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Prediction of extubation success using the diaphragmatic electromyograph results in ventilated neonates

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Abstract

Objectives: Extubation failure is common in infants and associated with complications.

Methods: A prospective study was undertaken of preterm and term born infants. Diaphragm electromyogram (EMG) was measured transcutaneously for 15–60 min prior to extubation. The EMG results were related to tidal volume (Tve) to calculate the neuroventilatory efficiency (NVE). Receiver operating characteristic curves (ROC) were constructed and areas under the ROCs (AUROC) calculated.

Results: Seventy-two infants, median gestational age 28 (range 23–42) weeks were included; 15 (21%) failed extubation. Infants successfully extubated were more mature at birth ($p=0.001$), of greater corrected gestational age (CGA) at extubation ($p<0.001$) and heavier birth weight ($p=0.005$) than those who failed extubation. The amplitude and area under the curve of the diaphragm EMG were not significantly different between those who were and were not successfully extubated. Those successfully extubated required a significantly lower inspired oxygen and had higher expiratory tidal volumes (Tve) and NVE. The CGA and Tve had AUROCs of 0.83. A CGA of >29.6 weeks had the

highest combined sensitivity (86%) and specificity (80%) in predicting extubation success.

Conclusions: Although NVE differed significantly between those who did and did not successfully extubate, CGA was the best predictor of extubation success.

Keywords: extubation; transcutaneous diaphragmatic electromyography; ventilated infants.

Introduction

Mechanical ventilation of neonates can be life-saving, but is associated with complications such as lung injury and nosocomial infection. It is, therefore, important to extubate infants as soon as possible. Premature extubation, however, may result in cardiorespiratory compromise and need for reintubation, leading to longer hospital stay and increased morbidity [1, 2]. A variety of methods have been tested as to whether, compared to readily available clinical data, they better predict successful extubation in the neonatal population. To date no such predictor has been found, many suffer from low specificity or involve complicated and invasive testing inappropriate for routine clinical use [3]. Indeed, this may reflect why an international survey demonstrated periextubation practices in extremely preterm infants varied considerably and decisions were frequently physician dependent [4].

Adequate neural respiratory drive is important if extubation is to succeed; this can be assessed by measuring the electromyogram (EMG) of the diaphragm. There have been studies examining whether the diaphragm EMG signal alters in response to changes in respiratory support [5, 6], but with mixed results. In one study, the diaphragm EMG measured transcutaneously was used in 59 infants to assess whether there were changes in the signal when the infants were weaned from nasal continuous positive airway pressure to low flow nasal cannula oxygen. Significant increases in the EMG amplitude, peak and tonic activity were seen [5]. There were, however, no consistent statistically significant difference in the amplitudes of the diaphragm EMG signals at all time points between those infants who were or were not successfully weaned from nasal continuous positive airway

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pressure [5]. In 25 preterm infants in whom the diaphragm EMG was monitored via an oesophageal catheter, both the peak EMG (Edi) and the amplitude increased immediately following extubation (mean peak 9.8–19.3 μV and mean amplitude 6.2–13.2 μV). In the 10 infants who failed extubation and required reintubation within 72 h, the change in both the peak EMG and the amplitude were significantly smaller between the pre-extubation period and 120 min post-extubation ($p=0.023$, $p=0.01$ respectively) [6]. Whether the EMG signal measured transcutaneously predicts extubation failure in prematurely and term born infants has not been determined, hence an aim of this study.

Successful extubation is determined by both the load on and the capacity of the respiratory system, as well as the infant's respiratory drive, hence composite predictors may be more useful and indeed a systematic review [3] highlighted they had the best performance characteristics. In adults and children, the performance of the ratio of tidal volume to Edi measurement (neuroventilatory efficiency [NVE]) in predicting extubation has been explored with mixed results [7, 8]. In adults, higher NVE during extubation readiness testing predicted those who would successfully extubate [8], whereas in children the converse was true [7]. A further aim of our study then was to assess whether NVE results assessed transcutaneously predicted successful extubation in ventilated infants born either prematurely or at term.

Materials and methods

All mechanically ventilated infants without major congenital abnormality were eligible for inclusion into the study. Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration and has been approved by the Health Research Authority and by the London – Camden and King's Cross NHS Research Ethics Committee. Parents gave written informed consent for their infant to be recruited into the study. The study was performed between November 2016 and May 2018.

Each infant was only included in the study once. The decision to extubate was made by the medical team based on their clinical judgement and the Unit's protocol (that is, $\text{FiO}_2 < 0.4$, acceptable blood gases with $\text{pH} > 7.25$ and $\text{PCO}_2 < 8.5$ kPa, and breathing above the set ventilator rate). Within an hour prior to the planned extubation, the transcutaneous diaphragm EMG and ventilatory parameters were monitored for between 15 and 60 min. Infants were assessed while receiving their current level of ventilation. The clinical team were not informed of the results of the transcutaneous diaphragm EMG monitoring. Infants were extubated by the clinical team to air, incubator oxygen, humidified high flow nasal cannula oxygen, or continuous positive airway pressure depending on their gestational age and requirement for ongoing support. No physiotherapy was performed following extubation and no inhaled medications were prescribed. The decision to reintubate was based on the Unit's protocol – that is development of a respiratory acidosis $\text{pH} < 7.2$, prolonged or repeated apnoeas or

bradycardias, a supplementary fraction of inspired oxygen requirement greater than 0.7 and/or an excessive work of breathing. Successful extubation was defined as not requiring reintubation for 48 h after extubation [9, 10].

Infants were ventilated using SLE 5000 and 6000 ventilators (SLE Ltd, Croydon, UK) via appropriately sized Coles endotracheal tubes (Portex, Smiths Medical, Kent, UK). Both pressure-limited and volume-targeted ventilation were used during the study period. In born preterm infants of less than 34 weeks of gestational age received a loading dose of 20 mg/kg caffeine citrate following admission to the neonatal unit followed by a maintenance dose of 5 mg/kg 24 hourly whilst on respiratory support. There was no routine additional administration of caffeine prior to extubation. A portable 16 channel digital amplifier (Dipha-16, Inbiolab BV, Groningen, Netherlands) was used to record the transcutaneous diaphragm EMG. Three electrodes (H59P Cloth Electrodes, Kendall) were placed on the infant's chest – the reference electrode on the sternum and the other two electrodes on the costal margin in the nipple line bilaterally. No skin preparation was required. Data were transmitted wirelessly to a bedside portable computer (PolyBench Medical Research Terminal A, Applied Biosignals, Weener, Germany) running PolyBench (Applied Biosignals, Weener, Germany). The signal was automatically processed with a band pass filter (40–140 Hz) and a gating technique used to remove the electrocardiograph signal from the EMG. Filtering and signal processing was performed by the software as previously described [11]. The EMG was recorded at 500 Hz.

Ventilator data: inflation time, inspiratory and expiratory tidal volume (Tve), peak inflation and positive end expiratory pressures, inspired oxygen concentration (FiO_2) and respiratory rate, were imported to a portable computer from the SLE 5,000 and 6,000 ventilators (SLE Limited, Croydon, UK) via an RS232 cable at 2 Hz.

Data analysis

Analysis of the EMG data was performed offline using MATLAB and Statistics Toolbox Release 2016a (The MathWorks, Inc., Natick, Massachusetts, United States), with custom functions and a function (findClosest) from the *k*-wave Toolbox [12]. EMG data were imported to Matlab from Poly5 format using the TMSi Matlab Interface (Twente Medical Systems International, Oldenzaal, the Netherlands).

Thirty second periods of the EMG signal during quiet breathing were selected at random which avoided movement artefact, which was identifiable by high amplitudes and loss of EMG peaks relating to tidal breathing. The amplitude of EMG peaks, the area under the curve of the EMG peaks and the neural respiratory rate, that is the number of EMG peaks per minute, were calculated. Ventilator data from the same time period were located and the mean peak inspiratory pressure and expiratory tidal volume calculated. The NVE was calculated as the expiratory tidal volume (related and not related to body weight) divided by the EMG amplitude. Three periods were selected for each infant and the mean of these data calculated.

Statistical analysis

Data were assessed for normality using the Kolmogorov-Smirnoff test and found to be not normally distributed, hence the Mann Whitney U test was used to determine if differences were statistically significant between those who successfully and not successfully extubated. Spearman rank correlations were calculated to assess the strength of relationships. Analyses were performed using IBM SPSS Statistics for

Windows version 24. Receiver-operator characteristic (ROC) curves were constructed for those variables in which there was a significant difference between those who were and were not successfully extubated and also for the EMG amplitude and the area under the EMG curve. Areas under the ROCs (AUROCs) were calculated. The Youden J index was calculated to provide the cut off values to predict successful extubation. Analyses were performed using medcalc.net (MedCalc Software, Ostend, Belgium).

Sample size calculation

Based on previous work, we anticipated that 25% of infants would fail extubation [9, 10]. A sample size of 72 infants allowed detection of one standard deviation in the EMG results between the pass and fail groups. We used one standard deviation as, at the time of starting the study, there were no results on which to base a sample size calculation. In this study, one standard deviation of the EMG amplitude results equated to 2.4 μV , that is less than 10% of the median signal.

Results

Seventy-two infants were included in the study, 33 were male (46%) and 15 (21%) were born at term. They were born at a median gestational age of 28.4 (range 23.4–42.1) weeks with a median birthweight of 1,118 (range 470–5,000) g. They were studied at a median postnatal age of 6 (range 1–213) days, when their median corrected gestational age (CGA) was 32.3 (25.4–55.3) weeks and weight was 1,370 (range 630–5,000) g. Their diagnoses when studied were respiratory distress syndrome ($n=34$), bronchopulmonary dysplasia ($n=14$), hypoxic ischaemic encephalopathy ($n=7$), meconium aspiration syndrome ($n=5$), persistent

pulmonary hypertension of the newborn ($n=4$), sepsis ($n=3$), post-surgery ($n=3$), and apnoea ($n=2$).

Fifteen infants (21%) failed extubation. Infants who successfully extubated were more mature at birth (median gestational age 30.9 (range 23.4–42.1) weeks versus median 25.7 (range 23.4–32.3) weeks, $p=0.001$) and of heavier birthweight (median 1,270 [range 470–5,000] grams, versus 854 [range 538–1,910] grams, $p=0.005$) than those who failed extubation. There were no significant differences between those who successfully extubated and those who did not in terms of the postnatal age, the peak inspiratory pressure, respiratory rate, the tidal volume adjusted for body weight or the NVE adjusted for body weight. Those who were successfully extubated required a significantly lower FiO_2 and had higher absolute expiratory tidal volumes and NVEs (Table 1).

The CGA and expiratory tidal volume had the largest AUROCs, both being 0.83. A CGA of greater than 29.6 weeks had the highest combined sensitivity and specificity predicting successful extubation with 86% sensitivity and 80% specificity (Table 2).

The amplitude of the EMG signal significantly, but weakly correlated with both the weight at the time of measurement and the tidal volume related to bodyweight. Both correlations remained significant after adjustment for CGA ($r=-0.32$, $p=0.008$, $r=0.27$, $p=0.024$ respectively). There was no significant correlation between the EMG signal and the peak inspiratory pressures at the time of assessment ($r=-0.235$, $p=0.054$). If only those infants who were born prematurely were considered (Table 3), the EMG amplitude was negatively correlated with weight

Table 1: Demographic, ventilator and EMG parameters of infants who were or were not successfully extubated Data are displayed as the median (range).

	Successfully extubated ($n = 57$)	Not successfully extubated ($n = 15$)	p-Value
Gestational age, weeks	30.9, 23.1–40.2	25.7, 23.4–32.3	0.001
Birth weight, g	1,270, 470–5,000	854, 538–1910	0.005
CGA, weeks	33.3, 25.4–55.3	28.6, 26.9–35.3	<0.001
Weight at study, g	1,570, 630–5,000	1,001, 930–1910	<0.001
Peak inspiratory pressure, cmH_2O	15.7, 9.3–26.5	18.1, 9.6–26.8	0.092
Positive end expiratory pressure, cmH_2O	5.7, 2.7–7.5	5.7, 4.9–8.0	0.743
Tidal volume (VTe), mL	9.0, 3.6–33.0	5.6, 2.9–7.4	<0.001
VTe, mL/kg	5.4, 2.7–9.8	5.5, 2.8–6.2	0.819
Respiratory rate, breaths per minute	60, 39–93	55, 47–76	0.39
FiO_2 , %	0.25, 0.21–0.6	0.35, 0.21–0.6	0.013
EMG amplitude, μV	3.3, 0.87–10	4.3, 1.7–10.1	0.295
Area under EMG curve	1.7, 0.36–7.1	1.8, 0.93–5.7	0.379
NVE, mL/ μV	3.8, 0.50–20.3	1.3, 0.59–3.5	0.002
NVE related to body weight, mL/kg/ μV	1.5, 0.6–10.5	1.5, 0.6–3.5	0.168

Table 2: AUROC and sensitivity and specificity of possible predictors in all infants of successful extubation.

	AUROC (95% CI)	p-Value	Cut off	Sensitivity	Specificity
VTe, mL	0.83, 0.73–0.92	<0.0001	>7.4	64	100
CGA, weeks	0.83, 0.72–0.94	<0.0001	>=29.6	86	80
Weight at study, kg	0.82, 0.71–0.92	<0.0001	>1.14	77	87
GA, weeks	0.77, 0.66–0.89	<0.0001	>28.1	60	87
NVE, mL/ μ V	0.77, 0.65–0.86	<0.0001	>3.5	51	100
BW, kg	0.74, 0.62–0.86	0.0001	>1.12	60	93
FiO ₂ , %	0.72, 0.55–0.89	0.01	<=0.33	88	54
NVE related to bodyweight, mL/kg/ μ V	0.62, 0.45–0.78	0.24	>1.65	51	73
EMG amplitude, μ V	0.59, 0.43–0.75	0.27	<=3.1	49	73
AUC EMG	0.57, 0.41–0.74	0.38	<=1.29	38	80
VTe, mL/kg	0.52, 0.40–0.64	0.8	>5.8	33	87

Table 3: AUROC and sensitivity and specificity of possible predictors of successful extubation in infants born at <37 weeks gestation.

	AUROC (95% CI)	p-Value	Cut off	Sensitivity	Specificity
CGA, weeks	0.77, 0.64–0.87	<0.001	>29.6	81	80
VTe, mL	0.76, 0.63–0.87	<0.0001	>=7.4	52	100
Weight at study, kg	0.75, 0.62–0.86	<0.001	>=1.14	69	87
FiO ₂ , %	0.73, 0.59–0.84	0.009	<=0.24	56	84
NVE, mL/ μ V	0.70, 0.56–0.81	0.006	>3.5	40	100
GA, weeks	0.69, 0.56–0.81	0.013	>=28.14	45	87
BW, kg	0.64, 0.51–0.77	0.069	>1.12	48	93
NVE related to bodyweight, mL/kg/ μ V	0.63, 0.50–0.76	0.12	>0.9	93	33
VTe, mL/kg	0.59, 0.45–0.72	0.29	>5.8	43	87
EMG amplitude, μ V	0.58, 0.45–0.71	0.31	<=3.1	48	73
AUC EMG	0.57, 0.43–0.7	0.4	<=1.29	40	80

($r=-0.417$, $p=0.002$) and positively correlated with tidal volume related to body weight (mL/kg) ($r=0.33$, $p=0.018$).

Discussion

We have found that the CGA and expiratory tidal volume were the best predictors of successful extubation in that they had the highest AUROC results. The CGA had the highest combined sensitivity and specificity. Others have shown demographic data such as the gestational age and body weight were better predictors of successful extubation than assessment of physiological variables [9, 10, 13–15]. In a recent study, however, we demonstrated that a higher tidal volume in prematurely born infants better predicted extubation success than gestational age after adjustment for confounders [16]. In the study currently reported, we also found that the tidal volume and neuroventilatory efficiency differed significantly between those who were and were not successfully extubated.

An earlier study of a sample of 21 prematurely born infants, who were also studied on positive pressure

ventilation, found no significant differences in the Edi (measured via an oesophageal catheter) or in the tidal volume: Edi ratio between those who extubated successfully and those who did not [17]. The failure of the EMG data to accurately predict extubation success may have resulted from the infants being measured on invasive ventilation, as the electrical activity of the diaphragm is influenced by the level of respiratory support provided [18]. Previous studies have shown that in adults, higher NVE during extubation readiness testing predicted those who would successfully extubate [8], whereas in children the converse was true [7]. This may reflect that the NVE could be affected by patient-ventilator interaction and by levels of the support delivered. In our study, although the NVE differed significantly between those who were and were not successfully extubated, the NVE when related to body weight at the time of measurement did not. This may reflect the wide range of weights and therefore tidal volumes in the infants studied.

There were strengths and some weaknesses to our study. Our study population was heterogeneous as we wished to identify a predictor of extubation success that was generalisable to infants receiving neonatal intensive

care. The inclusion of both term and preterm infants may, however, have reduced our ability to detect clinically significant differences in the diaphragm EMG results. Successful extubation was defined as remaining off mechanical ventilation for 48 h, in line with our previous studies [9, 10, 13]. There is no consensus as to the most appropriate time to define extubation success and the results of a systematic review of neonatal studies suggested that extending the window to one week may not capture all infants who would require reintubation [19]. Use of our definition, however, is supported by the finding that, following extubation of infants with birthweight < 1,250 g, reintubation within 48 h carries the highest risk for subsequent death or development of bronchopulmonary dysplasia [20]. We did not undertake a spontaneous breathing test (SBT) as, although it might be highly sensitive, a recent meta-analysis has demonstrated it adds little benefit in the identification of extubation failures [3] as the SBT has poor specificity. Transcutaneous assessment of the diaphragm EMG can be influenced by movement artefact, hence we chose EMG results that were not affected by movement artefact. Electrode placement may affect the magnitude of the diaphragm EMG signals, with placement medial to the standard placement giving the most attenuated signal [21]. We feel it is unlikely that the electrodes were placed more medially than intended, due to the small chest size of infants, but this should be carefully noted for future studies. Additionally, the magnitude of transcutaneous EMG may be affected by the skin and subcutaneous tissue thickness, but we showed that infants of higher birth weight had higher EMG amplitude. An alternative explanation for our negative results is that transcutaneous measurements were too insensitive to detect differences. We, however, think this is unlikely as we have demonstrated changes in the transcutaneous EMG signal following the administration of a loading dose of caffeine [22]. We calculated the NVE using expiratory tidal volumes, as these are less prone to errors due to leak around the endotracheal tube and we used Coles tubes around which there is minimal or no leak [23].

In conclusion, the results of measurement of the diaphragm EMG prior to extubation in ventilated neonates did not accurately predict which infants would remain extubated at 48 h. There was, however, a significant difference in the absolute NVE results between those who were and were not successfully extubated. Whether results during a SBT would be a better predictor merits investigation.

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Author contributions: KAH and AG contributed to the conception and design of the study; KAH, IH, KA, TD and AG contributed to the acquisition of data, analysis and interpretation of data; KAH, IH, KA, TD and AG were responsible for drafting the article and revising it critically for important intellectual content; KAH, IH, KA, TD and AG gave final approval of the version to be published. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration and has been approved by the Health Research Authority and by the London – Camden and King's Cross NHS Research Ethics Committee.

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