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Automated Analysis of Respiratory Behavior in Extremely Preterm Infants and Extubation Readiness

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Summary. Background: Rates of extubation failure of extremely preterm infants remain high. Analysis of breathing patterns variability during spontaneous breathing under endotracheal tube continuous positive airway pressure (ETT-CPAP) is a potential tool to predict extubation readiness. Objective: To investigate if automated analysis of respiratory signals would reveal differences in respiratory behavior between infants that were successfully extubated or not. Methods: Respiratory Inductive Plethysmography (RIP) signals were recorded during ETT-CPAP just prior to extubation. Signals were digitized, and analyzed using an Automated Unsupervised Respiratory Event Analysis (AUREA). Extubation failure was defined as reintubation within 72 hr. Statistical differences between infants who were successfully extubated or failed were calculated. Results: A total of 56 infants were enrolled and one was excluded due to instability during the ETT-CPAP; 11 out of 55 infants studied failed extubation (20%). No differences in demographics were observed between the success and failure groups. Significant differences on the variability of some respiratory parameters or 'metrics' estimated by AUREA were observed between the 2 groups. Indeed, a simple classification using the variability of two metrics of respiratory behavior predicted extubation failure with high accuracy. Conclusion: Automated analysis of respiratory behavior during a short ETT-CPAP period may help in the prediction of extubation readiness in extremely preterm infants. **Pediatr Pulmonol. 2015;50:479–486.**

Key words: respiratory behavior; extubation readiness; extubation failure; ventilation weaning; extreme preterm infants.

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INTRODUCTION

Despite recent advances in the use of non-invasive respiratory support the majority of extremely preterm infants still require endotracheal intubation and invasive mechanical ventilation (MV) during hospitalization.[1] As prolonged ventilation has been associated with increased mortality and short- and long-term morbidities, early extubation is desired.[2] Commonly, preterm infants are extubated based on clinical expertise, evaluation of blood

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gases, oxygen requirements and ventilatory parameters.[3] These evaluations are subjective and imprecise leading to significant intra- and inter-hospital variability in the timing and success rates of planned extubations.[3]

Over the past decades, a number of studies have investigated prediction tools to evaluate extubation readiness.[3] Human ventilation exhibits a breath-by-breath variability and a complexity of which the characteristics may be interesting both physiologically and clinically. Indeed, breathing pattern during unassisted ventilation through an endotracheal tube (ETT) prior to extubation is an important factor in determining whether a patient can be successfully extubated.[4] A proper interpretation and analysis of these patterns has been the subject of several investigations in critically ill, intubated adult patients.[5–8] In preterm infants, respiratory variability estimated from pneumotachography improved the prediction accuracy of a spontaneous breathing test.[9] However, another study using Respiratory Inductive Plethysmography (RIP) reported no differences in respiratory behavior between infants that were successfully extubated or failed.[10] The advantage of using RIP is that it does not have the effects on ventilation described with the pneumotachograph and provides timing relations from ribcage and abdominal compartments. However, RIP signals are usually analyzed manually which is operator-dependent, subjective, and highly variable. The analysis is restricted to linear time series using conventional statistics, limiting its applicability to complex biological systems that are intrinsically nonlinear and exhibit complex behavior.

Recently, a method using a series of algorithms was developed for automated, unsupervised, respiratory event analysis (AUREA) of respiratory signals obtained from RIP.[11,12] Indeed, using automated analysis of RIP in combination with electrocardiogram signals and support vector machine methodology, we demonstrated the potential use of cardiorespiratory variability measurements to predict extubation readiness in extremely preterm infants.[13] The aim of this study was to investigate if automated analysis of respiratory signals would reveal differences in respiratory behavior between infants that were successfully extubated or not.

METHODS

Subjects

Infants admitted to the participating units, receiving MV and with a birth weight (BW) $\leq$ 1250g were eligible for study at the time of their first extubation attempt. Exclusion criteria included major congenital anomalies, congenital heart disease, and use of high-frequency ventilation, vasopressors or sedative drugs at the time of extubation. The study was approved by the Ethics Committee of each institution and written informed consent was obtained from the parents.

Respiratory Management

The study protocol did not interfere with the respiratory care practices. Decisions concerning ventilation weaning, extubation readiness and post-extubation management were made by the responsible physician and recorded by the research team. Nevertheless, before initiation of the study, criteria were proposed to guide the decision for both extubation and reintubation: 1) for infants $<$ 1000 g: mean airway pressure (MAP) $\leq$ 7 cm H_2O and fraction of inspired oxygen (FiO_2) $\leq$ 0.3; 2) for infants $\geq$ 1000 g: MAP $\leq$ 8 cm H_2O and $FiO_2 \leq 0.3$; and 3) loading dose of caffeine citrate (20 mg/kg) $\geq$ 24 hr prior to extubation. For infants already on caffeine, the maintenance dose (5 mg/kg) was given 2–6 hr prior to extubation.

Post-extubation respiratory support with nasal continuous positive airway pressure (CPAP) or nasal intermittent positive pressure ventilation (NIPPV) was recommended. All units used an oxygen saturation (SpO_2) target range of 88–95%, and a permissive hypercapnia strategy ($\leq$7 days of life = PCO_2 between 45–60 mmHg if pH > 7.25, and > 7 days = PCO_2 between 50–70 mmHg if pH > 7.25).

The following clinical data were also collected: 1) antenatal and maternal variables; 2) infant characteristics; 3) ventilatory settings prior to extubation; 4) blood gases prior to and after extubation; 5) ventilatory support post-extubation; 6) reason and age of extubation failure.

Measurements and Protocol

All infants were studied while stable and in supine position. Respiratory data was collected immediately prior to extubation, during a 3 min period of ETT-CPAP. The CPAP level used was the level of positive end expiratory pressure (PEEP) the patient was receiving during MV. The ETT-CPAP period was interrupted if the oxygen saturation decreased to <80% and/or the heart rate was <100 bpm. At the end of the ETT-CPAP period, all patients were extubated.

Respiratory signals were collected using the Respitrace QDC system (Viasys, Healthcare, USA), which records respiratory signals from two transducers called respibands. The first signal was obtained from a respiband placed around the infant's chest at the level of the nipple line (ribcage) and the second from a respiband placed around the infant's abdomen (abdomen), approximately half a centimeter above the umbilicus. Signals were recorded with a PowerLab data acquisition system (ADInstruments, Colorado Springs, CO, USA), which applied an anti-alias, low-pass filter at 500 Hz, then sampled the signals at 1 kHz using a 16 bit analog-todigital converter, and stored the data on a dedicated laptop computer.

Data Analysis

RIP signals were analyzed with AUREA, which characterizes the respiratory pattern in terms of a series of 7 continuous respiratory parameters, termed metrics, related to the amplitude, frequency, and thoraco-abdominal synchrony of the uncalibrated RIP signals for ribcage and abdomen at each time (i.e., sample-by-sample). These metrics are: 1) instantaneous respiratory frequency (f_{max}); 2) phase between ribcage and abdomen (ϕ); 3) sum of root mean squares of ribcage and abdomen (r^{+}), which quantifies the amplitude information of the RIP signals; 4) two pause metrics (p^{rc} and p^{ab}), which measure the RIP power in the breathing band (i.e., 0.4–2 Hz) relative to the median breathing power; and 5) two movement artifact metrics (m^{rc} and m^{ab}), which compare the power in the movement artifact band (i.e., 0–0.4 Hz) to that in the breathing band. These metrics are general descriptors of respiratory behavior that were developed for automated classification of the infant respiratory state,[11] and have been shown to be useful for detection of infant postoperative apnea and estimation of thoraco-abdominal asynchrony.[11,12,14,15] Figure 1 shows a representative example of the RIP signals during the ETT-CPAP, and the corresponding metrics computed by AUREA. Prior to further analysis, the metrics r^{+}, p^{rc} and p^{ab} were transformed with the natural logarithm operator (*ln*).

Continuous estimates of the variability of these metrics as functions of time were determined by computing their Interquartile Range (IQR) over a two-sided, sliding window of length W. The start time of the sliding window (τ) was varied from $\tau = 0$ s, the start of the ETT-CPAP period, to its end $\tau = 180$ s. Different values of window length were evaluated to account for the trade-off between the variance of IQR estimates and time resolution. Thus, the value of W was varied from 40 to 160 s (in 10 s increments) to evaluate the discriminative ability of all metrics for different window lengths during the ETT-CPAP.

Statistical Analysis

A convenience sample size of 56 infants was used to assess respiratory behavior during ETT-CPAP. Fisher's exact test was used for categorical variables and the Student's *t-test* to compare clinical outcomes. A P-value

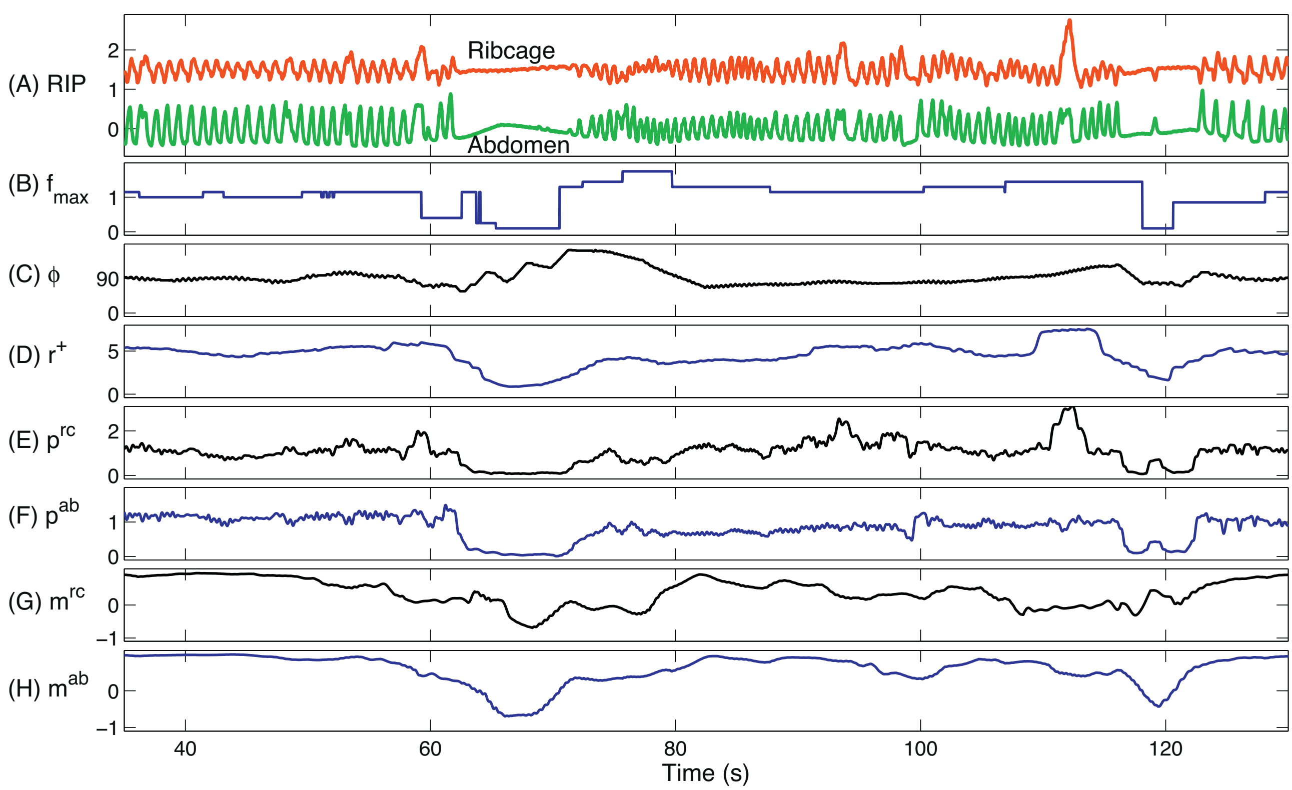

Fig. 1. Representative example of ribcage and abdominal RIP signals during a spontaneous breathing 3 min ETT-CPAP period, and the corresponding metrics computed by AUREA. f_{max} = instantaneous respiratory frequency (Hz); ϕ = phase between ribcage and abdomen (degrees); r^{+} = sum of root mean square of ribcage and abdomen (arbitrary units); p^{rc} and p^{ab} = pause metrics for ribcage and abdomen (arbitrary units); m^{rc} and m^{ab} = movement artifact metrics for ribcage and abdomen (arbitrary units).

< 0.05 was considered statistically significant. In the automated analysis, the discriminative ability of each respiratory metric was examined as a function of the window start time (τ) and length (W) by applying the Wilcoxon *rank-sum* test[16] at each sample for each value of W. Nonparametric testing was used because we have previously shown that AUREA's respiratory metrics have non-Gaussian distributions.[11]

Assessment of Extubation Readiness

The two variables with the greatest univariate discriminatory power (i.e., lowest P-values) were used together to classify between successful and failed extubation. Thresholds for classification were selected by a grid search of all possible threshold combinations; standard formulae were used to calculate sensitivity, specificity, positive, and negative predictive values (PPV and NPV) for each threshold combination. The pair of thresholds that maximized the sum of sensitivity and specificity was selected for classification.

RESULTS

Study Population and Clinical Outcomes

Between March 2010 and June 2011, a total of 164 infants met the inclusion criteria and 56 were enrolled (Figure 2). One infant became unstable during the ETT-CPAP period and the spontaneous breathing trial was interrupted. Population characteristics, ventilatory settings and blood gases prior to extubation are described in Table 1. Eleven of the 55 infants (20%) failed their first extubation attempt (Table 2).

Respiratory Behavior Analysis

The analysis with AUREA computed the respiratory metrics of all 55 infant data sets. The interquartile range (IQR) of three metrics, namely f_{max}, m^{rc}, and $ln(r^{+})$, exhibited significant differences between infants who succeeded and failed extubation (Figure 3). These differences varied with the start time (τ) and length (W) of the window used to compute the IQR. The left column of Figure 3 shows heat maps of the P-values as functions of W and τ. The minimum P-values occurred near the second minute of the ETT-CPAP period for window lengths between 40 and 60 s. Thus for IQR$\{f_{max}\}$ the minimum P-value ($P < 0.0001$) occurred at $\tau = 57$ s, $W = 60$ s; that for IQR$\{m^{rc}\}$ ($P = 0.0001$) occurred at $\tau = 50$ s, $W = 40$ s; and for IQR$\{ln(r^{+})\}$ ($P = 0.0018$) at $\tau = 75$ s, $W = 40$ s. The right column of Figure 3 shows slices of these heat maps at the value of W corresponding to the minimum P-values; the variation of these P-values across the 3-min trial demonstrates the strongly non-stationary nature of respiratory behavior during the ETT-CPAP period.

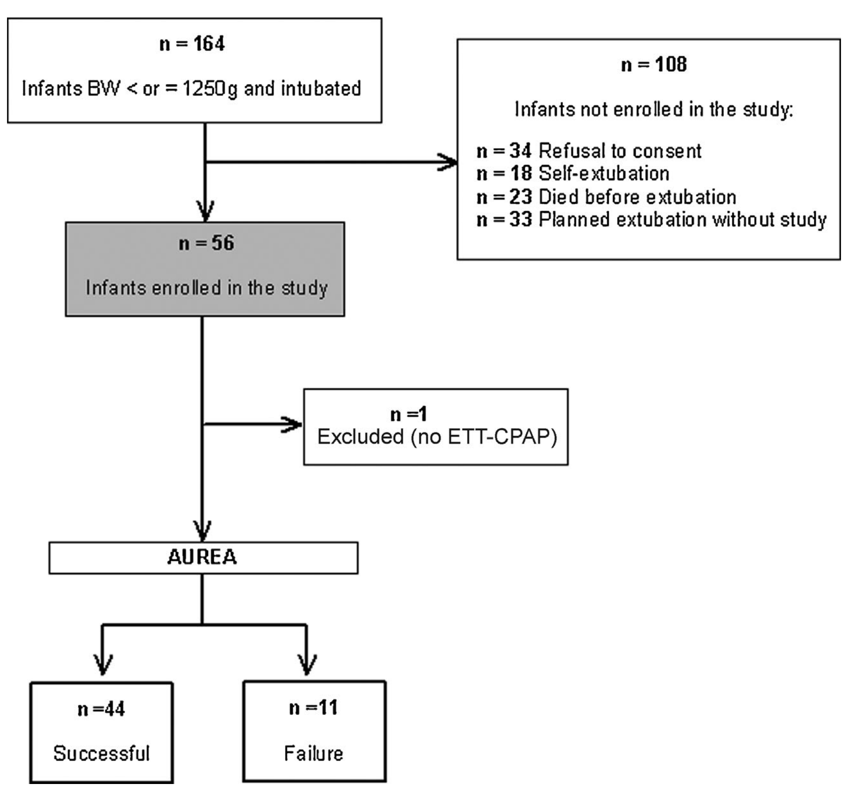

Fig. 2. Study enrollment

TABLE 1— Patient Demographics

	Success (n = 44)	Failure (n = 11)
Population characteristics		
Antenatal steroids	38/42 (90)	8 (73)
C-section	27 (61)	7 (64)
Multiple birth	14 (32)	1 (9)
Antibiotics during labour	25/42 (60)	7 (64)
Chorioamnionitis	15/41 (37)	2/8 (25)
Birth weight (g)	903 ± 186	847 ± 227
Gestational age (weeks)	26.7 ± 1.6	26.3 ± 1.4
Male	21 (48)	8 (73)
Apgar 1 minute	5 [2–6]	4 [1.5–6]
Apgar 5 minutes	7 [5–8]	7 [4.5–8]
Surfactant	42 (95)	11 (100)
Weight at study (g)	1022 ± 297	911 ± 231
Age at extubation (days)	4.1 [1.6–16.8]	1.8 [1.2–4.8]
Caffeine prior to extubation	31 (70)	8 (73)
Postnatal steroids prior to extubation	10 (23)	3 (27)
Ventilatory Settings		
PIP (cmH_2O)	13 ± 2	14 ± 2
PEEP (cmH_2O)	4.4 ± 0.6	4.6 ± 0.8
Mean airway pressure (cmH_2O)	5.9 ± 0.9	6.4 ± 1.2
Fraction of inspired oxygen	0.26 ± 0.06	0.26 ± 0.06
Inflation time (seconds)	0.39 ± 0.03	0.37 ± 0.03
Ventilator rate (breaths per minute)	21 ± 8	24 ± 11
SpO_2 (%)	95 ± 3	95 ± 2
FiO_2 during ETT-CPAP	0.26 ± 0.07	0.32 ± 0.23*
SpO_2 during ETT-CPAP (%)	94 ± 4	94 ± 3
Blood Gases		
pH	7.35 ± 0.05	7.31 ± 0.04*
pCO_2 (mmHg)	47 ± 12	45 ± 9
HCO_3 (mEq/L)	21.9 ± 3.3	21.9 ± 3.0
Base Excess	−3.2 ± 3.2	−2.0 ± 4.1

Values are expressed as mean ± standard deviation, median [inter-quartile range], n (%) or n/N (%). *$P < 0.05$ for success vs failure for each type of analysis.
PIP = peak inflation pressure; PEEP = Positive end-expiratory pressure, ETT-CPAP = Endotracheal tube continuous positive airway pressure; FiO_2 = Fraction of inspired oxygen; SpO_2 = oxygen saturation.

TABLE 2— Extubation Failure and Timing of Reintubation

	(n = 11)
Cause of extubation failure	
Multiple apneas and bradycardias	6 (55)
Respiratory acidosis (pH<7.20 and $PCO_2 > 60$)	4 (36)
$FiO_2 > 0.5$ in order to maintain $SpO_2 > 88\%$	1 (9)
Age of reintubation	
< 12 hours	3 (27)
12–24 hours	3 (27)
24–48 hours	4 (36)
> 48 hours	1 (9)

Values are expressed as n (%). Legend: FiO_2 = Fraction of inspired oxygen and SpO_2 = Oxygen saturation

Assessment of Extubation Readiness

Figure 4 shows a scatter plot of IQR$\{f_{max}\}$ against IQR $\{m^{rc}\}$; a clear separation between infants who succeeded and failed extubation is evident. Subjects who failed extubation had a combination of low variability in the instantaneous respiratory frequency (f_{max}) and high variability in the ribcage movement artifact metric (m^{rc}). The dashed lines indicate the optimal thresholds that best separated the two groups (sensitivity = 0.82, specificity = 1, PPV = 1 and NPV = 0.96).

DISCUSSION

This is the first study to investigate the ability of an automated analysis of respiratory behavior to predict extubation readiness in extremely preterm infants. Using respiratory signals collected during a 3 min spontaneous breathing ETT-CPAP period prior to extubation we observed differences in the respiratory behavior between infants that failed or were successfully extubated. Indeed, a very good differentiation was obtained with a combination of variability of two metrics: instantaneous respiratory frequency and ribcage movement artifact (Figure 4).

It has been previously demonstrated that measurements of respiratory behavior over time can provide predictive information, including weaning from MV. In adults, Bien et al. monitored breath-to-breath variability of breathing patterns and demonstrated that greater variability was associated with successful extubation.[8] Similarly, Wysocki et al. reported a reduced variability in inspiratory flow in patients that failed MV weaning.[7] During a 30 min ETT-CPAP period, a decreased variability in the inter-breath intervals was found in adult patients who failed extubation,[17] and even small increases in respiratory load were associated with a reduction in respiratory variability.[18] Recently, the performance of respiratory pattern parameters to predict successful weaning was studied and an accuracy of 93% was obtained using a classifier built by the CART algorithm.[19]

In preterm infants, Kaczmarek et al[9] calculated respiratory variability using data collected during a 3 min ETT-CPAP. Analysis of the respiratory patterns showed a significantly decreased variability in the mean inspiratory flow of infants that failed extubation. The addition of two variability indices to the clinical response to the test increased the PPV for successful extubation. However, respiratory variability was calculated using data obtained with a pneumotachograph.[9] This has limitations related to variable leaks around the ETT, addition of dead space and resistance, and inability to assess thoraco-abdominal movements and asynchrony, which may provide useful information.[20] In an investigation conducted with the same population of the present study we performed manual analysis of the RIP signals. No differences on respiratory behavior were detected between

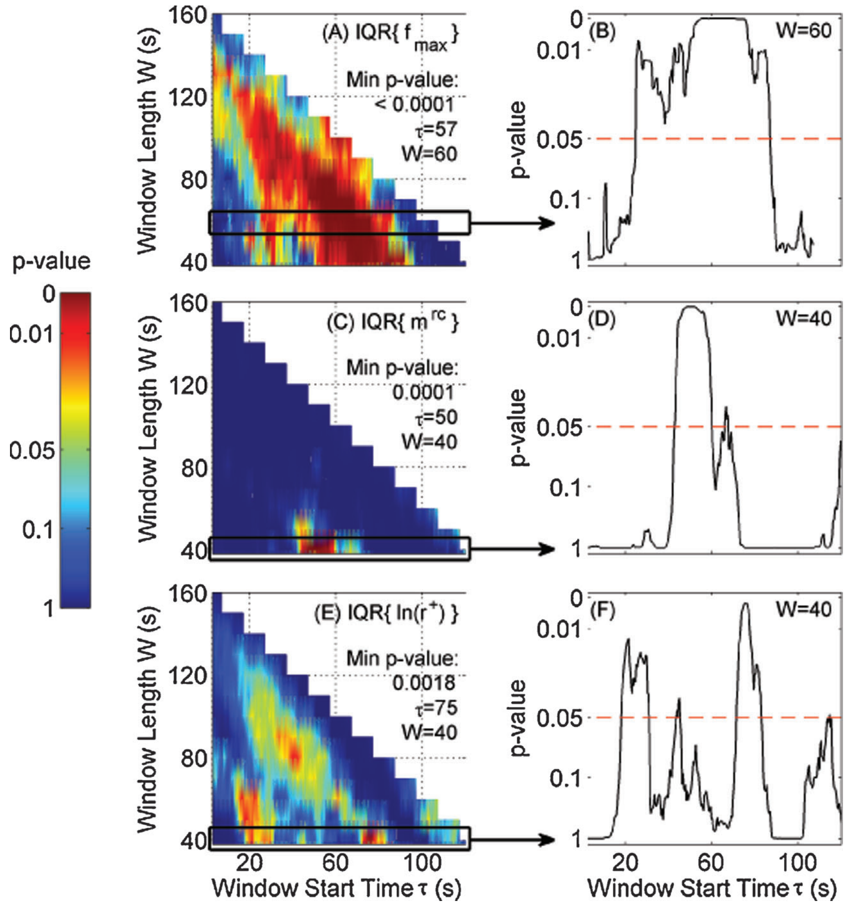

Fig. 3. ***P*-value heat maps for the three metrics that exhibited significant differences between infants who succeeded and failed extubation. (A) *P*-value of the interquartile range (IQR) of f_{max}, the instantaneous respiratory frequency (in Hz), as a function of the start time (τ) and length (W) of the window used to estimate the IQR. Statistical significance is color-coded showing the most significant differences in red (*P*-value = 0) and the least significant in blue (*P*-value = 1). The lowest *P*-value was <0.0001, and it was identified at the middle of the ETT-CPAP period, with a window of length W = 60 s. (B) *p*-value of IQR{f_{max}} as a function of window start time (τ) for W = 60 s. The red dashed line indicates the threshold for statistical significance. The *P*-value varied substantially during the 3-min period, evidencing the non-stationary nature of this respiratory behavior metric. (C) *P*-value of the IQR of m^{rc}, the movement artifact metric for ribcage (in arbitrary units). Statistically significant *P*-values were observed mostly at the middle of the ETT-CPAP period using short window lengths. The lowest *P*-value for IQR{m^{rc}} was 0.0001, which occurred at the middle of the period (τ = 50 s and W = 40 s). (D) *P*-value of IQR{m^{rc}} as a function of window start time (τ) for W = 40 s. (E) *P*-value of the IQR of $ln(r^+)$, the natural logarithm of the sum of root mean square of ribcage and abdomen (in arbitrary units). The minimum *P*-value = 0.0018 was observed at τ = 75 s using a window length of W = 40 s. (F) Detailed *P*-value of IQR{$ln(r^+)$} as a function of τ for W = 40 s.***

infants that were successfully extubated or failed,[10] which could be related to the fact that manual analysis requires segmentation of the signal on a breath-by-breath basis, is subjective, and operator-dependent. Indeed, a significant number of patients were excluded due to poor quality of the recordings as judged by the responsible investigator.[10] Using AUREA the respiratory metrics are computed automatically with reproducible, quantitative measures of the respiratory behavior. AUREA's algorithms are robust in high noise conditions and analysis of all 55 patients was possible. Another advantage is that AUREA estimates respiratory variables at each sample time, following the non-stationary conditions of complex biological signals such as breathing. Indeed, the discrimination ability of AUREA's metrics changed throughout the test period; the second minute was the most useful to predict extubation readiness (Figure 3). This is in accordance with previous studies in adults where the second third of a 30 min spontaneous breathing trial was the most useful period,[21,22] since the beginning of the ETT-CPAP may represent a

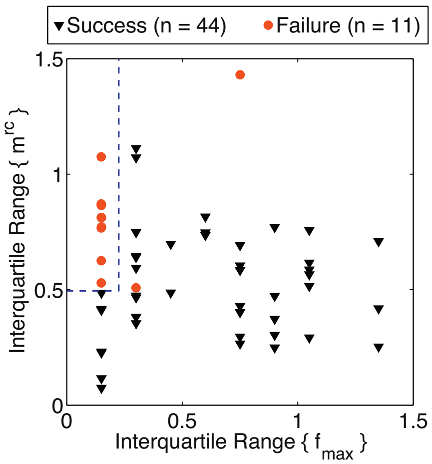

Figure 4. Assessment of extubation readiness based on AUREA analysis. Group analysis as a function of the variability of two prediction metrics: the instantaneous respiratory frequency (estimated from the abdominal signal) and the ribcage movement artifact. The interquartile range values correspond to the window start time (τ) and length (*W*) with minimum *P*-value. The blue dashed lines indicate the thresholds identified for the discrimination between the two groups. f_{max} = instantaneous respiratory frequency (Hz); m^{rc} = movement artifact metric for ribcage (arbitrary units).

feeling of anxiety or an adaptation phase related to the change from assisted ventilation to ETT-CPAP.

Consistent with studies in adult patients, we observed a decreased variability in the instantaneous respiratory frequency during ETT-CPAP in infants that failed extubation. The accuracy improved if infants also had an increased variability of the ribcage movement artifact metric. This metric is an indicator of the relative distribution of power in the frequency components of the ribcage signal, it tends to -1 when the signal is dominated by low frequency components (0–0.4Hz), and to 1 during breathing (either synchronous or asynchronous). Therefore, a large variability in this metric reflects a breathing pattern that oscillates between breathing and lower frequency components. While originally designed to detect low frequency movement artifact, negative values of m^{rc} may also represent movement due to agitation, shallow breathing, or other physiological states. Thus, we speculated that the combination of low variability of the instantaneous respiratory frequency coupled with high variability of m^{rc} during ETT-CPAP may represent a more unstable respiratory system, with a decreased ability to tolerate the increased workload of breathing associated with the ETT-CPAP, and subsequently, extubation.

Our study has some other important limitations and should be regarded as a hypothesis generator. The pathophysiological relevance of the metrics derived from AUREA is unknown. We studied a limited number of infants and only 11 patients failed extubation. A study including a larger number of patients and a prospective validation of this tool is underway (the APEX study - NCT 01909947). The length of the ETT-CPAP period was empirically chosen as 3 min. A longer period of data recording may be better in the evaluation of non-stationarity of the respiratory behavior. Nevertheless, automated measurements of respiratory behavior may offer a way to assess for important hindered information since they reflect the development, maturation and stability of the respiratory control centers and feedback mechanisms. Ultimately, these measurements may help to predict extubation readiness in extremely preterm infants, a population with the highest rates of extubation failure.

In summary, using an automated analysis of RIP signals, several respiratory metrics were found to be significantly different between the two extubation outcome groups. A simple classification using two metrics was able to accurately predict the outcome of extubation readiness, using as little as 3 min of respiratory data during ETT-CPAP. The introduction of new tools capable of performing automated evaluations of respiratory patterns in a more comprehensive manner, and taking into account changes that occur over time, offers a step forward from the current, more subjective nature of clinical judgment.

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