relation to pulmonary perfusion. Arterial to end-tidal carbon dioxide difference [P(a-ET)CO_2] may provide a valuable surrogate measure of V_{Dphys} and may be useful as an index of weaning success. **Aim:** To evaluate the utility of [P(a-ET)CO_2] as a weaning index. **Methods:** This prospective study enrolled 52 invasively mechanically ventilated adult patients treated in Medical Intensive Care Unit (MICU) between December 2010 and December 2011. The end-tidal carbon dioxide concentration was measured using a side stream capnograph at each attempt at decreasing ventilatory support and when they were ready to be weaned. A receiver operating characteristic (ROC) curve was constructed for weaning success, progressive weaning and extubation success. A cut-off point was obtained from these curves from which the sensitivity, specificity, positive and negative predictive values were obtained. **Results:** The ability of [P(a-ET)CO_2] as a predictor of progressive reduction in ventilator support (n = 118), predictor of weaning from mechanical ventilation (n = 40) and for extubation success (n = 39) was evaluated. The area under the curve (AUC) for progressive weaning, spontaneous breathing trial and extubation success were 0.852, 0.905 and 0.702 and a threshold of 10.5 mm Hg, 9.4 mm Hg and 9.5 mm Hg respectively were obtained. **Conclusion:** P(a-ET)CO_2 of ≤ 10 mm Hg may be used as an index of weaning during progressive weaning from mechanical ventilation, spontaneous breathing trial and to predict success of extubation.

Keywords: Weaning index, arterial to end-tidal carbon dioxide gradient, dead space.

Introduction

Monitoring of physiological variables in patients with respiratory failure may be useful in establishing the degree of severity of lung injury, predicting response to treatment and following the course of the disease. Quantification of physiological dead space (V_{Dphys}) provides important insight into the efficiency of ventilation and its relation to pulmonary perfusion.[1] Hubble *et al* found that routine monitoring of dead space to tidal volume ratio (V_D/V_T) in paediatric patients had permitted early extubation and reduced unexpected extubation failures.[2]

The lack of a simple, practical method for the calculation of dead space (V_D) components simultaneously has hindered the clinical application of V_D measurement.[3] The arterial to end tidal carbon dioxide difference P(a-ET)CO_2 quantifies efficiency

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of ventilation. The normal value of $P(a\text{-}ET)CO_2$ is 0 – 5 mm Hg and it increases with increase in V_{Dphys}. Hence $P(a\text{-}ET)CO_2$ may provide a valuable surrogate measure of V_{Dphys} and may be useful as an index of weaning success.

The present study was undertaken to evaluate the utility of arterial to end-tidal carbon dioxide difference [$P(a\text{-}ET)CO_2$] as a weaning index.

Methods

This prospective study enrolled 52 invasively mechanically ventilated adult patients who were treated in Multidisciplinary Intensive Care Unit (MICU) of Kasturba Hospital, Manipal University, in the period December 2010 to December 2011. Adult patients, who were ≥ 18 years of age, who were orotracheally intubated, receiving positive pressure mechanical ventilation for at least 12 h were included. Those who required noninvasive mechanical ventilation, who were tracheostomised and who had their life support limited were excluded. The mechanical ventilators used were equipped with basic graphic monitoring and the calibrations were done as per manufacturer's recommendations. The ventilators used were Dräger Savina™ – Dräger Medical Inc., Lübeck, Germany, Dräger Evita™ 2 Dura – Dräger Medical Inc., Lübeck, Germany and Datex Ohmeda Engström ventilator- Datex-Ohmeda Inc.

The end-tidal carbon dioxide concentration was measured using a side stream capnograph. Gas sampling was done at a point immediately proximal to the endotracheal tube. The measurement was done each time an attempt was made at decreasing ventilatory support as well as when they were ready to be weaned. Correlation of the arterial to end tidal carbon dioxide difference $P(a\text{-}ET)CO_2$ to the success of weaning at each decremental step in mechanical ventilation, at low levels of pressure support and continuous positive airway pressure (spontaneous breathing trial) as well as success of extubation was attempted.

Classification of weaning and extubation outcome

Weaning success: If the patient could sustain the weaned setting without any step up of ventilatory support for a period of 12 h.

Weaning failure: Weaning was considered as unsuccessful outcome if the patient required step up of ventilatory support within 12 h.

Extubation success: If the patient could sustain without any form of mechanical ventilation (noninvasive ventilation or re-intubation) for 24 h.

Extubation failure: Resumption of any form of mechanical ventilation (MV) within 24 h of extubation.

A receiver operating characteristic (ROC) curve was constructed for weaning success, progressive weaning and extubation success. A cut-off point was obtained from these curves for which the sensitivity, specificity, positive and negative predictive values were obtained.

The outcomes and results were categorised as follows: True positive result - correctly predicts successful MV weaning/extubation, a true negative test result correctly predicts unsuccessful MV weaning. A false positive test result predicts successful MV weaning but the patient fails weaning from MV and a false negative test result predicts unsuccessful MV weaning, although the patient is weaned successfully from MV.

Statistical analysis: Statistical analysis was done with statistics software SPSS 16, SPSS, Chicago, Illinois. All data are reported as mean ± standard deviation (SD). The threshold predictive value was obtained from receiver operating characteristic curve. Statistical significance was set at $p < 0.05$.

Results

A heterogeneous group of 51 mechanically ventilated adult patients were included. The demographic characteristics of the patients are given in *Table 1*. The clinical diagnosis was broadly classified as medical and surgical.

Table 1: *Demographic data*

Variables	
Age (years) (Mean ± SD)	51.8 ± 12.6
Height (cm) (Mean ± SD)	162 ± 9.2
Weight (kg) (Mean ± SD)	62 ± 13.2
Gender (M/F) (%)	54.9 /45.1
Medical/Surgical (%)	43.1 / 56.9

Table 2: Diagnostic tests used to evaluate the accuracy of the parameter for weaning/extubation from mechanical ventilation.

Test	Formula
Sensitivity	TP/(TP + FN)
Specificity	TN/(TN + FP)
PPV	TP/(TP + FP)
NPV	TN/(TN + FN)
PLR	Sensitivity/(1 – specificity)
NLR	(1 – sensitivity)/specificity

TP = true positive; TN = true negative; FP = false positive; TN = true negative; PPV= positive predictive value; NPV= negative predictive value; PLR = Positive likelihood ratio; NLR = Negative likelihood ratio.

118 data points were obtained for analysis of end-tidal carbon dioxide for progressive weaning and various diagnostic tests were applied *(Table 2)*. The ability of arterial to end-tidal carbon dioxide difference as a predictor of progressive reduction in ventilator support was evaluated by applying it to all 118 data points. A ROC curve was constructed *(Figure 1)*. The area under the curve (AUC) was 0.852. A threshold of 10.5 mm Hg arterial to end-tidal carbon dioxide difference was obtained. The sensitivity, specificity, positive and negative predictive values of this threshold were calculated *(Table 3)*. The positive likelihood ratio was 4.84 and negative likelihood ratio was 0.20 which means that it was 4.84 times more likely that $P(a\text{-}ET)CO_2 \leq 10.5$ mm Hg was successful in weaning from mechanical ventilation than who had $P(a\text{-}ET)CO_2 \geq 10.5$ mm Hg. It was also 0.2 times likely that $P(a\text{-}ET)CO_2 \geq 10$ was successful in weaning from mechanical ventilation than who had $P(a\text{-}ET)CO_2 \leq 10.5$.

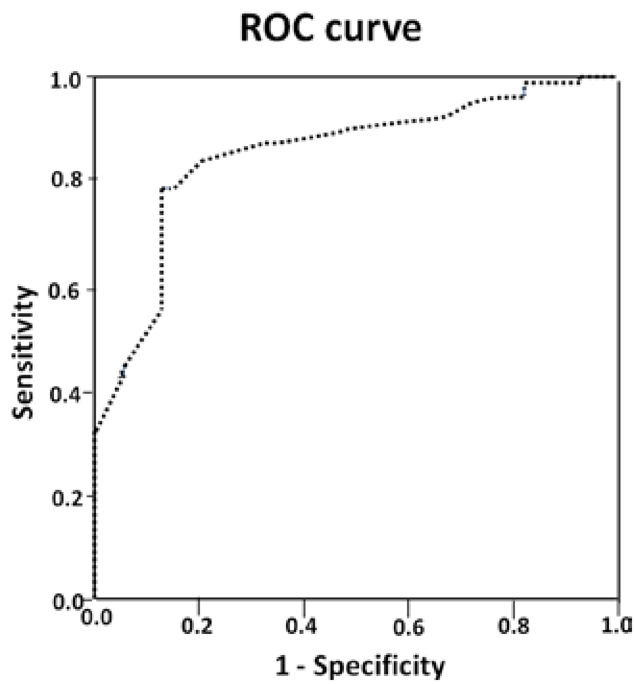

Figure 1: Receiver operating characteristic curve for arterial to end-tidal carbon dioxide difference as an index for progressive weaning from mechanical ventilation

Spontaneous breathing trial was considered when inspired oxygen concentration was ≤ 40%, CPAP was 5-8 cm H_2O and PSV, 5 – 10 cm H_2O. The arterial to end-tidal concentration of carbon dioxide at the time of decision to wean and the success of weaning from mechanical ventilation were correlated. All

Table 3: Arterial to end-tidal carbon dioxide difference with a threshold of 10.5 mm Hg as an index for progressive weaning from mechanical ventilation

		Actual weaning	
Predicted weaning		Possible	Not possible
	≤10.5 mm Hg Possible	69	06
	≥10. 5 mm Hg Not possible	14	29

measurements were done on ventilator. 40 data points were obtained for weaning from mechanical ventilation *(Figure 2)*. The AUC was 0.905. As per the ROC curve, a threshold cut-off value of 9.4 mm Hg was obtained. The sensitivity, specificity, positive and negative predictive values of this threshold were calculated *(Table 4)*.

The positive likelihood ratio was 5.30 and negative likelihood ratio was 0.04. This means that it was 5.3 times more likely that P(a-ET)CO_2 ≤ 9.4 mm Hg was successful in weaning from mechanical ventilation than who had P(a-ET)CO_2 ≥ 9.4 mm Hg. It was 0.04 times likely that P(a-ET)CO_2 ≥ 9.4 mm Hg was successful in weaning from mechanical ventilation.

Out of 51 patients initially included, 12 had to be excluded. Five patients died, four were discharged against medical advice and three shifted to other ICU. Hence 39 data points were used to construct an ROC curve *(Figure 3)* and the threshold value obtained was 9.5 mm Hg.

The area under the curve (AUC) was 0.72. A threshold of 9.5 mm Hg arterial to end-tidal carbon dioxide difference as a predictor of extubation success was used and calculations were made as before *(Table 5)*. The positive likelihood ratio was 2.42 and the negative likelihood ratio was 0.165 which means that it was 2.42 times more likely that P(a-ET) CO_2 ≤ 9.5 mm Hg was successful in weaning from mechanical ventilation. It was 0.165 times likely that P(a-ET)CO_2 ≥ 9.5 mm Hg was associated with successful weaning from mechanical ventilation.

Table 4: Arterial to end-tidal carbon dioxide difference with a threshold of 9.4 mm Hg as a weaning index

Predicted weaning	Actual weaning		
		Possible	Not possible
	≤ 9.4 mm Hg possible	28	02
	≥ 9.4 mm Hg not possible	01	09

Discussion

This study concentrated on the routine use of an indicator of physiological dead space as a weaning index. A volume capnograph would directly provide

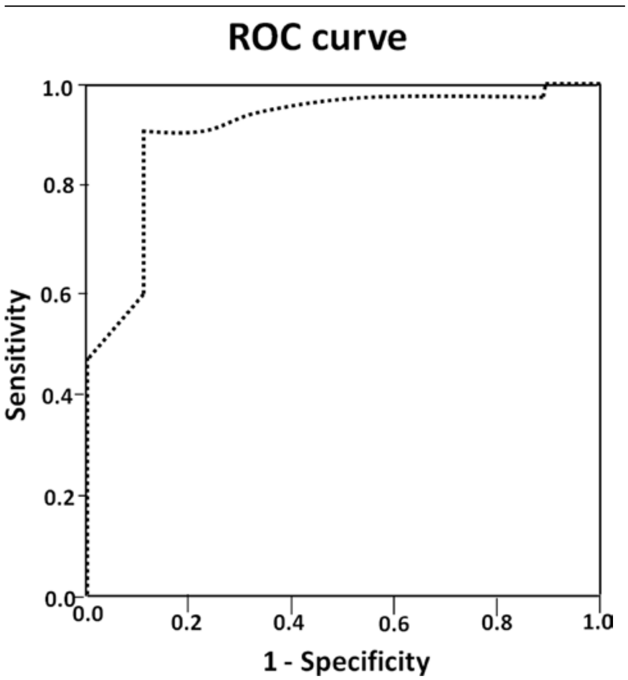

Figure 2: Receiver operating characteristic curve for arterial to end-tidal carbon dioxide difference as a weaning index.

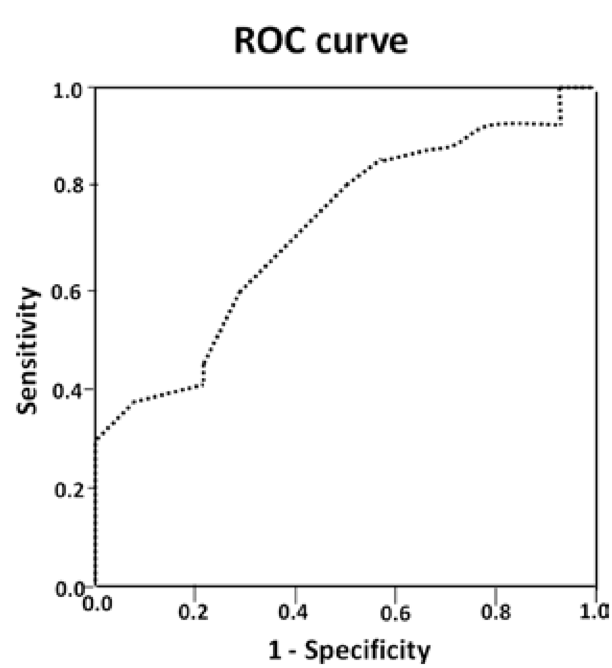

Figure 3: Receiver operating characteristic curve for arterial to end-tidal carbon dioxide difference as a predictor of extubation success

Table 5: Arterial to end-tidal carbon dioxide difference with a threshold of 9.5 mm Hg as an index to predict extubation success

Predicted extubation	Actual extubation		
		Possible	Not possible
	≤ 9.5 mm Hg Possible	26	03
	≥ 9.5 mm Hg Not possible	03	07

measurements of physiological dead space unlike a timed capnograph. However, a volume capnograph is not available freely. Arterial blood gases are considered essential investigation in the ICU for mechanically ventilated critically ill patients but cannot be done frequently.

This study concentrated on difference between arterial to end tidal carbon dioxide as an indicator of physiological dead space and success of weaning from mechanical ventilation. Secondary objective of the study was to evaluate utility of this difference in extubation success.

The V_D/V_T is a standard measure of contribution of lung units with high $\dot{V}/\dot{Q}$, indicating the proportion of wasted ventilation. Increased P(a-ET)CO_2 is a measure of high $\dot{V}/\dot{Q}$. This indicates that, there is a close relationship between V_D/V_T and P(a-ET)CO_2. Nuckton *et al* studied the pulmonary dead space fraction as a risk factor for death in the acute respiratory distress syndrome in the early phase.[3] The mean dead-space fraction was markedly elevated (0.58+/-0.09) early in the course of the acute respiratory distress syndrome and was higher among patients who died than among those who survived (0.63+/-0.10 vs. 0.54+/-0.09, $p<0.001$). The dead space fraction was an independent risk factor for death: for every 0.05 increase, the odds of death increased by 45 percent (odds ratio, 1.45; 95 percent confidence interval, 1.15 to 1.83; $p=0.002$). Yamanaka *et al* compared the P(a-ET) CO_2 and V_D/V_T in respiratory failure patients and found that they closely correlated ($r= 0.80$, $p<0.05$).[4] Bousso *et al* established a cut-off point of $V_D/V_T \geq 0.65$ to detect extubation failure.[5] They identified that there is increased likelihood of patients with $V_D/V_T \geq 0.65$ being at high risk of failure.

Moreover, studies done by Jonathan *et al* concluded that P(a-ET)CO_2 can be used to calculate alveolar dead space (V_{Dalv}).[6] By definition, we know that physiological dead space is sum of alveolar and anatomical dead space. Measuring V_D/V_T using partial pressure of carbon dioxide in mixed expired gases ($P\bar{E}CO_2$) is sophisticated. Hence the use of V_D in ICU has been limited. Volume capnography with a direct read out of physiological dead space is also not routinely available. This could be replaced by $P_{ET}CO_2$ which can be obtained by timed capnography which is simple, practical, reliable, real time and more easily available.

A study done by McSwain *et al* showed that P(a-ET)CO_2 correlated across all level of V_D/V_T.[7] With increasing V_D/V_T strength of correlation decreased. In their study, the P(a-ET)CO_2 level for V_D/V_T ranging between 0.56 to 0.70 is 13.6 ± 5.2 mm Hg, *i.e.*, between 8.4 mm Hg to 18.8 mm Hg. The result obtained from our study is 10.5 mm Hg falls in this range. This adds to the fact that P(a-ET)CO_2 of 10.5 mmHg corresponds to the value between 0.55 to 0.60 of V_D/V_T.

Since the cut-off values of P(a-ET)CO_2 for weaning during spontaneous breathing trial, progressive weaning from mechanical ventilation and extubation were 9.4, 10.5 and 9.4 mm Hg respectively, a round value of 10 mm Hg is suggested by this pilot study as an index to predict success of weaning in all three situations. A larger study along with the use of a volume capnograph would be required to confirm these findings.

Conclusion

P(a-ET)CO_2 of ≤ 10 mm Hg can be used as an index of weaning during spontaneous breathing trial, progressive weaning from mechanical ventilation and to predict success of extubation.

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