Prediction of extubation outcome in infants using the tension time index

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ABSTRACT

Objective Approximately one-third of ventilated infants fail extubation. The objective of this study was to determine whether assessment of the load relative to the capacity of respiratory muscles by measurement of the tension time index (TTI) successfully predicted extubation outcome in infants.
Design Prospective study.
Setting Tertiary neonatal intensive care unit.
Patients Twenty ventilated infants, with a median gestational age of 31 (range 24–39) weeks, were studied at a median postnatal age of 2.5 (range 1–37) days.
Interventions The diaphragm tension time index (TTdi) was derived from measurements of transdiaphragmatic pressure using a dual-pressure transducer tipped catheter. The respiratory muscle tension time index (TTmus) was derived from non-invasive airway pressure measurements. Measurements were made within the 6 h prior to extubation.
Main outcome measures Extubation failure was defined as the need for reintubation within 48 h of extubation.
Results Five infants failed extubation; their median TTdi ($p=0.001$) and TTmus ($p=0.001$) were significantly higher than those of the successfully extubated infants. A TTdi of >0.15 and a TTmus of >0.18 were 100% sensitive and 100% specific in predicting extubation failure
Conclusion In ventilated infants, invasive and non-invasive measurements of the TTI could provide an accurate prediction of extubation outcome.

What is already known on this topic

- Approximately one-third of ventilated infants fail extubation.
- Univariate indices have not been consistently reliable predictors of extubation success.

What this study adds

- The tension time index (TTI) is a measure of the load on and capacity of the diaphragm.
- Invasive and non-invasive assessments of the TTI were 100% sensitive and 100% specific in predicting extubation success in ventilated infants.

INTRODUCTION

Mechanical ventilation can be life-saving, but prolonged mechanical ventilation can increase the risk of nosocomial infection, airway and lung injury and bronchopulmonary dysplasia. Premature extubation, however, can lead to cardiorespiratory compromise, necessitating reintubation. Currently, up to 30% of infants fail extubation. A variety of univariate indices have been assessed in an attempt to improve prediction of extubation success, including minute ventilation,[1–3] compliance[4 5] and resistance[6] of the respiratory system, but none have been found to be consistently reliable predictors. In addition, although respiratory muscle strength, as measured by maximal inspiratory pressure (Pimax), has been reported to differ significantly according to extubation outcome,[7 8] in another study[4] the significant difference in Pimax results according to extubation outcome disappeared when the Pimax results were corrected for weight.

Extubation success depends on the adequacy of respiratory drive, the capacity of the respiratory muscles and the load imposed upon them. It is likely, therefore, that composite indices may be more predictive than univariate indices. The tension time index of the diaphragm (TTdi)[9 10] is a measure of the load on and capacity of the diaphragm. A TTdi in excess of 0.15 has been demonstrated to indicate an unsustainable load on the respiratory muscles in adults[9 10] and to be a 100% sensitive and specific predictor of extubation failure in children.[11] Unfortunately, the measurement of TTdi is invasive, requiring measurement of intrathoracic and intra-abdominal pressure to obtain transdiaphragmatic pressure. A non-invasive tension time index of the respiratory muscles (TTmus) based on airway pressure (Paw) measurements, however, has been developed and was also 100% sensitive and specific in predicting extubation failure in children.[11]

The aim, therefore, of this study was to test the hypothesis that the tension time index (TTI), as assessed by measurement of TTdi and TTmus, would accurately predict extubation outcome in ventilated infants. In addition, we wished to determine if previously determined cut-offs of TTdi >0.15 (10–12) and TTmus >0.18[11] were appropriate in infants.

PATIENTS AND METHODS

Infants were studied if they were deemed by the clinician in charge to be ready to be extubated within the next 6 h. Respiratory function measurements were performed as part of a randomised trial assessing the effect of two different ventilator modes (pressure support and assist control ventilation) in weaning from mechanical ventilation. Results from consecutive infants who were extubated within 6 h of the respiratory function measurements being made were analysed to determine the predictive ability of the TTI. The study was approved by the King's College Hospital Research Ethics Committee, and all parents gave informed written consent for their infant to take part.

All infants followed the routine weaning policy. Once the decision to wean was made, all sedation was stopped, and in infants of less than 34 weeks' gestation, caffeine was administered. The peak inflating pressure (PIP) was reduced as blood gas results permitted. The decision to extubate and reintubate was made by the clinical team who were unaware of the results of the respiratory function tests. Infants who weighed less than 1 kg were routinely extubated on to nasal *continuous positive airway pressure (*CPAP), and larger babies were only commenced on CPAP if they developed recurrent minor apnoeas postextubation. Following extubation, blood gases were checked at least four-hourly, but more frequently if indicated by changes in the continuous respiratory, heart rate and oxygen saturation monitoring. Extubation was deemed to have failed if the infant required reintubation and ventilation within 48 h of extubation. Infants were reintubated if they had a major apnoea, had frequent apnoeas with bradycardia, developed a severe respiratory acidosis (pH <7.20) or failed to improve despite instituting CPAP.

Equipment

Airflow was measured using a pneumotachograph (Mercury F10L; GM Instruments, Kilwinning, UK) connected to a differential pressure transducer (MP45; Validyne Corporation, Northridge, California). The pneumotachograph was positioned between the endotracheal tube and the ventilator manifold. Paw was measured from a side port on the pneumotachograph using a differential pressure transducer (MP45; Validyne Corporation). To measure TTdi, oesophageal (Poes) and gastric (Pgas) pressures were measured using a dual-pressure transducer tipped catheter and associated amplifier (Gaeltec, Dunvegan, UK). The two pressure transducers were 5 cm apart, with the lower transducer 0.3 cm from the catheter tip. Correct positioning of the Pgas transducer was confirmed by a positive pressure deflection during inspiration. The position of the Poes transducer was determined by comparing Poes with Paw during an occluded inspiratory effort. Agreement 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.[12 13] The signals from the flow and Paw transducers were amplified using a carrier amplifier (CD280; Validyne Corporation). The pressure and flow signals were recorded and displayed in real time on a computer (Dell Optiplex 170L) running an application written with Labview software (National Instruments, Austin, Texas) with 100 Hz analogue-to-digital sampling (PCI-MIO-16XE-50, National Instruments). Transdiaphragmatic pressure was calculated by digital subtraction of the oesophageal from the gastric pressure and tidal volume obtained by digital integration of the flow signal by the acquisition software. Pimax was measured using a two-way non-breathing valve attached to the distal end of the pneumotachograph during a brief period of disconnection from the ventilator, m. Airway occlusion was initiated by occluding the inspiratory limb of the two-way valve during the preceding expiratory phase; the valve in the expiratory limb allowed expiration, but not inspiration, thus ensuring that airway occlusion occurred at end expiration.

Protocol

All measurements were performed with the patient supine and with stable blood gases (pH 7.25–7.45, $Paco_2$ 5–7 kPa, Pao_2 7–10 kPa) at the ventilator settings determined by the clinical team. The pressure transducer catheter was inserted and correctly positioned (see above). Airway occlusions were then performed to simultaneously measure the Pimax and maximal inspiratory transdiaphragmatic (Pdimax) pressures and the Paw generated during the first 100 ms of the first inspiratory effort of each occlusion ($P_{0.1}$) which would subsequently be used in the calculation of TTmus and TTdi. Each occlusion was made at end expiration and maintained for five to seven breaths. At least three prolonged airway occlusions were performed. Subjects were monitored and the airway occlusion discontinued if a pronounced desaturation or bradycardia occurred. Sufficient time was allowed between occlusions for the patient to settle to quiet tidal breathing. Pimax and Pdimax were defined as the maximum airway or transdiaphragmatic pressures generated from all sets of occlusions. Following measurement of Pimax, Pdimax and $P_{0.1}$, the patient was returned to mechanical ventilation and allowed to stabilise. The patient was then switched onto CPAP, and after a further period of stabilisation, a period of tidal breathing was recorded, from which TTdi and TTmus were assessed per breath.

TTdi was calculated using the equation Pdimean/Pdimax×Ti/Ttot, where Pdimean was obtained by averaging Pdi every 100 ms during inspiration, as indicated by the respiratory flow trace; the inspiratory time (Ti) and the total time for the breath (Ttot) were measured from the respiratory flow trace (figure 1). TTmus was calculated using the equation Pimean/Pimax×Ti/Ttot, where the mean inspiratory airway pressure (Pimean) was obtained from the formula $5 \times P_{0.1} \times Ti$ (figure 1). Both TTdi and TTmus were calculated as the mean of 20 consecutive breaths.

The nurses recorded at hourly intervals the infant's ventilator settings on observation charts. From the observation charts, the PIP and inspired oxygen concentrations (FiO_2) immediately before extubation were noted, and the hours of ventilatory support prior to extubation calculated.

Analysis

Differences between infants in whom extubation failed or succeeded were assessed for statistical significance using the Mann–Whitney U test. Receiver operating characteristic plots were constructed and the area under each curve calculated for those factors shown to differ significantly on univariate analysis between infants who failed or succeeded extubation. The sensitivity and specificity for TTdi and TTmus were calculated using the predefined values of 0.15 and 0.18 respectively.[11]

Sample size

Recruitment of 20 infants, assuming a 30% extubation failure rate, allowed detection of a difference equivalent to two SDs in the TTI results between infants who succeeded or failed extubation with at least 80% power at the 5% level.

Patients

Twenty infants (13 male) with a median gestational age of 31 (range 24–39) weeks and birth weight of 1602 (range 670–3685) g were studied at a median postnatal age of 2.5 (range 1–37) days. Fourteen of the infants had had respiratory distress syndrome, and six infants were studied postsurgical intervention (four with congenital diaphragmatic hernia

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(CDH) and two with bowel atresia). Three infants were born at term, two had CDH, and one had a bowel atresia. All the infants were ventilated via shouldered endotracheal tubes, which have been demonstrated to have minimal or no leak.[14]

RESULTS

Five infants failed extubation, four were prematurely born (24, 24, 27 and 30 weeks of gestation) and had had RDS, and one was prematurely born (35 weeks of gestation) with CDH. Four were reintubated because of frequent apnoeas and bradycardias, and one because of poor respiratory effort and the development of a respiratory acidosis. The infants who failed extubation differed significantly from the rest of the cohort with regard to having a lower median birth weight (p=0.049), Pimax (p=0.002) and Pdimax (p=0.002). Neither Pimax/weight nor Pdimax/weight results differed significantly between the two groups (table 1). The infants who failed extubation had a significantly higher median TTdi (p=0.001) and TTmus (p=0.001) (table 1). TTdi and TTmus performed equally well in predicting extubation outcome (table 2) and had 100% sensitivity and 100% specificity in predicting extubation failure using cut-off values of 0.15 and 0.18 respectively.

DISCUSSION

We have demonstrated that TTdi and TTmus differed significantly between infants who did and did not fail extubation. In addition, we have highlighted that TTdi >0.15 and TTmus >0.18 were 100% sensitive and specific in predicting extubation failure in neonates. The median FiO_2 and PIP prior to extubation did not differ significantly between infants who did and did not fail extubation, thus highlighting that results routinely available to the clinician are unlikely to improve extubation outcome prediction. Pimax can be relatively easily measured, even in ventilated infants, but when corrected for body weight, failed to differ significantly between the two groups, again highlighting that univariate indices are poor predictors of extubation success.

Our study has some potential limitations. The measurements were made during a randomised trial, and the infants were studied while receiving assist-control or pressure support ventilation. All measurements, however, were made prospectively, and the clinicians were blinded to the results of the respiratory function measurements. In addition, we analysed results from consecutive infants who were extubated within 6 h of the respiratory function measurements being made. Importantly, despite studying the infants on two ventilator modes, TTdi and TTmus results were 100% predictive, and so we feel the results are generalisable. We studied infants with either respiratory distress syndrome or surgically corrected anomalies, and included both term and preterm infants. Nevertheless, differences in TTdi and TTmus between infants who did or did not fail extubation were highly statistically significant. As, however, only three infants born at term were included, it would be important to confirm or refute our results in a further study of term born infants. Only five of the 20 infants failed extubation, but that failure rate is similar to that found in previous studies.[15 16] The decisions to extubate and, when necessary, reintubate were made by the clinical team who remained unaware of the measurement results. No trial of spontaneous breathing was performed prior to this decision being made; hence our results were not affected by including only infants who had passed a spontaneous breathing test and hence less likely to fail extubation.[17 18]

Pimax and Pdimax were significantly lower in the infants who failed extubation compared with the infants who were successfully extubated, but the differences were no longer significantly different when the results were corrected for weight. Previous data[19 20] have highlighted that patients able to generate substantial inspiratory pressures may fail extubation, while those with only modest strength can be successfully extubated. Our results emphasise that to predict

Table 1 Demographics and results according to extubation outcome

	Success	Failure	p Value
N	15	5	
Gestational age (weeks)	31 (26–39)	27 (24–35)	0.088
Birth weight (g)	1738 (1030–3685)	1020 (670-2225)	0.049
Male gender	10	3	0.792
Postnatal age (days)	2 (1–31)	5 (2- 37)	0.086
Duration of ventilation (h)	34 (17–732)	89 (25–872)	0.106
Peak inflating pressure before extubation (cm H_2O)	16 (13–17)	14 (14–16)	0.083
Inspired oxygen concentration before extubation	21 (21–27)	22 (21–24)	0.705
Pimax (cm H_2O)	45.5 (29.4–83.0)	19.0 (17.0–30.3)	0.002
Pimax/weight (cm H_2O/kg)	29.1 (9.9–50.6)	22.1 (8.0–29.4)	0.074
Pdimax (cm H_2O)	48.2 (30.1–83.0)	17.9 (17.0–33.1)	0.002
Pdimax/weight (cm H_2O/kg)	29.7 (9.9–51.9)	22.1 (8.0–26.7)	0.067
Pimean (cm H_2O)	6.3 (3.3–11.8)	10.6 (9.1–13.6)	0.013
Pdimean (cm H_2O)	7.8 (3.7–19.9)	8.5 (7.7–12.6)	0.275
Pdimean/Pdimax	0.17 (0.07–0.29)	0.48 (0.38–0.65)	0.001
Pimean/Pimax	0.12 (0.04–0.32)	0.56 (0.45–0.68)	0.001
First 100 ms of the first inspiratory effort of each occlusion	4.4 (2.0–7.7)	6.3 (4.8–7.1)	0.126
Inspiratory time/total time for the breath	0.33 (0.2–0.49)	0.34 (0.31–0.42)	0.513
Diaphragm tension time index	0.065 (0.02–0.12)	0.16 (0.15–0.20)	0.001
Tension time index	0.04 (0.01–0.13)	0.19 (0.19–0.21)	0.001

The results are displayed as median (range).
Pdimax, maximal transdiaphragmatic pressure; Pdimean, mean transdiaphragmatic inspiratory pressure per breath; Pimax, maximal inspiratory pressure; Pimean, mean inspiratory airway pressure.

extubation outcome more accurately, it is essential to examine the load imposed on the respiratory muscles relative to their capacity. In addition, TTmus and TTdi reflect the respiratory drive modulated load/capacity balance of the diaphragm/respiratory muscles and, therefore, are ideally suited for use in infants, as they are independent of the differences in respiratory muscle strength that occur with increasing maturity.[21 22]

Bellemare and Grassimo[9 10] first examined the relationship between the Pdi developed during each breath and the fraction of the duty cycle spent in inspiration. They highlighted that there was a critical value of TTdi (0.15) above which ventilation could not be sustained. We have demonstrated that that cut-off accurately predicts extubation failure in infants. The critical TTmus value of >0.18 we demonstrated in this study, however, is lower than the values quoted for cystic fibrosis (>0.33)[23] and neuromuscular disease (>0.4)[24] patients. The patients studied,[23 24] however, were clinically stable, and none were in respiratory failure. Using a cut-off for TTmus of 0.18 is broadly in agreement with cut-off values for TTmus (0.16 to 0.25) calculated by Ramonatxo *et al*[25] in healthy subjects. In the current study, TTmus >0.18 performed with 100% sensitivity and specificity in predicting extubation outcome in infants as we had reported earlier in children.[11] In contrast, Noizet *et al*[26] found TTmus performed poorly in predicting weaning outcome in ventilated children. In that study,[26] however, children who had failed a trial of spontaneous breathing were excluded,

Table 2 Prediction of extubation failure

	Area under receiver operating characteristic curve
Birthweight	0.8
Diaphragm tension time index	1
Tension time index	1

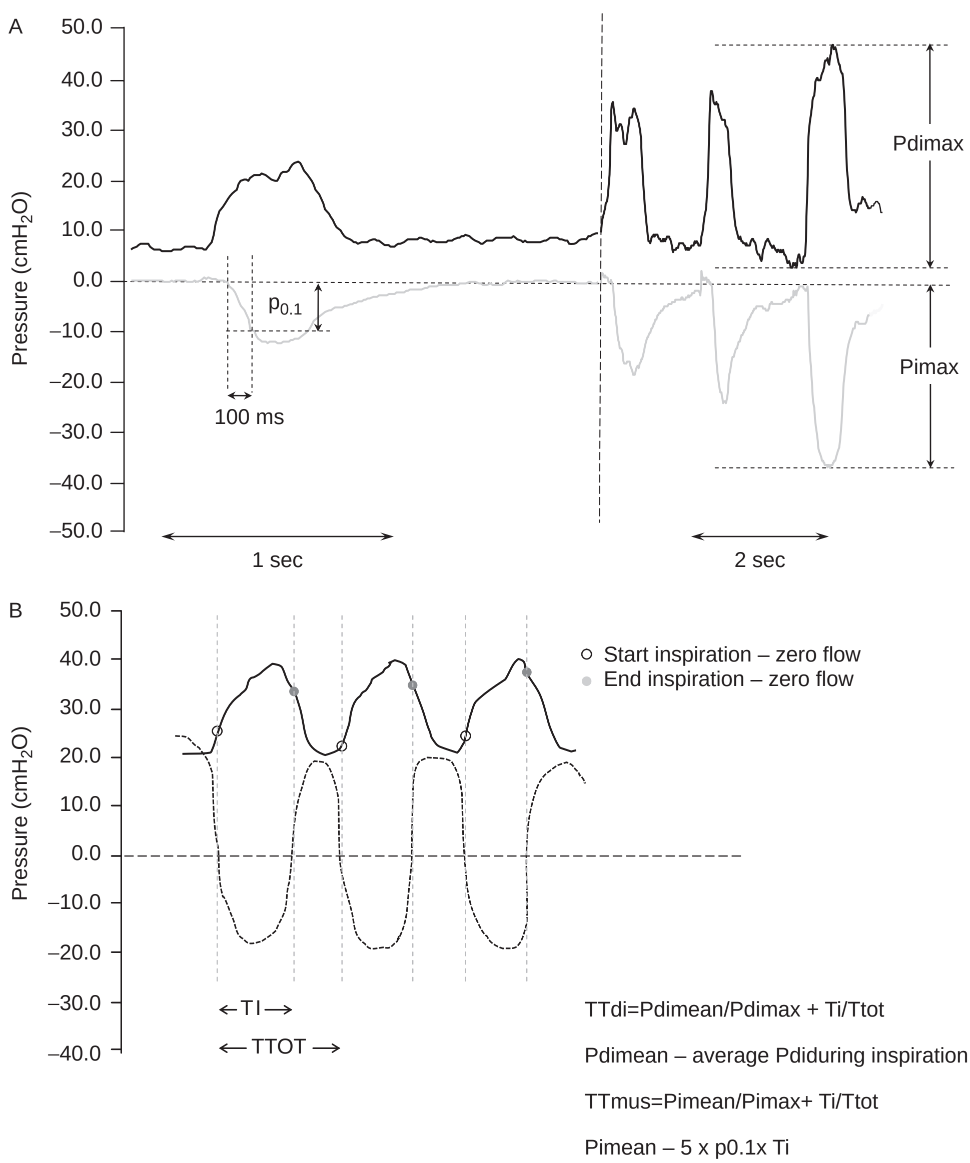

Figure 1 Representative airway (—) and transdiaphragmatic (—) pressure and flow (---) traces showing the analysis to calculate the diaphragm tension time index (TTdi) and the respiratory muscle tension time index (TTmus). (A) Measurement of airway pressure generated during the first 100 ms of the first inspiratory effort of each occlusion ($P_{0.1}$), maximal inspiratory pressure (Pimax) and maximal inspiratory transdiaphragmatic (Pdimax). The dashed vertical line indicates a change in timebase. (B) Measurement of mean inspiratory transdiaphragmatic (Pdimean) determined by respiratory flow, inspiratory time (Ti) and the total time for the breath (Ttot) to calculate TTdi. Dashed vertical lines indicate points of zero respiratory flow, indicating change between inspiration and expiration.

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and that may have affected their results. In infants of birth weight less than 1250 g, the spontaneous breathing test had 73% specificity and 97% sensitivity in predicting extubation failure.[3]

In our study, the median duty cycle did not differ significantly between the infants who did and did not fail extubation. The differences observed in the TTdi measurements between those who failed and succeeded extubation were due to differences in pressure changes across the diaphragm. The lower Pdimean/Pdimax was due to a lower Pdimax in those who failed extubation, and similarly the lower Pimean/Pimax was mainly due to a lower Pimax in those who failed extubation. The Pimean, but not the Pdimean, was significantly lower in the infants successfully extubated compared with those who failed exubation. Pdimean reflects transdiaphragmatic pressure, whereas Pimean reflects global inspiratory muscle function. Our results indicate a greater inspiratory demand in relation to inspiratory reserve in those who failed extubation. Respiratory muscle strength can be detrimentally affected by injury from overuse,[27] sepsis,[28] medications such as aminoglycosides or neuromuscular blockers, malnutrition and chronic illnesses,[29 30] and atrophy and remodelling from inactivity.[31] Prolonged mechanical ventilation can result in ventilator-induced diaphragmatic dysfunction.[32 33]

In this study, infants who failed extubation tended to have required more prolonged ventilation, and this may have acted to reduce respiratory muscle strength and contributed to extubation failure. There are no data currently available that describe changes in respiratory muscle strength associated with prolonged mechanical ventilation in infants, although a significant reduction in diaphragm myofibre cross-sectional area was observed in post mortem analyses of infants who had received ventilatory assistance for at least 12 days, immediately prior to death.[34] In the current study, however, the difference in the duration of ventilation between the two groups did not reach statistical significance.

In conclusion, our results suggest that assessment of the TTI can accurately predict extubation outcome in neonates. Importantly, a non-invasive assessment (TTmus) performed as well as an invasive assessment (TTdi). TTmus has the added advantage that it reflects the functional capacity of all the inspiratory muscles involved in inspiration, whereas TTdi represents only the pressure developed by the diaphragm. Our results, however, are based on five of 20 infants failing extubation. Studies are required to determine if TTmus is a sensitive and specific predictor of extubation failure in other populations, before it should be used in clinical practice.

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Competing interests None.

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Patient consent Obtained from the parents.

Provenance and peer review Ethics approval was provided by the King's College Hospital Research Ethics Committee.

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