

Online Data Supplement

Tension time index as a predictor of extubation outcome in ventilated children

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Methods

Patients

This prospective study was conducted in the Variety Club Children's Hospital Pediatric Intensive Care Unit at King's College Hospital, London and the Pediatric Intensive Care Unit at St Mary's Hospital, London. The pediatric intensive care unit at Kings College Hospital had 6 senior clinicians and at St Marys Hospital 7 senior clinicians. All children who were mechanically ventilated for more than 24 hours were eligible for entry into the study. Children were excluded from the investigation if prior attempts at extubation had not been successful or if long-term noninvasive ventilation had been required. Invasive measurements were not performed in children with esophageal varices. Parents or carers of eligible subjects were approached for enrolment into the study according to the availability of the researcher as this study was performed on two sites. Parents or carers were given at least 24 hours to decide whether to allow their child to take part in the study. The option to opt out of invasive measurements ie using balloon catheters was given. Informed written consent was obtained before performing the measurements. The study was approved the Research Ethics Committee of King's College Hospital NHS Foundation Trust. Measurements were performed when the children were deemed ready for extubation by the clinical team who were not informed of the results of the measurements.

Equipment

Respiratory flow was measured using a pneumotachograph (series 4500, Hans Rudolph Inc., Kansas City, Mo) attached to a three-way slide valve (Hans Rudolph Inc., Kansas City, MO),
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used to occlude the airway, and inserted into the ventilator circuit between the endotracheal tube and ventilator manifold. Mechanical ventilation was unaffected when the valve was in the standby position. Airway pressure (P_{aw}) was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45, Validyne Corporation, Northridge CA, USA). Transdiaphragmatic pressure (P_{di}) was recorded using 5 cm long balloon catheters positioned in the mid oesophagus (oesophageal pressure, P_{es}) and stomach (gastric pressure, P_{gas}) (Ackrad Laboratories, Cranford, NJ, USA). Correct positioning of the gastric balloon catheter was confirmed by positive pressure generation during inspiration while the position of the oesophageal balloon catheter was checked by comparing P_{es} to P_{aw} during an occluded inspiratory effort (E1, E2). Agreement of P_{es} and P_{aw} within 94% and 103% indicated that the balloon was correctly located in the lower third of the oesophagus and intrathoracic pressure could be reliably estimated.

The flow and pressure signals were recorded and displayed in real time on a computer running a Labview software application (National Instruments, Austin TX, USA) with 100 Hz analog to digital sampling (DAQ 16XE-50, National Instruments, Austin TX USA). Tidal volume was obtained by digital integration of the flow signal and P_{di} by digital subtraction of oesophageal pressure from gastric pressure by the recording software

Lung volume was determined by measurement of functional residual capacity (FRC) using a helium (He) dilution system (Equilibrated Biosystems EB52615, Melville, NY, U.S.A.) with a circuit specifically designed for paediatric use. The circuit contained a rebreathing bag, enclosed in an airtight cylinder, which was filled with a mixture of He and oxygen (O_2). The rebreathing bag was inserted into the ventilator circuit immediately above the endotracheal tube via a three-

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way valve. Actuation of the valve, at end-expiration, connected the patient to the rebreathing bag and diverted flow from the ventilator to the airtight cylinder, thus maintaining mechanical ventilation. The change in He concentration against time was displayed in real time on a flat panel display. Rebreathing of the He/O₂ gas mixture was continued until equilibration of He within the system. The FRC was corrected for oxygen consumption and to body temperature under atmospheric pressure and water vapour saturated conditions. The FRC was expressed as the mean of the paired measurements.

Protocol

All measurements were performed with the patient supine, with stable blood gases and blood pressure and mechanically ventilated at the settings determined by the clinical team. Endotracheal tube suction was undertaken 10 to 15 minutes prior to performing each study. At the start of the study, FRC was measured using the helium gas dilution technique. The three-way sliding valve and pneumotachograph were then inserted into the ventilator circuit and respiratory system compliance (Crs) and resistance (Rrs) measured using the single breath occlusion technique. We have previously shown this technique to provide reliable measurements in mechanically ventilated infants and children (E3). The three-way valve was actuated at end inspiration, briefly occluding the airway, and diverting the resulting passive expiratory flow to atmosphere. The resulting relaxed expiratory flow volume curve and the pressure time trace were analysed to calculate the expiratory time constant (Trs), Crs and Rrs. Crs was calculated by dividing the change in airway pressure by expired volume. Trs was measured as the slope of a best fit line fitted to the expiratory flow volume curve and Rrs by dividing Crs by Trs. Occlusions were maintained for at least 400 ms and only those with a pressure plateau of at least 100 ms were used. The flow volume curve was analysed using the software and those with a

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linearity of >0.99 for at least 40% of the curve were analysed. Eight to ten occlusions were recorded and the mean value calculated. At least 10 breaths were allowed between occlusions. The resistances of the pneumotachograph and slide valve were subtracted from the total measured resistance to obtain R_{rs} . In addition, dynamic compliance (C_{dyn}) was calculated from the volume delivered by a positive pressure inflation on breaths unaffected by spontaneous respiratory activity.

In those patients whose parents or carers had given consent, balloon catheters were then inserted and correctly positioned. The patient was switched over to continuous positive airway pressure (CPAP) and following stabilization, two minutes of spontaneous tidal breathing was recorded. From this recording respiratory flow and pressure variables including tidal volume (V_t), inspiratory time (T_i), total time for the breath (T_{tot}), respiratory rate, the mean transdiaphragmatic pressure per breath (meanPdi) and the transdiaphragmatic (PTPdi) pressure time products, were measured. The PTPdi provides an assessment of the work of breathing performed by the diaphragm and is calculated from the area subtended by the Pdi waveform (E4). A series of end expiratory airway occlusions were then performed using a unidirectional valve attached to the expiratory port of the slide valve, which allowed expiration but not inspiration. Baseline respiratory drive, as assessed by the pressure generated in the first 100 ms ($P_{0.1}$) of the first inspiratory effort of each occlusion, maximal inspiratory airway (P_{imax}) pressure and maximal transdiaphragmatic (P_{dimax}), if balloon catheters were present, were recorded. All occlusions were maintained for approximately 8 breaths or 15 seconds whichever was longer, at least three sets of occlusions were performed and the average for $P_{0.1}$ and the maximum for P_{imax} , and P_{dimax} recorded. Subjects were monitored and airway occlusion discontinued if

desaturation or bradycardia occurred. Sufficient time was allowed to elapse between occlusions for the patient to settle to quiet tidal breathing.

TTdi was calculated as the $\text{meanPdi/Pdimax} \times \text{Ti/Ttot}$ and TTmus calculated as $\text{mean inspiratory airway pressure/Pimax} \times \text{Ti/Ttot}$. Mean inspiratory airway pressure (meanPi) was obtained from the formula $5 \times \text{P0.1} \times \text{Ti}$. Two additional combined indices were also calculated, RSB, from the ratio of the spontaneous respiratory rate to tidal volume corrected for body weight and the CROP index calculated by multiplying Cdyn corrected for body weight by the arterial/alveolar oxygen ratio and Pimax and then divided by respiratory rate. Immediately before extubation a sample for blood gas analysis was taken from an indwelling arterial catheter sited for clinical purposes. Alveolar oxygen (PAO_2) was calculated using the simplified alveolar gas equation $\text{PAO}_2 = [\text{FIO}_2 \times (\text{P}_B - 47)] - \text{PaCO}_2$, where P_B is the barometric pressure, FIO_2 fractional concentration of inspired O_2 and PaCO_2 the partial pressure of arterial carbon dioxide.

In addition, the duration of mechanical ventilation, the peak inspiratory pressure (PIP), the maximum PIP (PIPmax) and maximum FiO_2 (FiO_2max) at any point during ventilation, the PIP and FiO_2 at extubation (PIPext, FiO_2 ext) as well as blood gas measurements and ventilator settings prior to extubation were recorded.

All patients were ventilated on pressure controlled modes using the Evita 4 (Dräger Medical, Lubeck, Germany) ventilator and were switched to patient triggered, pressure supported modes for weaning. Patients had been sedated using morphine and midazolam and these medications were reduced during weaning and stopped prior to extubation. A patient was deemed to be ready for extubation following assessment by the attending physician in charge. The criteria on which

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the decision to extubate was based primarily on each child's clinical condition, significant improvement or resolution of the underlying disease process, results of blood gas measurements and with ventilatory parameters ($PIP \leq 20$ cmH₂O and $FiO_2 < 0.5$ on a patient triggered ventilator mode and sufficient wakefulness with airway protective reflexes. The decision to reintubate was also made by the clinician in charge and was based on clinical examination and the results of blood gas analysis. Criteria for reintubation were primarily rising respiratory rates and PaCO₂ levels and failure to maintain oxygenation. Other criteria included intercostal recession, tracheal tugging, diaphoresis and a poor cough/inability to protect airway or clear secretions. Extubation was performed into an appropriate amount of supplemental oxygen. Non-invasive mechanical ventilation was not used for any study patient. The clinical team were unaware of the results of the patient's respiratory measurements.

Analysis

Data, tested using Shapiro-Wilk analysis, were demonstrated to be non-normally distributed and expressed, therefore, as median and range. Extubation failure was defined as reintubation and ventilation within 24 hours. Values of TTdi and TTmus in excess of their respective cutoffs were indicative of extubation failure, a true positive test. Patients achieving values above or below the cutoff who subsequently succeeded or failed extubation were either false positive or false negative results. Patients scoring below the cutoff values who subsequently were successfully extubated were true negative results.

Results

Table E1. Spearman correlation coefficients for physiological data and extubation outcome related to age and duration of mechanical ventilation

	Age		Duration of Ventilation	
	Coefficients	p value	Coefficients	p value
Age			-0.12	0.31
P0.1	-0.21	0.060	0.28	0.01
Pimax	-0.06	0.573	0.16	0.16
Vt/kg bodyweight	0.09	0.472	-0.13	0.28
Ti	0.71	p<0.0001	-0.12	0.30
Ttot	0.64	p<0.0001	-0.14	0.22
RR	-0.07	p<0.0001	0.13	0.24
ttmus	0.20	0.080	0.05	0.69
Crs/kg bodyweight	-0.15	0.296	-0.09	0.53
Rrs	-0.85	p<0.0001	0.14	0.34
FRC	0.95	p<0.0001	-0.12	0.33
FRC/kg	0.25	0.050	-0.15	0.25
Extubation outcome	0.01	0.937	0.14	0.22
RSB	0.49	p<0.0001	0.21	0.08
CROP	0.35	p<0.0001	-0.26	0.03
Duration of ventilation	-0.12	0.307		
FRC/cm	0.89	p<0.0001	-0.14	0.27
Ti/Ttot	-0.18	0.110	0.06	0.61

meanPi	0.31	0.005	0.12	0.31
meanPi/Pimax	0.28	0.012	0.01	0.90

Table E2 The results of the subgroup of 28 children in whom invasive measurements were performed according to extubation outcome

Data are presented as median (range)

Variable	Success (n=25)	Failure (n=3)	P value
Age (years)	1.4 (0.15 – 15)	3 (0.2 – 14)	0.681
Weight (kg)	12 (2.6 – 65)	14 (3 – 57)	0.457
Height (cm)	77 (52 – 165)	98 (54 – 160)	0.527
Vt/kg bodyweight (ml/kg)	7.2 (4.2 – 21.6)	5.5 (5.1 – 6.9)	0.244
Ti (s)	0.63 (0.34 – 1.55)	0.97 (0.58 – 0.98)	0.298
Ttot (s)	1.77 (0.71 – 10.4)	1.62 (1.11 – 2.19)	0.882
Ti/Ttot	0.36 (0.15 - 0.66)	0.52 (0.45 - 0.60)	0.044
RR (bpm)	35.2 (6.1 – 85)	37.2 (27.5 – 57.5)	0.738
P0.1 (cmH ₂ O)	2.9 (1.5 – 6.4)	3.3 (2.5 – 3.6)	0.970
meanPi (cmH ₂ O)	11.3 (5.9 – 25.9)	10.7 (8.5 – 11.9)	0.710
Pimax (cmH ₂ O)	58.8 (33.4 – 98.5)	31 (21.5 – 42.1)	0.005
meanPi/Pimax	0.16 (0.07 – 0.46)	0.40 (0.39 - 0.44)	0.0116
meanPdi (cmH ₂ O)	10.3 (3.5 - 30.0)	10.0 (7.2 - 13.9)	0.372
Pdimax (cmH ₂ O)	46.4 (15.3 – 122.0)	28.3 (28.1 – 39.5)	0.106
meanPdi/Pdimax	0.18 (0.06 - 0.61)	0.35 (0.26 - 0.36)	0.0302
PTPdi (cmH ₂ O/s/min)	235.3 (85.9 – 668.0)	309.1 (259.2 – 357.0)	0.143
TTdi	0.07 (0.02 – 0.12)	0.16 (0.15 – 0.19)	0.005
TTmus	0.07 (0.02 – 0.12)	0.21 (0.2 – 0.23)	0.005

Crs/kg bodyweight (ml/cmH ₂ O/kg)	1.05 (0.55 – 1.83)	0.94 (0.94 – 0.98)	0.789
Rrs (cmH ₂ O/l/s)	26.54 (10.83 – 79.07)	37.7 (37.7 – 37.7)	0.535
FRC (ml)	255.0 (57.5 – 1585.0)	242.0 (54.5 – 1114.5)	0.694
FRC/kg bodyweight (ml/kg)	21.2 (19.2 – 24.9)	18.2 (17.3 – 19.6)	0.013
FRC/cm body length (ml/cm)	3.2 (1.0 – 9.6)	2.5 (1.0 – 7.0)	0.600
RSB	6.1 (0.3 – 17.3)	5.4 (5 – 11.3)	0.547
CROP	1.3 (0.3 – 2.9)	0.4 (0.2 – 0.5)	0.402
Duration of ventilation (days)	5 (1 – 83)	12 (12 – 43)	0.109
PIPmax (cmH ₂ O)	22 (16 – 28)	28 (26 – 36)	0.022
FIO ₂ max	0.5 (0.35 – 1)	1 (0.7 – 1)	0.022
PIP at extubation (cmH ₂ O)	16 (12 – 18)	17 (16 – 17)	0.338
FIO ₂ at extubation	0.3 (0.21 – 0.33)	0.3 (0.26 – 0.33)	0.560
PaO ₂ at extubation (mmHg)	92.3 (34.5 – 140.25)	53.3 (44.25 – 62.25)	0.064
PaCO ₂ at extubation (mmHg)	44.3 (32.2 – 61.4)	44.6 (38.6 – 51)	0.603
Mean airway pressure			
at extubation (cmH ₂ O)	7.0 (5.0 – 8.0)	7.0 (7.0 – 8.0)	0.262
PAO ₂ (mmHg)	168.8 (99.5 – 190.7)	169.3 (134.4 – 196.7)	0.795
Time from measurements			
to extubation (hrs)	1.0 (0.25 – 6.0)	1.0 (1 – 2.0)	0.497

Table E3. Sensitivity and specificity of predictors of extubation failure and areas under the ROC curve for the 28 subjects in whom invasive measurements were performed.

Variable	Area under ROC curve	Value	Sensitivity (%)	Specificity (%)	P value
TTmus	1.000	>0.18	100	100	0.005
TTdi	1.000	>0.15	100	100	0.005
Pimax (cmH ₂ O)	1.000	>32.2	100	100	0.005
FRC/kg bodyweight (ml/kg)	0.956	>18.7	67	100	0.013
PIPmax (cmH ₂ O)	0.907	>27	67	84	0.023
PaO ₂ at extubation (mmHg)	0.902	<64.5	100	87	0.064
FIO ₂ max	0.900	>0.95	67	92.0	0.026
meanPdi/Pdimax	0.818	<0.12	50	91	0.144
Duration of Ventilation (days)	0.787	>11	100	72	0.11
PTPdi (cmH ₂ O/s/min)	0.722	>308.05	67	79.2	2.17
Vt/kg bodyweight (ml/kg)	0.710	<6.7	67	52	0.245
Rrs (cmH ₂ O/l/sec)	0.692	>36.1	100	69.2	0.535
Crs (ml/cmH ₂ O)	0.692	<13.34	100	69.2	0.535
Inspiratory Time (s)	0.687	>0.905	67	80	0.298
CROP Index	0.674	<0.1	50	57	0.423
PIP at extubation (cmH ₂ O)	0.667	>16.5	33	64	0.353
Mean airway pressure at extubation (cmH ₂ O)	0.660	>7.5	33	88	0.373

meanPdi (cmH2O)	0.66	<6.91	33	64	0.373
TToes	0.659	>0.045	33	100	0.38
meanPi/Pimax	0.64	<0.14	33	68	0.435
Ti/Ttot	0.627	>0.48	33	76	0.48
RSB Index	0.609	>10.9	33	87	0.547
FRC/cm body length (ml/cm)	0.595	<1.05	33	95	0.6
PaCO ₂ at extubation (mmHg)	0.593	>50.8	33	96	0.603
FIO ₂ at extubation	0.587	>0.315	33	96	0.629
Crs/kg bodyweight (ml/cmH ₂ O/kg)	0.583	<0.99	100	58	0.789
meanPi (cmH2O)	0.573	<9.66	67	64	0.683
FRC (ml)	0.571	<104.85	33	81	0.694
RR (bpm)	0.560	>57.2	33	80	0.738
Ttot (s)	0.527	<1.13	33	68	0.882
P0.1 (cmH2O)	0.493	>3.5	33	64	0.970
PAO ₂ (mmHg)	0.453	>136.06	33	88	0.795
Pdimax (cmH ₂ O)	0.206	>38.15	33	33.3	0.106

References

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