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An evaluation of extubation failure predictors in mechanically ventilated infants and children

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Abstract *Objective:* To assess the accuracy of traditional weaning indices in predicting extubation failure, and to compare their accuracy when indices are measured at the onset of a breathing trial (SBT) and at the end of the SBT before extubation. *Design*: Prospective study. *Setting*: Medical-surgical intensive care unit at a tertiary care hospital. *Patients:* Four hundred eighteen consecutive infants and children who received mechanical ventilation for at least 48 h and were deemed ready to undergo a SBT by their primary physician. *Interventions:* Respiratory frequency (RR), tidal volume (V_T), maximal inspiratory pressure (P_{imax}) and frequency-to-tidal volume ratio (f/V_T) were obtained within the first 5 min of breathing through a T-piece. The primary physicians were unaware of those measurements and the decision to extubate a patient was made by them. RR, V_T, f/V_T were remeasured before extubation by the respiratory therapists. Extubation failure was defined as needing re intubation within 48 h after extubation. The area under the receiver operating characteristic (ROC) curve was calculated for each index as a measure of the accuracy in predicting extubation outcome. *Measurements and main results:* Three hundred twenty-three patients successfully underwent the SBT and were extubated, but 48 of them (14%) required re-intubation. The ROC curve for V_T, RR, P_{imax} and f/V_T measured within the first 5 min of breathing were 0.54, 0.56, 0.57 and 0.57, respectively. The ROC curve did not increase significantly when the above indices were remeasured before extubation. *Conclusions:* In a population which had passed SBT, the ability of the traditional weaning indices to discriminate between children successfully extubated and children re-intubated is very poor.

Keywords Weaning · Mechanical ventilation · Weaning indices · Extubation failure · Infants · Children

Introduction

Mechanical ventilation should be discontinued as soon as the patient can sustain spontaneous breathing with adequate gas exchange. Recent studies [1, 2] have shown that children can be successfully weaned from mechanical ventilation after a trial of spontaneous breathing (SBT) lasting 2 h. However, around 15% of patients who are extubated after passing a SBT will be re-intubated within 48 h [1, 2]. Since unsuccessful extubation increases mortality [2, 3], it would be of paramount importance for clinicians to be able to identify those patients who are likely to fail a trial of extubation.

Several studies have been performed to identify useful indices for predicting successful extubation in pediatric patients [1, 4, 5, 6, 7, 8, 9, 10, 11], but the results have been quite different from one study to another. The statistical methods employed for testing the accuracy of the indices may account, at least in part, for the discrepancies among the studies. Furthermore, the number of extubation failures has been relatively low, ranging from 6 to 13, in six out of the nine studies published [1, 5, 6, 8, 9, 11] and the threshold value of the weaning index selected for a positive diagnosis varied extensively among the studies.

Receiver operating characteristic (ROC) curve is a measure of accuracy that is independent both of the relative frequencies of the two events studied (for example, successful extubation and re-intubation) and of the threshold value used for a positive diagnosis. To date, the accuracy of the predictors for extubation outcome in children has been evaluated by means of ROC curves in only four studies [6, 8, 9, 11].

All of the studies published evaluating predictors of extubation outcome in children have measured the respiratory parameters used as predictors at only one time, either immediately before extubation [4, 7, 9, 10, 11], 2 h before extubation [1, 5] or several hours before extubation [8]. Two studies in adult patients have demonstrated that the accuracy of the frequency-to-tidal volume ratio (f/V_T) in predicting the extubation outcome may be enhanced by measuring the ratio at different times over the SBT before extubation [12, 13].

This study evaluates the usefulness of several respiratory measurements, easily performed at the bedside, in predicting extubation failure in children and compares the accuracy of each index when measured immediately after the discontinuation of mechanical ventilation and immediately before extubation.

Methods

Patients

The study was conducted from May 1997 to December 2000 in a medical-surgical pediatric intensive care unit (PICU) located at a tertiary-care hospital. All infants and children admitted to the PICU who received mechanical ventilation for at least 48 h and were judged by the primary physician as ready to undergo a SBT before extubation were eligible for the study. Patients were enrolled if they met all of the following conditions: (1) age between 1 month and 15 years; (2) improvement or resolution of the underlying cause of acute respiratory failure; (3) adequate gas exchange as indicated by a partial pressure of arterial oxygen (PaO_2) higher than 60 mmHg while breathing with a fractional inspired oxygen (FIO_2) of 0.40 or less and a positive end-expiratory pressure (PEEP) of 5 cmH_20 or less; (4) a core temperature below 38.5°C; (5) alert mental status after removal of sedative agents; (6) a hemoglobin level above 10 g/dl; (7) no further need for vasoactive agents. Patients with tracheostomy (*n*=9), neuromuscular disease (*n*=9) or audible air leak around the endotracheal tube (*n*=16) were excluded from the study.

Protocol

When a patient was enrolled in the study, mechanical ventilation was stopped and the patient breathed through a T-piece with the FIO_2 set at the same level as used during mechanical ventilation. The following measurements were taken within the first 5 min: respiratory frequency (RR), exhaled minute volume and maximal inspiratory pressure (P_{imax}). Exhaled minute volume was measured with a Wright Infanta spirometer (Ferraris Medical, London, UK) over 1 min. Tidal volume (V_T) was calculated by dividing exhaled minute volume by RR and was indexed to body weight. P_{imax} was measured by occluding the airway using a one-way valve and the most negative value of three efforts was selected. F/V_T was calculated by dividing RR by V_T indexed to body weight. The respiratory therapists caring for the patients collected the above data and all of the physicians in the PICU were unaware of the results of each patient's respiratory measurements.

After the above measurements had been performed, patients underwent a SBT with either pressure support ventilation of 10 cmH_2O or a T-piece lasting up to 2 h. The primary physicians terminated the trial if a patient had any of the following signs of poor tolerance: (1) RR higher than the value corresponding to the 90th percentile for a given age [14, 15]; (2) signs of increased respiratory work: use of accessory respiratory muscles, intercostal-suprasternal-supraclavicular retraction, a paradoxical breathing pattern; (3) diaphoresis and anxiety; (4) heart rate higher than the value corresponding to the 90th percentile for a given age [14]; (5) change in mental status (agitation or somnolence); (6) blood pressure lower than the value corresponding to the 3rd percentile for a given age [16]; (7) oxygen saturation lower than 90% when measured by pulse oximetry; (8) partial pressure of arterial carbon dioxide higher than 50 mmHg or an increase of more than 10 mmHg; (9) arterial pH lower than 7.30. If a patient had any of the above signs at any time during the breathing trial, mechanical ventilation was re-instituted.

The exhaled minute volume and RR were measured again at the end of the breathing trial in those patients successfully passing the 2h period. A sample of arterial blood was collected for gases analysis and pulmonary gas exchange was assessed by calculation of the ratio of PaO_2 to FIO_2 (PaO_2/FIO_2 ratio). After the above measurements had been performed, patients were immediately extubated and received supplemental oxygen by face mask. Weaning was considered successful if extubation was performed after the SBT and re-intubation was not required within 48 h of extubation. The primary physicians decided the need for re-intubation according to clinical examination, blood gases or both.

The institutional ethics committee of the hospital approved the study and parents provided informed consent.

Data analysis

The data are shown as medians with the 25th and 75th percentile ranges or proportions with 95% confidence interval (CI). The Chi square test with Yates correction was used to compare categorical data, except when small size required the use of Fisher's exact test. Comparisons were made of the continuous variables among the following three groups: (1) patients who failed the SBT (trial failure group), (2) patients re-intubated (re-intubation group) and (3) patients successfully extubated (successful extubation group), using one-way analysis of variance for continuous variables with normal distribution and the Kruskall-Wallis test for variables with non-normal distribution.

A true positive result (TP) was defined as occurring when an index predicted extubation failure and the patient was, in fact, re-intubated; a false positive result (FP) was defined as occurring when an index predicted extubation failure but the patient was, in fact, successfully extubated; a true negative result (TN) was defined as occurring when an index predicted extubation success and

Table 1 Characteristics of the study population at baseline according to weaning outcome. Values are median (25th percentile, 75th percentile)

	Successful extubation n=275	Re-intubation n=48	Trial failure n=95
Age (months)	11 (4, 36)	9 (4, 42)	7 (3, 13)[a]
Body weight (kg)	8 (6, 15)	7 (5, 15)	6 (4, 10)[a]
PRISM score at the PICU admission	13 (9, 16)	12 (8, 16)[b]	12 (9, 16)[a]
Duration of ventilator support before breathing trial (days)	6 (3, 9)	7 (4, 12)	8 (4, 13)[c]
Reason for the initiation of mechanical ventilation, *n* (%)			
Acute on chronic pulmonary disease	39 (14.1)	5 (10.4)	15 (15.8)
Coma	38 (13.8)	5 (10.4)	6 (6.3)
Acute respiratory failure	198 (72.0)	38 (79.2)	74 (77.9)
Cause of acute respiratory failure, *n* (%)			
Pneumonia or bronchiolitis	88 (44.4)	21 (55.3)	32 (43.2)
Postoperative state	42 (21.2)	4 (10.5)	11 (14.9)
Septic shock	24 (12.1)	4 (10.5)	11 (14.9)
Heart failure	13 (6.6)	6 (15.8)	9 (12.1)
Upper airway obstruction	10 (5.0)	2 (5.3)	4 (5.4)
Other	21 (10.6)	1(2.6)	7 (9.4)

[a] $p<0.01$ for the comparison between successful extubation and trial failure groups
[b] $p<0.05$ for the comparison between successful extubation and re-intubation groups
[c] $p<0.05$ for the comparison between successful extubation and trial failure groups

the extubation actually succeeded; a false negative result (FN) was defined as occurring when an index predicted extubation success but the patient was, in fact, re-intubated. Standard formulas were used to calculate the sensitivity (TP/TP+FN), specificity (TN/TN+FP), positive likelihood ratio (sensitivity/1-specificity) and negative likelihood ratio (1-sensitivity/specificity). The cutoff values selected were those resulting in the fewest false classifications.

The predictive performance of each index was also assessed with the receiver operating characteristic (ROC) curve. ROC curve analysis provides a powerful means of assessing the ability of each index to discriminate between two groups of patients (re-intubated and successfully extubated), with the advantage that the analysis does not depend on the cutoff value selected.

Results

A total of 418 patients were enrolled in the study and 323 (77%; 95% confidence interval 73–81%) successfully underwent the SBT and were immediately extubated. The remaining 95 patients (23%; 95% confidence interval 19–27%) were reconnected to the ventilator because of poor tolerance of the SBT after a median time of 30 min (25th, 75th percentiles: 12, 45 min). Among the 323 patients who tolerated the SBT and were extubated, 48 (14%; 95% confidence interval 11–19%) required re-intubation within 48 h. The characteristics of the patients according to weaning outcome are shown in Table 1. The three groups were similar with respect to the indication for mechanical ventilation, but patients failing the SBT were smaller and younger than those successfully extubated. The duration of ventilatory support before weaning was longer in patients failing the SBT as compared with patients successfully extubated and patients re-intubated.

The values of the respiratory measurements performed both at the beginning of the SBT and immediate-

Table 2 Respiratory measurements performed at the onset of the breathing trial and immediately before extubation. Results are median (25th percentile, 75th percentile)

	Onset of the breathing trial	Immediately before extubation	*p* value
Tidal volume (ml/kg)			
Extubation success	7 (5, 8)	7 (6, 9)	0.41
Extubation failure	6 (5, 8)	6 (5, 8)	0.20
p value	0.16	0.06	
Respiratory frequency (breaths/min)			
Extubation success	36 (26, 48)	35 (26, 46)	0.57
Extubation failure	41 (25, 55)	40 (29, 54)	0.94
p value	0.20	0.07	
f/V_T ratio (breaths/min/ml/kg)			
Extubation success	5 (4, 8)	5 (3, 8)	0.15
Extubation failure	7 (4, 11)	7 (4, 11)	0.77
p value	0.10	0.016	
P_aO_2 (mmHg)			
Extubation success	106 (89, 123)	102 (86, 120)	0.41
Extubation failure	104 (88, 135)	100 (80, 118)	0.20
p value	0.99	0.14	
P_aCO_2 (mmHg)			
Extubation success	39 (35, 44)	39 (35, 40)	0.86
Extubation failure	39 (34, 43)	40 (35, 44)	0.86
p value	0.62	0.62	
PaO_2/FIO_2 ratio			
Extubation success	283 (230, 340)	271 (233, 337)	0.50
Extubation failure	296.5 (242.5, 367)	270.5 (228.5, 333)	0.24
p value	0.55	0.94	
Maximal inspiratory pressure (cmH_2O)			
Extubation success	35 (30, 40)		
Extubation failure	30 (25, 47)		
p value	0.10		

Table 3 Area under the receiver operating characteristic curve for the prediction of extubation outcome

Index	Area (95% confidence interval)
Tidal volume measured in the first 5 min	0.54 (0.44–0.64)
Tidal volume measured at 120 min	0.58 (0.49–0.68)
Respiratory frequency measured in the first 5 min	0.56 (0.46–0.65)
Respiratory frequency measured at 120 min	0.58 (0.49–0.67)
Maximal inspiratory pressure measured in the first 5 min	0.57 (0.47–0.67)
Frequency-to-tidal volume ratio measured in the first 5 min	0.57 (0.48–0.67)
Frequency-to-tidal volume ratio measured at 120 min	0.61 (0.51–0.70)
PaO_2/FIO_2 during mechanical ventilation	0.49 (0.40–0.58)
PaO_2/FIO_2 at 120 min	0.51 (0.42–0.60)

Table 4 Sensitivity, specificity, positive likelihood ratio and negative likelihood ratio for each index according to the selected cutoff values (*CI* confidence interval, *MV* mechanical ventilation)

	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio	Negative Likelihood ratio
Tidal volume at 5 min ≤ 4 ml/kg	23.9 (11.0–34.8)	90.9 (87.5–94.3)	2.52	0.85
Tidal volume at 120 min ≤ 4 ml/kg	20.8 (9.3–32.3)	93.1 (90.1–96.1)	3.02	0.85
Respiratory frequency at 5 min ≥ 45 breaths/min	37.5 (23.8–51.2)	68.0 (62.3–73.5)	1.17	0.92
Respiratory frequency at 120 min ≥45 breaths/min	41.7 (27.2–55.6)	72.4 (67.1–77.6)	1.51	0.81
Maximal inspiratory pressure at 5 min ≤20 cmH_2O	12.5 (3.1–21.9)	95.6 (93.2–98.1)	2.86	0.91
Frequency-to-tidal volume ratio at 5 min ≥11 breaths/min/ml/kg	27.1 (14.5–39.7)	90.9 (87.5–94.3)	2.98	0.80
Frequency-to-tidal volume ratio at 120 min ≥11 breaths/min/ml/kg	27.1 (14.5–39.7)	91.6 (88.4–94.9)	3.24	0.80
PaO_2/FIO_2 during MV ≤ 200 mmHg	16.7 (6.1–27.2)	86.5 (82.5–90.6)	1.24	0.96
PaO_2/FIO_2 at 120 min ≤200 mmHg	22.9 (11.0–34.8)	85.5 (81.3–89.6)	1.58	0.90

ly before extubation are shown in Table 2. There were no differences in the respiratory parameters between the beginning of the SBT and the end immediately before extubation, in either patients successfully extubated or patients re-intubated. However, the f/V_T ratio measured immediately before extubation was significantly higher in patients failing extubation as compared with those successfully extubated. The areas under the ROC curves for the measurements performed at the end of the SBT were not significantly different from the areas corresponding to the measurements performed at the beginning of the trial for each of the indices studied (Table 3). The areas under the ROC curves for V_T, RR, P_{imax} and f/V_T ratio were not statistically different from one another, either at the beginning of the SBT or at the end of it. The cutoff values that discriminated best between the successfully extubated patients and the patients in whom extubation failed were 4 ml/kg for V_T, 11 breaths/min per ml per kg for f/V_T ratio, 45 breaths/min for RR, 20 cmH_2O for P_{imax} and 200 mmHg for PaO_2/FIO_2 ratio.

The accuracy of the indices studied in predicting extubation failure is shown in Table 4. According to our results, a f/V_T higher or equal to 11 breaths/min per ml per kg measured at the end of the SBT is 3 times more likely to occur in a patient who will fail extubation than it is to occur in a patient who will be successfully extubated.

Table 5 Post-test probabilities of re-intubation for different pre-test probabilities according to the likelihood ratios obtained for the frequency-to-tidal volume ratio (*f/V_T*) indexed to body weight measured at the end of the breathing trial

Pre-test probability	Post-test probability	
	$f/V_T \geq 11$	$f/V_T < 11$
0.05	0.15	0.04
0.10	0.26	0.08
0.15	0.36	0.12
0.20	0.45	0.17
0.25	0.52	0.21
0.30	0.58	0.25
0.35	0.64	0.30
0.40	0.68	0.35
0.45	0.73	0.39
0.50	0.76	0.44

Taking into account the likelihood ratios for the f/V_T ratio measured at the end of the SBT, we have calculated the post-test probabilities of extubation failure for different pre-test probabilities (Table 5).

Discussion

Our study produced two main findings. First, respiratory parameters easily measured at the bedside such as V_T, RR, P_{imax} and f/V_T ratio are poor predictors of extubation failure in children who have passed a trial of breathing. Second, the accuracy of the aforementioned weaning indices does not improve when they are remeasured immediately before extubation.

Very recently, an international study of mechanical ventilation in children [3] found that patients who failed extubation and were re-intubated within 48 h had significantly higher mortality than those successfully extubated (20% versus 2%, p<0.001). By identifying patients who are likely to fail a trial of extubation, weaning indices could prevent premature extubation and the development of severe cardiorespiratory decompensation. It seems, therefore, that accurate indices to predict re-intubation are needed to reduce the re-intubation rate in children.

Any predictor of extubation failure that has 100% sensitivity would be an absolute contraindication for extubation since all the patients with a positive result for that predictor would be re-intubated. Studies assessing the accuracy of V_T, RR and f/V_T ratio in predicting extubation failure in children have reported sensitivities ranging from 33 to 71% for V_T [1, 7, 8], from 57 to 65% for RR [7, 8] and from 57 to 78% for f/V_T ratio [1, 6, 7, 8]. We found that sensitivity never reached a value above 50% for any of the weaning indices studied when the cutoff value selected was that producing the fewest false classifications for extubation outcome. Therefore, a trial of extubation may still be warranted in children when the measurement of any of the above indices produces a positive result.

The criteria adopted for a positive result has varied from one study to another. For example, the selected cutoff value for V_T was 4 ml/kg in the study by Farias et al. [1], 5.5 ml/kg in the study by Thiagarajan et al. [7] and 7.5 ml/kg in the study by Manczur et al. [8]. A measure of accuracy that is independent of the cutoff value selected is the ROC curve. The area under the curve corresponds to the probability of correctly discriminating between two groups of patients, those who could not be extubated and those who could be. An area of 0.50 means that the weaning index studied has no discriminatory value. Our results show that the highest area corresponded to the f/V_T ratio measured immediately before extubation, but the area was only 0.61. In the study by Manczur et al. [8] the highest area under the ROC curve reached a value of 0.80 and it corresponded to V_T, but the area under the ROC curve for the f/V_T ratio was only 0.55. Baumeister et al. [6] found that the predictive accuracy for the f/V_T ratio expressed as the area under the ROC curve was 0.84.

Chatila et al. [12] reported, in a population of medical adult patients, that the area under the ROC curve of the f/V_T ratio measured at the onset of a SBT was 0.74±0.05 and it increased to 0.92±0.03 when it was remeasured at 30 min of the breathing trial. Krieger et al. [13] also found that, in medical patients older than 70 years, the area under the ROC curve for the f/V_T ratio improved from 0.81 to 0.93 when measured at the beginning of the SBT and 3 h later, respectively. Our results do not support the above findings in a population of children, since the accuracy of the f/V_T ratio did not increase when it was remeasured at the end of the SBT.

The possibilities of weaning failure before an attempt of weaning (pre-test probability) can be estimated by experienced physicians by combining epidemiological data and personal experience. The post-test probability is the probability of weaning failure, taking into account the results of a weaning index measurement. The direction and magnitude of the change from pre- to post-test probability are determined by the likelihood ratio [18]. In the present study, the weaning index with a higher likelihood ratio was the f/V_T ratio measured at the end of the SBT. Like us, Baumeister et al. [6] reported that the cutoff value for the f/V_T ratio that best discriminated between the patients who were successfully extubated and those in whom extubation failed was 11 breaths/min per ml per kg. Using the data reported by those authors, we have calculated a likelihood ratio of 3.50 to predict extubation failure that is very similar to the likelihood ratio for the f/V_T ratio in the present study.

Several studies have reported that the probability of re-intubation in children ranges from 5 to 29% [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 17] when patients are identified by clinical judgment as being ready to be extubated. According to the results of the present study, in populations of children with a pre-test probability of re-intubation between 10 and 20%, those children with a f/V_T ratio higher than 11 breaths/min per ml per kg would have a probability of re-intubation ranging from 26 to 45%. In our opinion, a risk of re-intubation around 40% should not necessarily impede extubation of those patients who have successfully completed a SBT and, therefore, the usefulness of weaning indices in populations with a pre-test probability of re-intubation between 10 and 20% seems controversial. On the contrary, in populations with a pre-test probability of re-intubation between 30% and 50%, where children with a f/V_T ratio higher than 11 would have a probability of re-intubation between 58% and 76%, the measurement of the f/V_T ratio may help clinicians in the decision of whether to extubate the patient or not. However, the only populations of patients with a risk of re-intubation between 30% and 50% are those of patients with unplanned extubation [19, 20, 21, 22, 23], and we are not aware of any study reporting re-intubation rates higher than 30% when patients had a planned extubation based on the clinical judgment of their physicians.

In summary, in children passing a SBT with T-piece or low level of pressure support, the ability of V_T, RR and f/V_T ratio to discriminate between patients who could be extubated and those who could not is very poor. Since weaning practices vary across centers, our results should be validated in populations of children weaned without performing a SBT.

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