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Pattern of spontaneous breathing: potential marker for weaning outcome

Spontaneous breathing pattern and weaning from mechanical ventilation

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Abstract *Objective*: To quantitatively assess the spontaneous breathing (SB) pattern, during minimal ventilatory support, of patients who pass or fail weaning trials from mechanical ventilation.
Design: A prospective, clinical trial.
Setting: Intensive care unit of a university teaching hospital.
Patients: Fifty-two tracheally intubated and hemodynamically stable patients who were judged clinically ready for extubation.
Methods: Using a computerized respiratory profile monitor, continuous respiratory parameters were obtained while patients were receiving four or less synchronized intermittent mandatory (SIMV) breaths and during CPAP trials. Coefficients of variation (CV) of spontaneous tidal volumes and flows during SIMV trials as well as the entropies and dimensions of the breathing patterns during CPAP trials were used to assess the dynamical breathing behaviors of the patients who passed or failed weaning trials.
Measurements and results: Thirty-nine extubations were successful and 13 were not. The CV of the spontaneous tidal volumes (VT) and the spontaneous peak inspiratory flows (PF), the Kolmogorov entropy and the dimension of the SB patterns were compared in the two groups. The CV of VT (9.13 ± 4.11 vs 26.07 ± 6.94), the CV of PF (11.63 ± 4.18 vs 29.88 ± 12.07), the Kolmogorov entropy (0.09 ± 0.03 bits/cycle vs 0.39 ± 0.09 bits/cycle), and the dimension of the SB pattern (1.33 ± 0.07 vs 3.93 ± 0.47) were all significantly smaller ($P < 0.05$) in the successfully extubated group versus the group that failed extubation.
Conclusion: The spontaneous breathing pattern during minimal mechanical ventilatory support is more chaotic in patients who failed extubation trials compared to patients who passed extubation trials. Thus, we speculate that characterizing the SB pattern during minimal ventilatory support might be a useful tool in differentiating between extubation success and failure.

Key words Breathing pattern · Mechanical ventilation · Weaning outcome

Introduction

Mechanical ventilation is commonly used for both postoperative recoveries and as a life-saving measure for patients suffering from a multitude of medical conditions that result in respiratory failure [1]. However, numerous side effects related to its use exist [2, 3, 4, 5], and therefore mechanical ventilation should be discontinued as soon as the patient can sustain spontaneous respiration with adequate gas exchange [6]. Most commonly, patients are weaned from mechanical ventilation, a process which gradually removes mechanical support as the patient resumes spontaneous breathing. It is important to know when a patient's medical condition is most compatible with an extubation trial. An extubation trial undertaken too early may predispose the patient to severe cardio-respiratory [7] and/or psychological decompensation [8] while prolonged unnecessary mechanical ventilation exposes the patient to serious risks [9, 10].

Recent studies [10, 11, 12, 13] revealed that new integrative indexes, such as the rapid shallow breathing and CROP (Compliance, Rate, Oxygenation, Pressure) indexes, used to predict outcome of weaning and extubation from mechanical ventilation, were superior to traditional indexes such as vital capacity, maximal inspiratory pressure, blood gases, respiratory rate, and minute ventilation. Because of their mathematical nature (i.e., mathematical ratios), these new integrative indexes could be misleading (i.e., same numerical value for the integrative index could be obtained with an infinite combination of its constituent parameters). This originates from the fact that most of the constituent parameters of the integrative indexes, such as the tidal volume and the respiratory rate, are derived at a single point in time such as end of inspiration or expiration in the case of tidal volume and the total number of breaths in a 1-minute time interval in the case of respiratory rate. The different possible rates of change of tidal volume (i.e., fast or slow delivery of tidal volume) and the distribution of breaths in 1-minute intervals are not reflected in these integrative indexes. Therefore, quantitative assessment of the respiratory pattern, which is continuously providing information in real-time at any point during the breathing cycle, might be needed for a better and superior decision-making process regarding weaning from mechanical ventilation.

The purpose of the present study is to quantitatively assess the spontaneous breathing pattern of patients who pass or fail weaning trials from mechanical ventilation.

Materials and methods

This study was approved by the Institutional Review Board and written consent was waived due to the nature of the study.

Patient population

All hemodynamically and clinically stable patients receiving mechanical ventilation in the ICU due to acute respiratory failure of different origin, and judged ready to undergo an extubation trial by their primary physician, were included in the study. The primary physicians were blinded to the study design and to the measurements obtained during the study, although arterial blood gas values and routine measurements by respiratory therapists (i.e., spontaneous tidal volume, spontaneous and total respiratory rate, peak airway, and peak alveolar pressures) were available to them. All patients were monitored with continuous electrocardiography, blood pressure, and pulse oximetry during the whole study.

Study protocol

At the time of the inclusion in the study, all patients were mechanically ventilated (Puritan-Bennett 7200, Mallinckrodt, St. Louis, Mo., USA) with minimal ventilatory support (i.e., synchronized intermittent mandatory ventilation (SIMV) rate ≤4 breaths/min) with no pressure support ventilation and with an FiO_2 of 40%. A computerized pulmonary mechanics monitoring system (COSMO+, Novametrix Medical Systems, Conn., USA), incorporating an adult flow sensor placed between the endotracheal tube (ETT) and the Y-piece of the breathing circuit, was used to measure the pressure, volume, and flow signals for at least 60 min. These parameters were displayed and stored using a laptop computer. An additional 60 min of data were collected, as previously described, during a CPAP of 5 cmH_2O trial with no pressure support ventilation (PSV). Heart rate and blood pressure were also recorded. Once the above data have been collected, patients underwent extubation trials under the direction of the primary medical team responsible for their management. The decision to extubate the patient or to re-institute mechanical ventilation was made solely by the primary medical team who was totally blinded to the data collected. Unsuccessful extubation was defined as the need for re-intubation within the first 24 h following extubation trials. Re-intubation due to upper airway trauma (stridor) was not considered as failure and those patients were excluded from the study. Patients were finally separated into two different groups according to their extubation outcomes (group 1: passed extubation; group 2: failed extubation).

Data and statistical analysis

In both patient groups, breath-to-breath values for airway flow, volume, and proximal airway pressure collected on each patient were divided into three different intervals each of 300 breaths. During the SIMV trials, the spontaneous and mechanical peak flow versus the spontaneous and mechanical tidal-volume scattergrams were constructed for each data interval of each patient. Coefficients of variation for spontaneous peak flow (PF) and spontaneous tidal volume (VT) were determined for each data interval separately and for the whole 900 breaths.

Furthermore, in both groups, advanced chaos theories were employed for quantitative assessment of the breathing patterns during the continuous positive airway pressure trial (CPAP). The Kolmogorov entropy [14, 15, 16], which measures the amount of regularity in a series, and is defined as the divergence of nearby breaths within the respiratory phase space (i.e., flow-volume loops) was determined using at least 300 breaths collected during CPAP trials. Similarly, the dimension of the spontaneous respiratory pattern(s), defined as the number of clusters or clouds of trajectories in the flow-volume loops space was determined for each data interval. As such, higher values for the entropy and/or the dimension indicate less regularity in the pattern and thus more variability and chaos.

The Student *t*-test was used to compare the coefficients of variation of spontaneous peak flows and volumes, the Kolmogorov entropies, and the dimension of the spontaneous breathing pattern between the successful and unsuccessful extubation patient groups. Statistical significance was considered at the 5% level (i.e., $P < 0.05$).

Table 1 Age, days on ventilators, arterial blood gases (mean ± SD) and gender in the two groups of patients (*ETT* endotracheal tube, *ID* internal diameter)

	Age (years)	M/F	Days on ventilator	ETT ID (mm)	ETT length (cm)[a]	PaO_2	$PaCO_2$	pH
Successful outcome (n = 39)	52 ± 17	27/12	11.8 ± 3.1	7.6 ± 0.3	31.4 ± 0.7	103 ± 27	42 ± 7	7.42 ± 0.05
Unsuccessful outcome (n = 13)	49 ± 18	9/4	11.3 ± 3.3	7.6 ± 0.5	31.8 ± 0.4	101 ± 24	41 ± 6	7.41 ± 0.09

[a]Including plastic connector

Results

Fifty-two patients in the intensive care unit (ICU) were included in the study. Their mean age was 50.3 ± 17.7 years old (range, 27–76 years). There were 36 males (69 %) and 16 females (31 %). Patients were ventilated for 11.5 ± 3.1 days (range, 8–16 days).

Thirty-four patients (65 %) had underlying lung disorders or pneumonia, five patients (10 %) had a neurologic condition, four patients (6 %) had pulmonary edema, and nine patients (17 %) had miscellaneous conditions.

Of the 52 patients included in the study, 39 (75 %) patients were successfully extubated. The remaining 13 patients (25 %) were re-intubated and mechanical ventilation was re-instituted within 24 h following the extubation trials. The two patient groups did not have any significant difference in terms of gender, age, duration on mechanical ventilation, and arterial blood gases prior to data collection (Table 1).

The scattergrams of the peak flows versus tidal volumes for one patient in the successfully extubated group and another patient from failed extubation group are presented in Figs. 1 and 2, respectively. Breaths at high peak flows and tidal volumes represent mechanical breaths, whereas breaths at lower peak flows and tidal volumes represent spontaneous breaths. While the mechanical breaths are very reproducible, the spontaneous breaths remain reproducible in the successfully extubated patient (Fig. 1) and become variable in the patient who failed the extubation trial (Figure 2).

During CPAP trials, patients in the successfully extubated group reflected a more reproducible breathing pattern and less breath-to-breath variability in tidal volume and peak inspiratory flow (Fig. 3) in contrast to patients in the failure extubation group (Fig. 4).

The coefficients of variation of the spontaneous peak flows and spontaneous tidal were statistically higher ($P < 0.05$) in the group of patients that failed the weaning trials compared to the group of patients that passed the weaning trials for each data interval (Table 2).

Furthermore, the Kolmogorov entropy and the breathing pattern dimension were statistically higher ($P < 0.05$) in the group of patients that failed the weaning trials compared to the group of patients that passed weaning trials (Table 3).

Discussion

The findings of the current study suggest that breath-to-breath variability in the spontaneous tidal volumes and

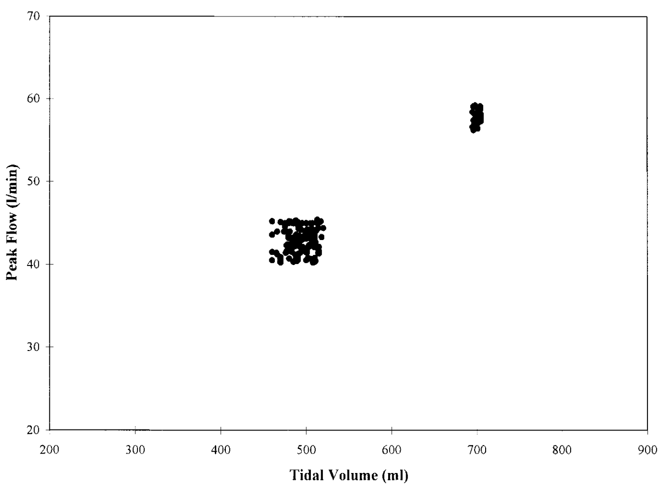

Fig. 1 Peak flow rates and tidal volumes for a patient who passed a weaning trial (data collected during SIMV)

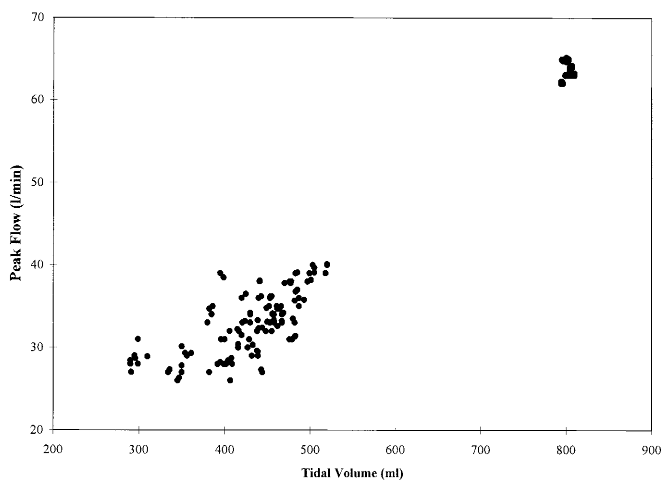

Fig. 2 Peak flow rates and tidal volumes for a patient who failed a weaning trial (data collected during SIMV)

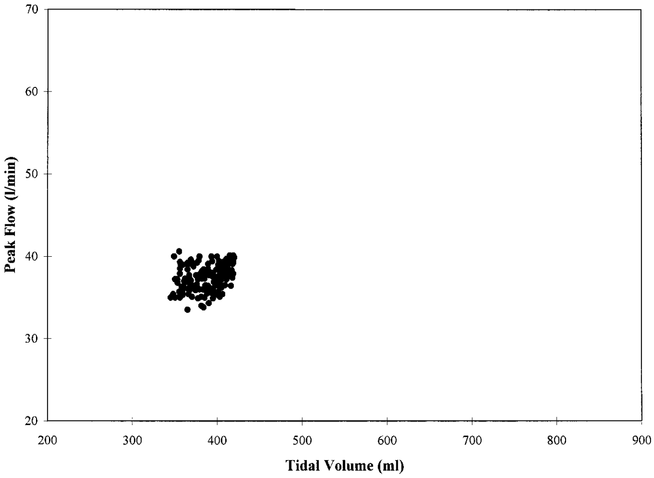

Fig. 3 Peak flow rates and tidal volumes for a patient who passed a weaning trial (data collected during CPAP)

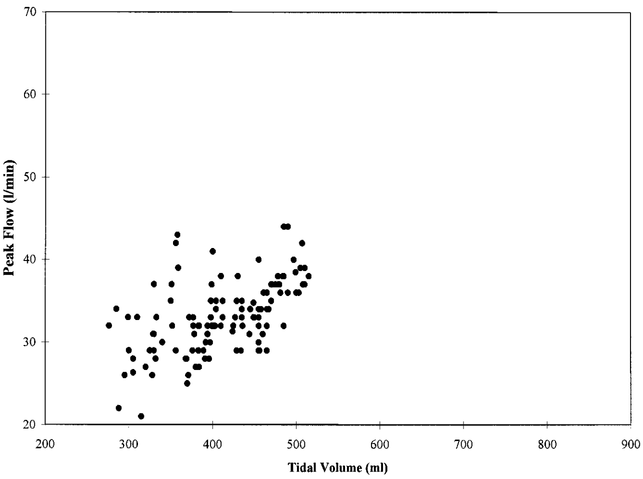

Fig. 4 Peak flow rates and tidal volumes for a patient who failed a weaning trial (data collected during CPAP)

spontaneous flows during minimal ventilatory support are more irregular in patients who fail weaning trials than in patients who pass weaning trials from mechanical ventilation. Furthermore, the spontaneous breathing pattern, reflected by the entropy and dimension of the flow-volume respiratory phase space, is more chaotic in patients who fail weaning trials in comparison to patients who pass weaning trials from mechanical ventilation.

The characteristics of the group of patients who passed weaning trials were not different from those who failed weaning trials. Patients in both groups were similar in gender, age, previous days on mechanical ventilation, and blood gases at study entry. The distribution of diagnoses in the successful group (26 patients with primary lung disease/pneumonia, four patients with neurological diseases, two patients with lung edema, and seven patients with miscellaneous conditions) was also similar to the failure group (eight patients with primary lung disease/pneumonia, one patient with neurological disease, two patients with lung edema, and two patients with miscellaneous conditions). As such, it is less likely that the differences seen in the pattern of breathing of these patient groups could be contributed to the patient characteristics.

Table 2 Coefficients of variation (mean ± SD) of the spontaneous VT and PF for the three data intervals in the two patient groups during SIMV trials

Data interval (no. of breaths)	Group (no. of patients)	CV of VT	CV of PF
I (300)	Passed (39)	8.71 ± 3.74	10.76 ± 3.38
II (300)	Passed	10.28 ± 6.02	12.37 ± 5.15
III (300)	Passed	8.93 ± 4.01	11.11 ± 4.70
I+II+III (900)	Passed	9.13 ± 4.11	11.63 ± 4.18
I (300)	Failed (13)	24.14 ± 4.44*	26.73 ± 9.93*
II (300)	Failed	26.88 ± 6.31*	29.12 ± 10.88*
III (300)	Failed	27.52 ± 8.61*	32.55 ± 15.21*
I+II+III (900)	Failed	26.07 ± 6.94*	29.88 ± 12.07*

*$P < 0.05$ compared to interval in the "Passed" group

Table 3 The entropy and dimension (mean ± SD) of the spontaneous breathing pattern in the two patient groups during CPAP trials

	Successful outcome ($n = 39$)	Unsuccessful outcome ($n = 13$)
Entropy (bits/cycle)	0.09 ± 0.03	0.39 ± 0.09*
Dimension	1.33 ± 0.07	3.39 ± 0.47*

*$P < 0.05$

Fabry et al. [17] recently studied the breathing pattern and additional work of breathing due to ETT resistance with conventional inspiratory pressure support (IPS) and automatic tube compensation (ATC) modes of ventilatory support. They reported a more physiologic breathing pattern and a better compensation of added work of breathing due to ETT during ATC. In the current study, the ETT resistance was not different in the two patient groups. This is indicated by similar ETT inner diameter and length (Table 1). However, our data indicate higher interbreath variability and irregularity of flow in the group of patients who failed weaning outcome (Table 2). As such, although there was no difference in the ETT resistance, the pressure required to overcome the ETT resistance would still be more variable and irregular due to the interbreath variability of the flow in the group of patients who failed weaning outcome.

Various inputs are involved in the generation of the breathing pattern. Inputs from peripheral and central chemoreceptors, vagal afferents, chest wall and pulmonary receptors [18, 19, 20, 21], as well as non-respiratory central mechanisms [22, 23], are integrated into the central pattern generator in the brainstem to modulate the breathing pattern. Little has been done to characterize the effects of respiratory failure on respiratory pattern. Tobin et al. [24] indicated that the development of hypercapnia and respiratory acidosis in patients who fail weaning trials are due primarily to the immediate rapid, shallow breathing pattern following discontinuation of mechanical ventilation. Murciano et al. [25] reported that COPD patients with unsuccessful weaning outcome exhibited high values of mouth occlusion pressure, a sign of high neuromuscular inspiratory drive. Cohen et al. [26] attributed unsuccessful weaning outcome to inspiratory muscle fatigue. In fact, their patients demonstrated a shift in the electromyographic power spectrum of the diaphragm (increase of low-frequency power with concomitant decrease of high-frequency power, an index of impeding fatigue) virtually as soon as assisted ventilation was discontinued. Chemical feedback loops are affected in disease and their recovery would reflect improvement and recovery of the breathing regularity. For example, patients with congestive heart failure and poor cardiac output can develop a Cheyne-Stokes breathing pattern which is a typical manifestation of respiratory irregularity; this irregularity would reverse with the treatment of the congestive heart failure.

In recent years, there has been an increasing number of studies related to respiratory pattern analysis in patients with respiratory failure necessitating mechanical ventilation. Aarimaa et al. [27] reported that premature neonates had an irregular breathing pattern that necessitated mechanical ventilation and which became progressively regular over several days as the respiratory control systems matured. Previous studies [28, 29] have suggested that auto-regressive structures of VT in animals and humans reflected chemical feedback loops and thus could be associated with the breath-to-breath changes in blood gases. Samon and Bruce [16] reported that with anesthesia or following vagotomy, the breathing pattern is more regular and predictable. Bruce and Daubenspeck [30] suggested that a high degree in irregularity of the breathing pattern is considered abnormal and is associated with high morbidity. A recent study [31] found that approximate entropy (ApEn) of tidal volume is a moderately accurate predictor of weaning mechanical ventilation and that tidal volume patterns become increasingly irregular with failure to wean from mechanical ventilation. These findings are in agreement with our study. However, patients in the Engoren study [31] were cardiac patients undergoing cardiac surgeries, while our patient population consisted of medical ICU patients with predominantly lung diseases. In addition, in the study by Engoren [31], an average pressure support of 12 cmH_2O was applied during spontaneous trials. In contrast, our data was collected with no pressure support ventilation (PSV), although PSV might have been used in the management of the patients. Pressure-support ventilation is a form of mechanical ventilatory support that assists an intubated patient's spontaneous inspiratory effort with a clinician-selected amount of positive airway pressure [32]. This inspiratory pressure is held constant through continuous servo control of delivered flow and is terminated when a certain inspiratory flow minimum is reached [33]. In the current study, no restrictions or limitations in terms of inspiratory pressure and termination of inspiration were imposed on the spontaneous breaths and, as such, we elected not to use PSV during data collection. Wrigge et al. [34] reported that the degree of interbreath variability of spontaneous breathing pattern during PSV is smaller versus a proportional-assist ventilation of 80 % (PAV80) but not different from PAV50. They concluded that higher variability of tidal volume (VT) during PAV80 indicates an increased ability of patients to control VT in response to alteration in respiratory demand. These findings are not in disagreement with the current study because the studies designs are different. In the current study, the level of interbreath variability in the spontaneous pattern of the group of patients who failed weaning outcome was higher than that reported by Wrigge et al. (26 % vs 20 %). In addition, the variability of spontaneous breaths in the current study was determined from spontaneous breaths occurring between SIMV breaths. This is in contrast to the Wrigge et al. study in which data was obtained during either PSV where each breath is supported with a prescribed inspiratory pressure level ($PS = 18.7 \pm 3.5$ cmH_2O) or during PAV where compensation of the respiratory system compliance and resistance was the same for each breath (80 % and 50 %).

Our results showed that coefficients of variations obtained from data intervals of 300 breaths are similar to those obtained from data intervals of 900 breaths. During minimal ventilatory support, 900 breaths may take 45–60 min while 300 breaths may take only 15–20 min. A smaller data interval can permit a much faster determination of how well the patient is tolerating the weaning trial and expedite the advancement to a lower level of ventilatory support, and hence, a more accelerated weaning from mechanical ventilation or a return to a higher level of ventilatory support if the patient is not tolerating the weaning trial.

The current study was not designed to determine a cut-off threshold in terms of the regularity and/or the level of chaos in the spontaneous breathing that can best discriminate between successful and unsuccessful outcomes of weaning trials. As such, the sensitivity and specificity of the coefficients of variations of spontaneous tidal volumes, the spontaneous peak flows, the entropy, and the dimension of the breathing pattern was not determined and compared to other established weaning indexes. However, the fact that the spontaneous breathing pattern during minimal ventilatory support is more chaotic in patients who fail weaning trials is well supported in the current study.

In the current study, the pattern analysis was applied to inspiratory flow and tidal volume. Other pattern components such as minute ventilation, respiratory frequency, and the duty cycle (ratio of inspiratory time over total cycle time) are as important. However, the use of chaos theories such as the entropy and dimension of the breathing pattern necessitates the use of a respiratory pattern parameter and its rate of change over time. The inspiratory flow and tidal volume serve this requirement adequately.

The advanced mathematical computations and chaos theories remain the major limitation of this study. Data collection and analysis involve the use of advanced calculation algorithms to determine the entropy and dimension of the breathing pattern. However, with the new advancement in the technology of mechanical ventilators that are becoming microprocessor based, such sophisticated computations could be obtained and could be made readily available for health care providers at the patient's bedside.

The coefficient of variation was primarily used to characterize the SIMV trials, whereas the Kolmogorov entropy and dimension of the spontaneous breathing pattern was used primarily to characterize the CPAP trials. The use of the Kolmogorov entropy and the dimension of the pattern during SIMV trials will be influenced by the presence of reproducible and predictable mechanical breaths. Thus, the use of Kolmogorov entropy and the dimension of the pattern which are powerful indicators and measures of the amount of variability and regularity could only be used during CPAP trials although the coefficients of variation (CV) were used during CPAP trials (Figs. 3 and 4) and showed more interbreaths variability in the group of patients who failed weaning outcome. However, during CPAP, the use of the entropy remains more powerful and indicative than the CV in characterizing the breathing pattern. This is because where the CV only represents the tidal volume at one point in time (i.e., end inspiration or end expiration), the entropy reflects information in real-time over the whole inspiratory or expiratory time.

In summary, this study found that a more regular breathing pattern was associated with the ability to tolerate weaning from mechanical ventilation in ICU patients. In contrast, an irregular and chaotic breathing pattern was associated with the inability to tolerate weaning from mechanical ventilation in ICU patients. Thus, this regularity-irregularity pattern could be exploited as a sensitive indicator of recovery in complex disease states requiring mechanical ventilation. In this study, we were able to identify quantitative markers – entropy and dimension – which might be of great clinical usefulness in managing patients on mechanical ventilation. However, additional prospective and controlled studies are needed to identify cut-off values for entropy and dimension (which reflect the degree of irregularity and chaos) of the breathing pattern that can best discriminate between successful and unsuccessful outcomes of weaning trials from mechanical ventilation. If the characterization of the spontaneous breathing pattern during mechanical ventilation is capable of predicting when a weaning trial will be successful, this could decrease the length of stay of patients in the intensive care setting, improve health care delivery, successfully establish weanability from mechanical ventilation – thus saving resources, such as physician and nursing time – and decrease health care costs. In addition, more studies are needed to identify the sources that could affect or contribute to the breathing pattern irregularities. Such studies could be helpful in designing management strategies that can expedite successful discontinuation of mechanical support and minimizing risks associated with mechanical ventilation.

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