Lower Interbreath Interval Complexity Is Associated With Extubation Failure in Mechanically Ventilated Patients During Spontaneous Breathing Trials

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Objective: To determine whether lower complexity of interbreath interval as measured with nonlinear analysis techniques will identify patients who fail to separate from mechanical ventilation after 30-minute spontaneous breathing trials (SBTs).

Methods: Respiratory waveforms from SBT of patients in surgical or burn intensive care units were recorded for later analysis. The decision to extubate was made by attending physician. Extubated patients were observed for 48 hours; during this time, reintubation or noninvasive positive pressure ventilation was considered as a failure. Analysis of waveform data by software was performed post hoc. Sample entropy (SampEn) and other nonlinear measures were 48 hours of extubation.

Results: Thirty-two patients (24 burn, 8 trauma/surgical admissions; mean age, 40.2 ± 16.9 years; 26 men and 6 women) who were intubated >24 hours were extubated after SBT. Twenty-four patients were successfully separated from mechanical ventilation and eight failed. Age, gender, and mechanism of injury did not influence outcome. SampEn calculated for the two groups presented in this study was different with the cohort that failed extubation having a lower mean value (1.35 ± 0.39 vs. 1.87 ± 0.27; $p < 0.001$). Other nonlinear metrics were moved in concert with SampEn. The stationarity in the respiratory signal was not different between groups.

Conclusion: In intubated patients, the interbreath interval in those who were successfully separated from mechanical ventilation was more irregular than those who failed, as measured by nonlinear techniques. When available at bedside, these metrics may be useful markers of pulmonary health and assist in clinical decision making.

Key Words: Mechanical ventilation, Weaning, Respiratory variability, Sample entropy, Humans.

(*J Trauma.* 2010;68: 1310–1316)

Submitted for publication March 27, 2009.
Accepted for publication February 23, 2010.

From the U.S. Army Institute of Surgical Research, Fort Sam Houston, Texas.
Supported by the National Center for Research Resources contracts UL RR025767 and KL2 RR025766 for the Institute for Integration of Medicine and Science.

Presented as a poster at the 68th Annual Meeting of the American Association for the Surgery of Trauma, October 1–3, 2009, Pittsburgh, Pennsylvania.
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DOI: 10.1097/TA.0b013e3181da90db

The inability to tolerate separation from mechanical ventilation or the need for reintubation occurs in as many as 20% of mechanically ventilated patients and results in increased intensive care unit (ICU) and hospital length of stay, total hospital costs, and patient mortality.[1–3] Conversely, delaying extubation exposes the patient to the complications and discomfort of unnecessary mechanical ventilation and increased hospital costs.[4] Multiple studies have shown that a diverse collection of variables used to predict successful separation from mechanical ventilation perform poorly and add little to the physician's clinical judgment.[5] Recently, attention has focused on the use of breathing variability as a weaning predictor.[6–9] Implicit in this approach is that healthy subjects demonstrate considerable variability in breathing patterns;[10–12] however, in pulmonary disease states, breathing variability is reduced from normal levels.[13–15] Wysocki et al.[9] have postulated that respiratory variability is related to pulmonary load balance and that increased loading reduces breathing variability. Data from healthy human volunteers as well as two recent weaning studies support this hypothesis,[8–10,16–21] although contrasted findings have been reported.[6,7,22]

Breathing variability may be quantified by methods that involve nonlinear dynamical analysis. A nonlinear system is one whose behavior is not simply a summation of inputs into the system; nonlinearity is a fundamental characteristic of normal physiologic data.[23] These methods are distinct from variance, which measures dispersion about a mean, and take into account the nonlinear physiologic response to stimuli. As such, nonlinear methods may provide insight into organ system interconnectivity and regulatory control.[23,24]

Our group has previously applied a panel of nonlinear analysis tools for the assessment of waveforms and established that lower cardiovascular regulatory complexity, as sampled from electrocardiographic signal irregularity, is associated with adverse outcomes in prehospital trauma patients.[25] In this study, we explored the utility of nonlinear analysis tools in the assessment of perturbations in the respiratory domain. Sample entropy (SampEn) is a relatively new statistic measuring regularity of nonlinear, clinical, and experimental time series data. It examines the data for similar epochs (groups of consecutive points of the same length) in which more frequent and more similar epochs yield lower values of this metric.[26] This allows comparison of patterns to analyze which is the most regular (i.e., the least complex).

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 JUN 2010	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Lower interbreath interval complexity is associated with extubation failure in mechanically ventilated patients during spontaneous breathing trials	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)	5d. PROJECT NUMBER
White C. E., Batchinsky A. I., Necsoiu C., Nguyen R., Walker 3rd K. P., Chung K. K., Wolf S. E., Cancio L. C.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**7**	

Additionally, SampEn may be more powerful than previously used time series measures of regularity, such as approximate entropy (ApEn), especially in shorter data sets.[26,27] In addition, we complement the assessment of signal irregularity with methodologically distinct waveform analysis tools such as those derived from analysis of signal amplitude distribution as a function of time,[28] entropy of symbol dynamics distributions,[29,30] and assessment of baseline shifts or stationarity of the signal.[30]

The purpose of this study was to measure the regularity of breathing patterns of intubated patients undergoing spontaneous breathing trials (SBTs) using a comprehensive analysis of respiratory waveforms. We hypothesize that patients who successfully separate from mechanical ventilation will have a more irregular breathing pattern than those who fail extubation as measured by methodologically different nonlinear metrics. A comparative assessment of the utility of these measures as applied to respiratory physiology is provided below.

PATIENTS AND METHODS

Subjects and Protocol

Appropriate institutional review board approval was obtained before the initiation of this study. Because this was an observational study and all data were analyzed post hoc, it was considered minimal risk, and an informed consent was waived. The subjects were prospectively recruited from one Level I trauma center with separate burn and surgical/trauma ICUs during a 9-month period. For burn patients, all burn resuscitations were performed in standard fashion according to the Modified Brooke Formula.[31] Both ICUs used an identical SBT protocol. Criteria for inclusion into this study were mechanical ventilation with an endotracheal tube for >24 hours, regardless of underlying disease, and the ICU attending physician's judgment that the patient was ready for SBT and possible extubation at the end of the trial. Readiness criteria are listed in Table 1.[32] All SBTs were performed with 5 cm H_2O of both positive end-expiratory pressure (PEEP) and pressure support (PS) for 30 minutes. Sedation and analgesia were continued during SBTs at the physician's discretion. The patient was monitored during this time by a respiratory therapist and returned to the previous ventilator settings if the patient had one or more signs of cardiopulmonary distress listed in Table 2. If the patient tolerated the SBT, then measurement of respiratory rate (RR), rapid shallow breathing index (RSBI), and negative inspiratory force (NIF) were performed by the respiratory therapist, and the physician in charge was contacted and notified of results of SBT. The decision to extubate after "passed" SBT was made by the ICU attending physician. Subjects not extubated after SBT or subjects reintubated for elective surgery <48 hours after extubation were not included in our study. Once extubated, patients were supplied with supplemental oxygen by air entrapment mask or nasal cannula. Separation from mechanical ventilation was considered a failure if the subject required any ventilatory support, including noninvasive positive pressure ventilation, within 48 hours of extubation. Subjects who had undergone separation from mechanical ventilation and failed, or who had passed and were later reintubated for further surgery, were not considered again for analysis.

TABLE 1. Readiness Criteria for Spontaneous Breathing Trial

Significantly improved or resolved need for mechanical ventilation
Minimal ventilatory support required
Adequate oxygenation with Pao_2/FIO_2 >200
FIO_2 ≤40%
PEEP = 5 cm H_2O to keep SPO_2 >92%
pH >7.25
No confirmed or suspected upper airway obstruction

TABLE 2. Manifestations of Intolerance to SBT

Significant dyspnea
RR >30 bpm
Diaphoresis
Use of accessory muscles/thoracoabdominal paradox
Tachycardia (HR >120 bpm or increased 20% from baseline)
SBP >180 mm Hg or <90 mm Hg or need for vasopressors
SPO_2 <90%
Change in mental status (coma, confusion, agitation, and anxiety)

HR, heart rate; SBP, systolic blood pressure; SPO_2, pulse oximetry oxygen saturation.

Waveform Analysis

During the SBT, respiratory flow and pressure waveforms were continuously monitored on the Draeger Evita XL Ventilator (Drager Medical, Lubeck, Germany), and the subjects were instructed not to speak during the recording period. The waveform data were retrieved from the ventilator for off-line analysis by using an RS232 connection recorded at 500 Hz to the DREW digital data acquisition system.[33] Recorded data were stored on a personal computer and analyzed by personnel who were blinded to the results of the SBT. Two-hundred breath data sets, which were the most consistently available in all investigated subjects, were imported into WinCPRS software (Absolute Aliens Oy, Turku, Finland). Peaks denoting the beginning of each consecutive respiration were automatically identified by means of an isoelectric line-shift algorithm by the software in every data set, and correct identification of all the peaks was then manually verified. Both respiratory flow and pressure were used for peak detection to increase the reliability of the process. The software generated the instantaneous interbreath interval (IBI) time series. Before entropy calculations, linear trends were removed in all segments of the analyzed data. Analysis algorithms are identical to those reported before.[25,34] The following waveform analysis techniques were applied:

1. ApEn and SampEn measure the amount of irregularity in the IBI.[26,34,35] ApEn determines the conditional probability of finding specific patterns in the time series; i.e., the logarithmic likelihood that a run of patterns that is close remains close on the next incremental comparison. The template patterns are constructed from the signal itself,

and no a priori knowledge of the system is needed. SampEn is a similar concept to ApEn, with the computational difference that the vector comparison with itself is removed. For both ApEn and SampEn, the dimension parameter *m* used for calculation was 2, and the filter parameter *r* was 20% of the standard deviation (SD; see Richman and Moorman[26] for a discussion of techniques).
2. Similarity of distributions (SODs) explores the probability of similar IBI signal amplitude distributions as a function of time.[28]
3. Symbol-dynamics indices: Symbol-distribution entropy (DisNEn) and bit-per-word entropy (BPWEn) collectively measure the probability of patterns within the IBI time series. These metrics are based on re-creation of the dynamics of a complex system in phase space. The order in which the dynamics of the system visit the possible encoded regions creates a symbol distribution sequence, DisNEn. Symbol sequences are encoded into words (2–3 symbols in length), the frequency of occurrence of each word is then counted, and the normalized entropy BPWEn of these words is calculated from a histogram.[29]
4. Signal stationarity (StatAv) assesses whether the mean and the SD of the signal change over time during each data set.[30]

Statistical Analysis

SAS version 9.1 (SAS Institute, Cary, NC) was used for statistical analysis. Normality of continuous variables was assessed with the Shapiro-Wilk test. Univariate analysis was performed with two samples, Student's *t* test or Mann-Whitney *U* test as appropriate for continuous variables, and Fisher's exact test for categorical variables. In addition, Spearman correlation coefficients were calculated to determine relationships between variables. A p value of <0.05 was considered indicative of statistical significance.

RESULTS

Sixty-four nonconsecutive subjects underwent 73 SBTs with 5 cm H_2O PEEP and PS for 30 minutes, and 33 subjects were subsequently extubated at the completion of the SBT (five subjects were given two SBTs and two subjects were given three SBTs, all successfully separating from mechanical ventilation on the last SBT). Of these subjects, one data set was excluded from analysis because of artifacts in the signal. A total of 24 subjects were successfully separated from the mechanical ventilation. There were eight failures with one failure rescued with noninvasive positive pressure ventilation (5 burn, 2 trauma, and 1 surgical admission). The mean duration for time to failure was 22.4 hours (range, 0.96–47.25 hours). Hypoxia was cited as the reason for reintubation in five subjects, whereas tachypnea, hypercapnia, and upper airway edema were named in the remaining three subjects. There were no deaths in either cohort during the study period. The characteristics of the two groups, along with RR, duration of IBI, NIF, and RSBI calculated during SBT, are provided in Table 3. Age, sex, and mechanism of injury and duration of mechanical ventilation did not influence outcome, and there was no difference in recorded weaning parameters between groups. However, the Acute Physiology and Chronic Health Evaluation II score on admission was higher in the success group ($p < 0.05$).

TABLE 3. Group Characteristics

Variable	Pass (N = 24)	Fail (N = 8)	*p*
Age	37 ± 17	49 ± 15	0.08
APACHE II score	13 ± 4	9 ± 3	0.02
RR mean	30.86 ± 30.12	26.15 ± 8.37	0.78
NIF	−33 ± 10	−35 ± 11	0.60
RSBI	47 ± 29	40 ± 27	0.78
Ventilated days	4.71 ± 3.63	4.30 ± 3.95	0.75
Sex, F (%)	13	38	0.15
MECH, surgical/burn (%)	21/79	38/63	0.38

Mean ± SD.
MECH, mechanism of injury.

TABLE 4. Nonlinear Results

Variable	Pass (N = 24)	Fail (N = 8)	*p*
SampEn	1.87 ± 0.27	1.35 ± 0.39	0.00
ApEn	0.97 ± 0.06	0.93 ± 0.11	0.36
SOD	0.17 ± 0.03	0.23 ± 0.05	0.02
DisNEn	0.82 ± 0.06	0.75 ± 0.06	0.01
BPwEN	4.94 ± 0.38	4.51 ± 0.34	0.01
StatAv	0.33 ± 0.13	0.30 ± 0.10	0.88

Mean ± SD.

Nonlinear results are provided in Table 4. As measured by SampEn, the IBI in the success group was more irregular than in the failure group, in which the subjects had a lower SampEn and thus a more regular IBI distribution. ApEn, however, was not different between groups. SOD was lower in the success group, implying a more dissimilar signal distribution, and higher in the failure group, pointing to a more regular signal amplitude distribution. The StatAv value, which measures baseline shifts in the signal, was not different among groups (see below for discussion of this metric). BPWEn and DisNEn changed in concordance with SampEn and denoted lower signal irregularity in the failure group (Table 4). Finally, there was no correlation between nonlinear values and time to failure.

DISCUSSION

The primary finding of this study is that in intubated patients undergoing SBT, the IBIs of those who failed to separate from mechanical ventilation were more regular than in those who were successfully extubated. This finding implies a lower regulatory complexity of respiration as measured by different nonlinear methods. As collective measures of regulatory complexity, these methods may then be useful markers in predicting outcome of SBT when available at bedside. It is also interesting to note that RR, NIF, and RSBI did not differ between groups, and that all subjects who were extubated had weaning parameters predictive of success.

To explore the complexity of the respiratory signal, we used different statistical techniques. First, entropy metrics

(ApEn, SampEn, DisNEn, and BPWEn) were used to measure the amount of irregularity in the signal. Both ApEn and SampEn calculate the (logarithmic) likelihood that clusters of patterns that are close in time remain close in the next incremental comparison; that is, how knowing one portion of the signal will allow forecasting of the next portion as it is moved forward in time. They are nonlinear metrics that are scale and model independent and produce nonnegative numbers that can be used for comparisons across studies; a higher number represents higher irregularity. SampEn differs from ApEn by disallowing self-matches and appears more robust, because SampEn can provide meaningful clinical results using data sets as short as 100 beats or breaths in length.[26,35] SampEn calculated for the two groups presented in this study was different with the cohort that failed extubation having a lower mean value (1.35 ± 0.39 vs. 1.87 ± 0.27; $p < 0.001$), although ApEn was not different (0.93 ± 0.11 vs. 0.97 ± 0.06, fail vs. success, respectively; $p = 0.36$). We hypothesize that this difference is the effect of the small data sets used on this study. DisNEn and BPWEn tend to move in concert with SampEn, and all were lower in the failure group. These former two measures represent the signal distribution in phase space and, albeit methodologically distinct from SampEn, are complementary entropy measures of signal irregularity. Similar to this study, changes in DisNEn and BPWEn have followed the trend in SampEn in previous work by our group during hemorrhagic shock in animals[36] and burn shock in humans.[37]

Another technique used, SOD, converts the signal into histograms (amplitude distributions) that are set in arbitrary time windows and then explores the probability that similar histograms will recur as a function of time. SOD is indirectly related to complexity and is scored as a probability between 0 (no recurrence) and 1 (complete overlap of histograms). It is also robust in signal analysis and can provide meaningful results in small data sets.[27] In this study, SOD was higher in the cohort that failed extubation (0.23 ± 0.05 vs. 0.17 ± 0.03, respectively; $p < 0.02$).

Ectopic beats that occur during electrocardiogram recording or coughing with respiratory recordings can create noise and errors during signal analysis. These events can cause nonstationary signals, identified by changes in the mean and SD of the signal during the course of a data set. Both SampEn and SOD are generally more robust to nonstationarities in patient data than other metrics; the effect of noise on SampEn is predictable, causing a slightly greater value. Assessment of the signal quality used for the above comparisons was tested by means of StatAv. This metric assesses baseline shifts in means and SDs over the time course of the data set and is higher in less stationary signals. StatAv was low, pointing to low signal nonstationarity, and was also similar between the two groups (0.33 ± 0.13 vs. 0.30 ± 0.10, failure vs. success, respectively; $p = 0.88$), which indicates equal effects of nonstationarity on the metrics in both groups.

The respiratory center resides in the brain stem and integrates input from multiple areas to include both central and peripheral chemoreceptors, chest wall and muscle mechanoreceptors, pulmonary receptors, vagal afferents, the cerebrum, and other central nonrespiratory centers.[7,38–42] The respiratory pattern is a nonlinear, dynamic output signal that is a consequence of these mutual interactions, and the structural complexity of this signal may be a reflection of the regulatory complexity of its control system. In fact, a principal hypothesis in complexity theory holds that system stability "depends on the number, bias and types of interconnections among the system's constituents."[23] Conversely, greater signal regularity may be a surrogate for system isolation or "decomplexification" in nonlinear systems; and multiple system organ failure may be a consequence of this loss of coupling between communicating organ systems.[24,43,44] In these cases, loss of signal complexity may be a result of a relaxation of feedback mechanisms revealing more simple control of the system or an adaptive strategy in times of stress.[23,44] This has been extensively studied in the heart where decreased variability of R-R interval (RRI) was associated with disease states and aging.[45–49] In hemorrhage and/or shock models, resuscitation is associated with a progressive increase in RRI variability.[36,37]

In the respiratory system, loss of variability also occurs in healthy human volunteers, in whom adding elastic or resistive loads,[16] or challenge with endotoxin[17] decreased breath-to-breath variability. It is reduced during sleep and also degrades with age.[12,50] In disease states such as restrictive or obstructive pulmonary disease, patients adopt more constrained breathing patterns.[13,15] Under stress, the frequency to tidal volume (V_T) ratio increases, and both V_T and respiratory period become more monotonic. This adaptive strategy is more energy efficient because smaller breaths are less costly than one breath twice as large.[51] However, in patients who fail weaning trails, this rapid shallow breathing pattern occurs immediately after discontinuation of mechanical ventilation[3] and is also manifested simultaneously in the electromyographic power spectrum of the diaphragmatic muscles by changes in the ratio of high to low frequency power.[52,53] Assessed along two dimensions, respiratory sinus arrhythmia, which couples heart rate variability with respiration, is attenuated with hypoxia but strengthened by hypercarbia.[54] Moreover, "programming" variability into mechanical ventilators (i.e., fractal ventilation) improves gas exchange in animal models, which may be the result of increased recruitment of collapsed alveoli with nonlinear opening characteristics or perhaps stronger coupling between nonlinear biological oscillators or both.[55–57]

Wysoki et al.[9] compared 51 consecutive patients who were mechanically ventilated >24 hours and measured multiple respiratory variables while undergoing an hour-long SBT. In this study, patients were disconnected from the ventilator and received only supplemental oxygen during the SBT. The recordings were stratified into success and failure to remain free of ventilatory support for >48 hours (those who were reconnected to the ventilator during or at the end of the SBT were considered failed trials), and coefficients of variation (CV = SD expressed as a percentage of the mean) were derived from data. All CVs of the respiratory variables were higher in the patients who successfully separated from

the ventilator than in the subjects who failed. These results are consistent with the findings of Bien et al.[8] in which 78 mechanically ventilated systemic inflammatory response syndrome patients who had undergone abdominal surgery were studied for 30 minutes during SBT while receiving 5 cm H_2O PS. The CV of five respiratory variables were lower in the failure group than in those who successfully extubated. Both studies are in line with our data that increasing breathing variability predicted successful separation from mechanical ventilation.

El-Khatib et al.[6] studied 52 intubated patients for variability in V_T and peak inspiratory flow during synchronized mechanical ventilation (rate $\leq$4 breaths/min) followed by continuous positive airway pressure trials and showed that increased variability in both variables was associated with extubation failure. The majority of the patients in this latter study had underlying lung disease and required a longer duration of ventilator support. For this study, failure was defined as reintubation within 24 hours not caused by stridor. Of note, four patients in our study failed after 24 hours, with none requiring reintubation beyond 48 hours; one was reintubated for stridor. Although this study did not examine these variables, it is different from our hypothesis that variability is associated with improving respiratory health. In fact, these results are in contrast with the two former studies in which the CV of V_T of both success groups was similar (25% and 28%, respectively)[8,9] and also in line with the normal range of tidal variation reported in the literature;[10,21,58] however, the CV for V_T in the success group of El-Khatib et al.[6] was 9%.[6]

Using ApEn, Engoren[7] investigated the regularity of RR and V_T signals in three groups of postcardiac surgery patients. The first group was studied within 12 hours of surgery and underwent SBT with 5 cm H_2O continuous positive airway pressure; all were extubated successfully and served as the control group. The second and third groups consisted of 21 patients who were mechanically ventilated $\geq$7 days and underwent 60 minute to 120 minute SBTs with 5 cm H_2O PEEP and various levels of PS. These were then stratified into success versus failure to wean (with or without extubation), and many subjects contributed more than one weaning attempt to the analysis. In this study, although V_T did not vary between groups, its ApEn was highest in those who failed weaning trials with increasing RR across groups having no effect on pattern. These results are in contrast to recent studies.[8,9] The two experimental groups presented by Engoren were ventilator dependent at the time of the SBT, which were subsequently conducted for 60 minutes to 120 minutes with 5 cm H_2O of PEEP and higher levels of PS. In fact, those with the highest variability were supported with a mean of 12.2 $\pm$ 4.6 cm H_2O of PS. However, the use of PS should reduce V_T variability, because the pressure remains the same for all breaths.[59] Caminal et al.[60] have shown an indirect relationship between PS and the CV of V_T, T_I, and total breath duration.[9] This relationship reflects the unloading of the respiratory system by the ventilator and results in breathing patterns that are more characteristic of the ventilator/patient interface than the patient's own intrinsic rhythm[9,59] and highlights the need to assess "prevailing conditions" (i.e., underlying disease, level of ventilator support, mental status, secretions, drugs, fever, etc.) when studying respiratory variability.[9] Similarly, it may also explain the conflicting data on respiratory variables given the longer duration of mechanical ventilation in some studies.

This study was performed at one Level I trauma center with separate burn and surgical/trauma ICUs, both combining for >800 admissions during the study period. For logistic reasons, more burn patients were enrolled in this study; therefore, the results presented here may not be applicable to other patient populations and need to be validated in a larger, more diverse cohort. A second limitation of this study was that sedation and analgesia were not strictly controlled during the SBT but were left to the attending physician's judgment. General anesthesia has been shown to reduce breathing variability,[9,61] and propofol may cause rapid shallow breathing if continued during SBT.[62] Both benzodiazepines and narcotics depress the respiratory drive, and other drugs (e.g., β blockers and α adrenergics) given at the time of SBT may affect the measured respiratory pattern. Because it has been demonstrated that the respiratory pattern may "speed up" or "slow down" without changing entropy measures,[7] it is not clear what effect these drugs have on respiratory signal regularity. However, enrollment in this study was made at the attending physician's discretion that the patient was ready for the SBT and then possible extubation at the end of the trial. All SBTs were done according to the protocol, with 5 cm H_2O PEEP and PS for 30 minutes, which had been established across ICUs at our institution before initiation of the study. The decision to extubate was made at the end of the SBT by the attending physician, and no patient required reintubation beyond 48 hours, a time point also chosen in two recent studies.[8,9]

We examined the IBI with complexity metrics because previous work demonstrated the fractal organization of this respiratory variable[12,58] and that the central respiratory controller (rhythm generating function) was more constant than its drive components.[10] The use of SampEn has been extensively studied and validated in the cardiac system and was conducted here according to those methodologies. The SOD has complemented the results of SampEn in recent RRI studies.[26,27,34,37] One data set was removed from analysis as a result of artifacts, which made it impossible to analyze. Of the remaining data sets, 200-breath recordings were compared in toto (i.e., the signal was not edited and there were no discontinuities within data sets) from both success and failure groups for calculation of these complexity metrics and SOD; therefore, phasing between data sets remained true. Finally, this study was not designed to determine a threshold value for the tested complexity metrics or SOD that could best discriminate between successful separation and failure to separate from mechanical ventilation. As such, a receiver operating characteristic curve was not constructed for comparison against other established weaning indices.

CONCLUSION

This study found that lower SampEn, BPWEn, and DisNEn and a higher SOD of IBIs were associated with

extubation failure. These findings imply a lower regulatory complexity of respiration in patients who fail extubation as measured by these metrics. Therefore, the above metrics may be useful predictors of a patient's ability to tolerate separation from mechanical ventilation. An effort is underway to identify threshold values for the proposed nonlinear methods that could best discriminate between successful separation and failure to separate from mechanical ventilation. We have developed both software and hardware to interface with standard ventilators which will make calculations of these metrics available in real time. Also, any number of respiratory variables can be measured simultaneously with this microprocessor package, and when integrated together, may be a useful marker of overall pulmonary health.

ACKNOWLEDGMENTS

We acknowledge the expertise, dedication, and professionalism of the U.S. Army Institute of Surgical Research respiratory therapists who participated in the care and treatment of the patients described in this article. We also thank Ms. Otilia Sánchez for her assistance in the preparation of this manuscript.

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