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Breathing pattern variability: a weaning predictor in postoperative patients recovering from systemic inflammatory response syndrome

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Abstract *Objective:* To investigate whether breathing pattern variability can serve as a potential weaning predictor for postoperative patients recovering from systemic inflammatory response syndrome (SIRS). *Design and setting:* A prospective measurement of retrospectively analyzed breathing pattern variability in a surgical intensive care unit. *Patients:* Seventy-eight mechanically ventilated SIRS patients who had undergone abdominal surgery were included when they were ready for weaning. They were divided into success (n=57) and failure (n=21) groups based upon their weaning outcome. *Measurements and results:* Before weaning, tidal volume, total breath duration, inspiratory time, expiratory time, and peak inspiratory flow were continuously monitored for 30 min, while patients received 5 cmH_2O pressure support weaning trial. After the patients successfully completed the trial, they were extubated. Successful weaning was defined as patients free from the ventilator for over 48 h, whereas a weaning failure was considered as reinstitution of mechanical ventilation within 48 h of extubation. The coefficient of variation and two values of standard deviation (SD_1 and SD_2; indicators of the dispersion of data points in the plot) obtained from the Poincaré plot of five respiratory parameters in the failure group were significantly lower than those in the success group. The area under the receiver operating characteristic curve of these variability indices was within the range of 0.73–0.80, indicating the accuracy of prediction. *Conclusions:* Small breathing pattern variability is associated with a high incidence of weaning failure in postoperative patients recovering from SIRS, and this variability may potentially serve as a weaning predictor.

Keywords Respiratory center · Postoperative care · Sepsis syndrome · Ventilators, mechanical · Ventilator weaning · Receiver operating characteristic curve

Introduction

Both prolonged ventilatory support and premature weaning are adverse for patients with mechanical ventilation [1, 2]. Several weaning predictors, including tidal volume, respiratory rate, minute ventilation, rapid shallow breathing index (RSBI), maximal inspiratory pressure (Pimax) and airway occlusion pressure at 0.1 s ($P_{0.1}$), have been developed and applied in clinical settings [3, 4, 5, 6, 7]. Among these predictors the RSBI is better than the others for predicting weaning success [3, 7]. However, the RSBI loses some discriminatory power in certain patient groups [3, 8], and threshold values of RSBI and $P_{0.1}$ vary between different patient populations [3, 4, 5, 6, 7, 8, 9]. Patients with systematic inflammatory response syndrome (SIRS) or sepsis usually present rapid breathing pattern leading to hyperventilation [10]. When septic patients recover, they still have a higher respiratory rate to tidal volume ratio, lower Pimax, greater incidence of first-day weaning failure, and longer duration for ventilatory support than patients without sepsis [11]. The clinically used weaning predictors are usually unable to predict their weaning outcome accurately [11]. No study has been conducted to search for reliable weaning predictors for SIRS patients.

Two groups of time-series data may have the same mean values but different variabilities [12]. Analysis of variability thus provides an alternative method to describe the difference between two groups of data. The breathing pattern in normal subjects displays a certain variability [13, 14, 15], which is maintained by a central neural mechanism and the feedback loops of arterial chemoreceptors and lung vagal sensory receptors [14, 16]. Peripheral factors, such as mechanical and chemical changes within the respiratory system may modify the breathing pattern variability [17, 18, 19]. Deviations in breathing pattern variability from the normal level have been found in individuals under pathological conditions [20, 21, 22]. Quantitative methods, including calculations of coefficients of variation and the Poincaré plot, have been applied to the analysis of breathing pattern variability to serve as indicators of pathophysiological conditions in patients with respiratory diseases [20, 21, 22] or weaning outcome in patients with respiratory failure [23]. The Poincaré plot analysis is a scattergram that dynamically analyzes breathing pattern on a real-time, breath-to-breath basis and its clinical benefit has been well recognized in the analysis of heart rate variability [24]. SIRS is known dramatically to disturb the physiological regulation of nearly all organs [10]. Whether breathing pattern variability can serve as a weaning predictor for SIRS patients remains to be investigated.

A low level of pressure support ventilation (PSV) is commonly used during weaning trials [25], while patient's breathing pattern can be measured. Therefore this study investigated whether the breathing pattern variability measured during 5 cmH_2O PSV can serve as a potential weaning predictor in postoperative patients recovering from SIRS.

Methods

Further details of the methods can be found in the Electronic Supplementary Material.

Subjects

Seventy-eight consecutive, mechanically ventilated SIRS patients [10] who had undergone abdominal surgery were included when they were judged to be clinically ready for weaning. They were divided into success (*n*=57) and failure (*n*=21) groups based upon the weaning outcome. They were mechanically ventilated with PSV mode and the pressure level setting was between 10 and 20 cmH_2O to maintain a tidal volume around 10 ml/kg body weight. Other ventilator's settings were: fraction of inspired oxygen concentration 40% or less, positive end-expiratory pressure 5 cmH_2O, and sensitivity setting on –2 cmH_2O. Sedatives, hypnotics, and narcotics were discontinued after midnight and at least 8 h prior to the study. Appropriate institutional review board approval and written informed consent were obtained.

Protocol

Within 1 h before the measurement of breathing pattern variability routine measurements of clinically used weaning predictors including Pimax, respiratory rate, minute ventilation, calculated tidal volume, and RSBI were performed using methods reported previously [26, 27]. After obtaining these data the patient's mechanical ventilation was quickly resumed. When patients were subjected to the weaning trial, the ventilator mode was switched to 5 cmH_2O PSV plus 5 cmH_2O positive end-expiratory pressure (PEEP) [28] and other settings remained the same. A pulmonary mechanics monitoring system (Ventrak 1550; Novametrix Medical Systems, Wallingford, Conn., USA) was used to continuously measure the pressure, volume and flow signals for 30 min. The trial was terminated and the ventilator was switched back to the previous level of pressure support if the patient had one or more of signs of cardiopulmonary distress [25] listed in Table 1. When the patients completed the 30 min PSV trial, they were extubated and used nasal cannula or air-entrainment mask for supplemental O_2 therapy. Successful weaning was defined as patients free from the ventilator for over 48 h after extubation. A weaning failure was considered as reinstitution of either noninvasive or invasive mechanical ventilation within 48 h of extubation because patients presented any signs of cardiopulmonary distress listed in Table 1.

Data analysis

Data on expired tidal volume, total breath duration, inspiratory time, expiratory time, peak inspiratory flow, and $P_{0.1}$ were analyzed on a time-series breath-to-breath basis for a period of 30 min, and their average values over this period of time were calculated. Artifacts such as cough, swallowing, and ineffective respiratory effort were not included in our analysis. For the Poincaré plot analysis each value of the respiratory parameter of the current breath is plotted against the value of the immediately following breath for a predetermined segment (30 min; Fig. 1B). In each patient more than 300 successive breaths were plotted. The plot was quantified by two values of standard deviation, SD_1 and SD_2. SD_2 is defined as the dispersion of points along the line-of-identity,

Table 1 Signs of cardiopulmonary distress presented in patients of the failure group; all patients in the failure group presented at least two signs

	n
Tachypnea: respiratory rate >35 breaths/minute for $\geq$5 min	15
Hypoxemia: arterial oxygen saturation measured by the pulse oximeter <90% in spite of increasing FIO_2 to 50% for $\geq$30 s	10
Significant changes in heart rate: >140 beats/min or a 20% increase or decrease from baseline for $\geq$ 1 min	8
Hypertension or hypotension: systolic arterial blood pressure >180 or <90 mmHg for $\geq$1 min	6
Significant arrhythmia: $\geq$30 s	0
Agitation, diaphoresis, or anxiety	14

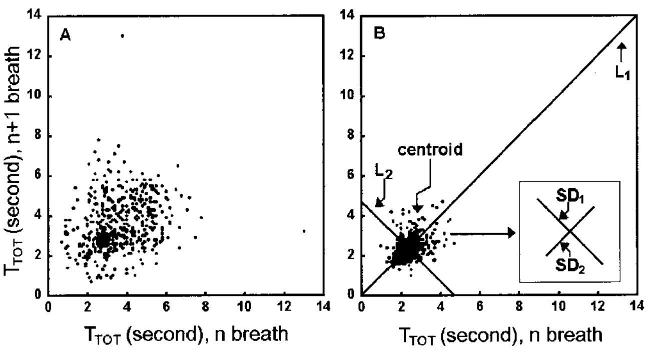

Fig. 1 Poincaré plots of total breath durations (T_{ToT}) measured in two patients from the success (**A**) and failure (**B**) groups. In each patient more than 300 successive breaths were plotted. Quantitative analysis of the plot is illustrated in **B** and presents as two values of standard deviation, SD_1 and SD_2. As shown, SD_2 is defined as the dispersion of points along the line-of-identity (L_1), whereas SD_1 is defined as the dispersion of points perpendicular to the line-of-identity (L_2) through the centroid of the plot. The centroid is located at the coordinates in the plot expressed mathematically as ($T_{TOTaver}$, $T_{TOTaver}$), where $T_{TOTaver}$ is the average value for T_{ToT} of the predetermined segment (30 min). Note that the distribution of the data points in panel B is less scattered than those in **A**

whereas SD_1 is defined as the dispersion of points perpendicular to the line-of-identity through the centroid of the plot. The centroid is located at the coordinates in the plot expressed mathematically as (X_{aver}, X_{aver}), where X_{aver} is the average value for each respiratory parameter of the predetermined segment. The SD_1-to-SD_2 ratio represents the shape of the scattergram, as suggested by previous studies [24, 29]. For each respiratory parameter the coefficient of variation and SD_1 as well as SD_2 obtained from the Poincaré plot analysis were calculated to give indices of breathing pattern variability. The average value of $P_{0.1}$ which was measured on a breath-to-breath basis when patients triggered the ventilator [30], and other clinically used weaning predictors were also calculated.

Statistical analysis

Categorical variables were analyzed by Fisher's exact test. Continuous variables were analyzed by t test or Wilcoxon two-sample test. The correlation between breathing pattern variability and the duration of ventilatory support before the measurement was analyzed by Spearman's rank-order correlation. The predictive performances of the indices of breathing pattern variability and clinically used weaning predictors were assessed by analysis of the receiver operating characteristic (ROC) curve [3, 31].The areas under the ROC curve are presented as mean±SEM and evaluated with paired t test for pairwise comparisons [32]. Other data are presented as mean±SD. Differences at the level of $p<0.05$ were considered statistically significant.

Results

Patient characteristics

All subjects in this study successfully completed the 30-min measurement during the 5 cmH_2O PSV weaning trial. However, 21 patients presented signs of weaning failure (Table 1) after extubation (mean duration 459±633 min, range 20–2600). Nine patients were treated with bilevel positive pressure ventilation via a face mask, and the remaining patients were reintubated and reconnected to the ventilator. The physical and clinical characteristics of these two groups are listed in Table 2. Values of the total duration of ventilatory support, intensive care unit (ICU) stay, hospital stay, and Acute Physiology and Chronic

Table 2 Physical and clinical characteristics. Systolic and diastolic blood pressure, SpO_2 and $PetCO_2$ were measured before the 30-min period of measurement (*ID* internal diameter, *SpO_2* oxygen saturation measured by pulse oximeter, *$PetCO_2$* end-tidal CO_2 tension measured by capnograph)

	Success (n=57)	Failure (n=21)
Age (years)	67.5±15.1	70.6±12.5
Sex: M/F	45/12	15/6
Artificial airway ID (7/7.5 mm)	13/44	5/16
Diagnosis: abdominal malignancy	20	3
Inflammatory bowel	12	6
Hollow organ perforation	11	9
Intestinal obstruction	6	3
Abdominal trauma	4	0
Biliary operation	1	0
Miscellaneous	3	0
Body mass index	23.4±4.6	23.1±4.9
Operation duration (h)	5.2±2.8	5.2±2.3
Systolic blood pressure (mmHg)	134.8±25.0	126.5±19.3
Diastolic blood pressure (mmHg)	74.3±13.5	68.9±9.7
SpO_2 (%)	97.7±1.3	97.1±2.2
$PetCO_2$ (mmHg)	31.8±5.9	31.6±5.1
APACHE II on admission to ICU	17.9±7.1	21.5±5.7*
Mechanical ventilation duration (h)	70.9±81.8	122.3±118.2*
ICU stay (days)	6.4±4.9	21.9±12.8*
Hospital stay (days)	35.7±21.9	56.5±28.0*

* $p<0.05$ vs. the success group

Table 3 Average values, coefficients of variations, and results of Poincaré plot analysis for five breathing pattern parameters measured from the success and failure groups. The units shown in the table for each parameter are for values of average, SD_1 and SD_2; values for CV and SD_1/SD_2 do not have units (*CV* coefficient of variation)

	Mean	CV	Poincaré plot		
			SD_1	SD_2	SD_1/SD_2
Tidal volume (l)					
Success	0.44±0.17	0.28±0.15	0.07±0.07	0.11±0.11	0.74±0.17
Failure	0.39±0.13	0.18±0.09*	0.04±0.02*	0.05±0.03*	0.74±0.21
Total breath duration (s)					
Success	3.37±0.80	0.31±0.15	0.75±0.52	0.83±0.50	0.87±0.14
Failure	2.75±0.97*	0.20±0.12*	0.38±0.34*	0.47±0.43*	0.82±0.21
Inspiratory time (s)					
Success	1.22±0.27	0.23±0.16	0.20±0.23	0.24±0.25	0.88±0.14
Failure	0.97±0.19*	0.14±0.10*	0.10±0.10*	0.11±0.10*	0.93±0.20
Expiratory time (s)					
Success	2.15±0.72	0.43±0.21	0.69±0.53	0.75±0.50	0.89±0.14
Failure	1.78±0.84*	0.27±0.16*	0.35±0.35*	0.43±0.41*	0.83±0.20
Peak inspiratory flow (l/min)					
Success	35.08±5.61	0.16±0.06	3.18±1.90	4.55±2.17	0.70±0.20
Failure	36.65±6.89	0.10±0.05*	1.96±1.09*	2.92±1.54*	0.68±0.19

* p<0.05 vs. the corresponding parameter in the success group.

Health Evaluation (APACHE) II score on admission to ICU recorded in the failure group were significantly greater than those in the success group. Other characteristics did not vary between these two groups.

Average values and coefficients of variation

Table 3 shows average values and coefficients of variation of five breathing pattern parameters measured in the success and failure groups. Average values of total breath duration, inspiratory time, and expiratory time, and coefficient of variation of all five breathing pattern parameters in the failure group were significantly lower than those in the success group (p<0.01). Average values of tidal volume and peak inspiratory flow between the two groups showed no statistical significance.

Poincaré Plot Analysis

Figure 1 shows typical examples of Poincaré plots of the total breath duration measured in two patients from each group. As shown, distribution of data points in the success group is more scattered than that in the failure group. The group data of the Poincaré plot analysis of five breathing pattern parameters measured are listed in Table 3. It was found that SD_1 and SD_2 of each breathing pattern parameter in the failure group were significantly lower than those in the success group (p<0.001); the SD_1-to-SD_2 ratio between these two groups showed no statistical significance.

Further analyses revealed that the mean, coefficient of variation, SD_1, and SD_2 of both expiratory time and total breath duration had an inverse correlation with the duration of ventilatory support before the measurement (r values between −0.297 and −0.409, p<0.01; Table 1 of Electronic Supplementary Material). However, tidal volume, inspiratory time, and peak inspiratory flow had no significant correlation with the duration of ventilatory support.

Table 4 Nine clinically used weaning predictors measured from the success and failure groups (*$P_{0.1}$* airway occlusion pressure at 0.1 s expressed as absolute value, *Pimax* maximal inspiratory pressure, *RSBI* rapid shallow breathing index)

	Success (n=57)	Failure (n=21)
$P_{0.1}$ (cmH_2O)	1.62±0.67	1.97±0.54*
Pimax (cmH_2O)	−42.37±13.09	−37.00±11.05
$P_{0.1}$/Pimax	0.0417±0.0203	0.0563±0.0183*
Tidal volume (l)	0.462±0.154	0.394±0.144
Tidal volume/body weight (ml/kg)	7.57±2.99	6.59±2.39
Respiratory rate (b/min)	18.21±5.45	24.29±6.49*
Minute ventilation (l)	8.00±2.29	9.19±3.08
RSBI ($b\ min^{-1}\ l^{-1}$)	44.99±22.64	68.94±29.67*
$P_{0.1}$x RSBI ($cmH_2O\ b^{-1}\ min^{-1}\ l^{-1}$)	73.94±47.50	140.05±81.78*

* p<0.05 vs. the success group.

Clinically used weaning predictors

Table 4 shows average values of nine clinically used weaning predictors measured in the success and failure groups. It was found that $P_{0.1}$, $P_{0.1}$/Pimax, respiratory rate, RSBI, and $P_{0.1}$×RSBI measured in the failure group significantly differed from those in the success group.

Table 5 Area under the receiver operating characteristic curve for predictors obtained from analysis of breathing pattern variability. Values were derived from the data set comparing 57 patients who had successful weaning and 21 patients who failed to wean

	CV	Poincaré plot	
		SD_1	SD_2
Tidal volume	0.75±0.06	0.75±0.06	0.77±0.06
Total breath duration	0.75±0.06	0.78±0.05	0.77±0.06
Inspiratory time	0.75±0.06	0.79±0.05	0.79±0.05
Expiratory time	0.76±0.06	0.76±0.06	0.74±0.06
Peak inspiratory flow	0.80±0.05	0.73±0.06	0.77±0.05

Average values of other four predictors between these two groups showed no statistical significance.

Accuracies of weaning predictors

For clinically used weaning predictors, areas under the ROC curve of $P_{0.1}$, $P_{0.1}$/Pimax, respiratory rate, RSBI and $P_{0.1}$×RSBI were 0.72±0.07, 0.75±0.07, 0.77±0.07, 0.71±0.07 and 0.75±0.07, respectively. Areas under the ROC curve for various predictors obtained from the analysis of breathing pattern variability are listed in Table 5 and were within the range of 0.73–0.80. None of the values of the areas under the ROC curve listed in Table 5 statistically differed from any of the values for these five clinically used weaning predictors.

Discussion

Results of this study demonstrate that mechanically ventilated postoperative patients recovering from SIRS who failed to wean had lower values for the coefficient of variation and for SD_1 and SD_2 obtained from the Poincaré plot of five breathing pattern parameters than postoperative patients recovering from SIRS who were successfully weaned. Analysis of the ROC curves reveals that the area under the curves for these indices was within the range of 0.73–0.80, which was similar to that (0.71) of RSBI, a weaning predictor that is widely used. These results suggest that small breathing pattern variability is associated with a high incidence of weaning failure in postoperative patients recovering from SIRS, and that the indices of breathing pattern variability can potentially serve as a weaning predictor in this patient population.

The exact reason why the failure group had breathing pattern variability distinct from that in the success group remains unclear. The use of 5 cmH_2O PEEP and 5 cmH_2O PSV may possibly affect the breathing pattern variability by unloading the respiratory system [17, 18] and/or by compensation for the added inspiratory work due to artificial airway resistance [28, 33]. However, the influence of 5 cmH_2O PSV on patient's breathing pattern variability, if any, is unlikely to be the reason because the two groups received the same level of PSV. The breathing pattern variability in normal subjects is unrelated random noise superimposed on the output of the respiratory central controller system [14]. Alterations in breathing pattern variability have been found to be associated with various lung diseases [20, 21]. Previous study has also shown that breathing pattern variability is lessened in postoperative and/or acutely ill patients [34] and in subjects receiving endotoxin challenge [35]. Endotoxin affects the physiological regulation of nearly all organs including respiratory center [35], arterial chemoreceptors [36], lung vagal sensory receptors [37] and lung mechanics [38], all of which are known to participate in the regulation of breathing pattern variability [14, 16, 17, 18, 19]. Since our patients were studied during the period recovering from SIRS, we cannot definitely reject the hypothesis that the observed differences were related to the possibility that patients who failed and with lower variability were not completely cured from the SIRS. We assumed that the regulatory mechanisms for maintaining breathing pattern variability in the failure group were still recovering and were thus being maintained at reduced breathing pattern variability. The incomplete recovery of respiratory regulatory mechanisms consequently may lead to tachypnea after extubation in 15 of our patients who failed to wean. In this study the breathing pattern variability of the time component (expiratory time and total breath duration), but not the volume component, had a reverse correlation with the duration of ventilatory support. Since the influence of ventilatory support on the central controller resulting in changes in breathing pattern variability is still obscure, the cause-effect relationship between these two outcomes is not known.

Different shapes of the scattergram in the analysis of heart rate variability have been found to be associated with various pathophysiological conditions of the heart [24, 29]. In this study data on the coefficient of variation alone may reflect the situation in which the failure group had reduced breathing pattern variability. However, SD_1 and SD_2 obtained from the Poincaré plot analysis describe deviations in the data points in a two-dimensional manner. We found that the SD_1-to-SD_2 ratios of the five breathing pattern parameters were within the range of 0.68-0.93 and did not vary between the two study groups. These observations suggest that the shape of the scattergram did not differ between the success and failure groups.

El-Khatib et al. [23] reported that the variability (coefficient of variation) in spontaneous tidal volume and peak inspiratory flow are greater in patients who failed weaning trials than in patients who passed weaning trials. Their patients (mean age 50 years) predominately had underlying lung diseases and a longer duration of ventilatory support (11 days), whereas our patients (mean age 68 years) had no history of chronic obstructive pulmonary disease, no ongoing lung disease before surgery, and a shorter duration of ventilatory support (3 days). Additionally, their measurements of breathing pattern were performed during synchronized intermittent mandatory ventilation at a rate of 4 breaths or fewer per minute, and our measurements were performed during 5 cmH_2O PSV. How and to what extent these differences between the study by El-Khatib et al. and ours affected the breathing pattern variability before weaning are unclear. In this study the success group had coefficient of variation in tidal volume of 0.28, which was consistent with the findings of the study by Tobin et al. [13]. The success group in the El-Khatib et al. study had a coefficient of variation of tidal volume of 0.09, a value that is far less than the normal range reported by Tobin et al. [13].

Engoren [12] investigated the regularity of breathing pattern in 21 patients after cardiac surgery during 60- to 120- min weaning trials mainly performed with various levels of PSV. Engoren's observations found that the pattern of tidal volume, but not the respiratory rate, became more irregular in patients who failed weaning trials. His study focused on the regularity of the breathing pattern during the stage of weaning trials, and a patient may have yielded more than one result. In contrast, all of our patients had completed 30-min PSV trials. In an editorial comment to Engoren's study, Brochard [39] pointed out that the patient's intrinsic breathing pattern variability may be disturbed by a mean pressure support of 12.2±4.6 cmH_2O, and he was quite surprised about the result that the highest variability was found in patients who received this level of pressure support.

In this study nearly all of the values of the clinically used weaning predictors obtained before the weaning trials in the failure group were within the range of prediction of successful weaning developed previously in other patient groups [3, 4, 5, 6, 7, 8], but 26.9% of the SIRS patients still failed to wean, and 15.4% of the SIRS patients required reintubation. These results indicate that the threshold values of these clinically used weaning predictors are not suitable for postoperative SIRS patients and thus need to be redefined. We found that $P_{0.1}$, $P_{0.1}$/Pimax, respiratory rate, RSBI, and $P_{0.1}$×RSBI in the failure group were greater than in the success group. We also found that RSBI, the most widely used weaning predictor, was not superior to other predictors in this study based upon the ROC curve analysis. The accuracy of prediction for indices of breathing pattern variability was as good as those for these five clinically used weaning predictors. Among them, measurement of Pimax, respiratory rate, and RSBI require disconnection of patients from the ventilator and O_2 supplementation [40], which may cause discomfort leading to a setback when these measurements are performed as daily screening [25]. Our measurements of breathing pattern variability are performed during 5 cmH_2O PSV have no such a setback and allow measurement of breathing pattern for a much longer period of time under a relatively stable conditions. The graphic data of the scattergram from Poincaré plot analysis may display variability information in a compact visual format and may be readily comprehended from a clinical monitor. Accordingly, the observations and methods suggested in this study can be integrated into the ICU monitor system, which allows an intensivist routinely to check the patient's status for weaning.

This study was the first to search for a reliable weaning predictor in SIRS patients. The use of a homogeneous population of patients in this study inevitably limits the generalizability of our findings. Because this study is a prospective acquisition of retrospectively analyzed breathing pattern variability, it was not designed to determine the threshold values for indices of breathing pattern variability or to redefine the threshold values for these five clinically used predictors that may best discriminate between successful and unsuccessful weaning outcomes. However, such threshold values for a single predictor or for a compound index involving both indices of breathing pattern variability and clinically used predictors are definitely required for future prospective studies.

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