ANESTHESIOLOGY

Reverse Triggering Dyssynchrony 24 h after Initiation of Mechanical Ventilation

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- In patients undergoing invasive mechanical ventilation, dyssynchrony between the patients' respiratory efforts and the programed ventilatory mode may have immediate adverse effects on oxygenation and ventilation, as well as potentially increasing lung injury.
- A variety of dyssynchrony subtypes have been previously categorized. Reverse dyssynchrony is characterized by the patients' inspiratory efforts occurring after ventilator-triggered breaths. It has only recently been reported in small observational studies, and its characteristics have been not well delineated.
- Using standardized placement of a catheter to continuously monitor electrical activity of the diaphragm in patients within 12 h of intubation along with recording of airway pressure and flow, the authors determined the incidence of reverse triggering (defined as electrical activity starting after initiation of a mechanical breath reaching more than 1 μV) in patients on either a volume or pressure assist–control ventilator mode using customized automated software. Differences in demographics, sedative depth, and ventilator management between patients with and without reverse triggering were also assessed.
- The performance of the software was assessed by three trained observers in the first 10 patients and validated in five additional patients.

What This Article Tells Us That Is New

- The automated software had positive and negative predictive values of 0.74 (95% CI, 0.67 to 0.81) and 0.97 (95% CI, 0.96 to 0.98), respectively.
- In 39 patients primarily intubated for medical reasons and studied for 1 h at 24 h after intubation, the median reverse triggering rate was 8% (95% CI, 0.1 to 75); 44% of patients had reverse triggering in greater than or equal to 10% of breaths. The wide variability in frequency was not explained by patient demographics, reason for intubation, disease severity, or depth or type of sedation.
- The authors suggest that reverse triggering is common at 24 h after intubation and occurs during the transition between deep sedation and onset of patient triggering, leading to extubation.

ABSTRACT

Background: Reverse triggering is a delayed asynchronous contraction of the diaphragm triggered by passive insufflation by the ventilator in sedated mechanically ventilated patients. The incidence of reverse triggering is unknown. This study aimed at determining the incidence of reverse triggering in critically ill patients under controlled ventilation.

Methods: In this ancillary study, patients were continuously monitored with a catheter measuring the electrical activity of the diaphragm. A method for automatic detection of reverse triggering using electrical activity of the diaphragm was developed in a derivation sample and validated in a subsequent sample. The authors assessed the predictive value of the software. In 39 recently intubated patients under assist-control ventilation, a 1-h recording obtained 24 h after intubation was used to determine the primary outcome of the study. The authors also compared patients' demographics, sedation depth, ventilation settings, and time to transition to assisted ventilation or extubation according to the median rate of reverse triggering.

Results: The positive and negative predictive value of the software for detecting reverse triggering were 0.74 (95% CI, 0.67 to 0.81) and 0.97 (95% CI, 0.96 to 0.98). Using a threshold of 1 μV of electrical activity to define diaphragm activation, median reverse triggering rate was 8% (range, 0.1 to 75), with 44% (17 of 39) of patients having greater than or equal to 10% of breaths with reverse triggering. Using a threshold of 3 μV, 26% (10 of 39) of patients had greater than or equal to 10% reverse triggering. Patients with more reverse triggering were more likely to progress to an assisted mode or extubation within the following 24 h (12 of 39 [68%]) *vs.* 7 of 20 [35%]; $P = 0.039$).

Conclusions: Reverse triggering detection based on electrical activity of the diaphragm suggests that this asynchrony is highly prevalent at 24 h after intubation under assist-control ventilation. Reverse triggering seems to occur during the transition phase between deep sedation and the onset of patient triggering.

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Reverse triggering is a type of patient–ventilator interaction whereby a respiratory muscle contraction occurs after the onset of a mandatory breath and is triggered by mechanical insufflation of the thorax by the ventilator.[1] A regular and repeated activation of respiratory muscles after time-initiated ventilator cycles during controlled mechanical ventilation is usually referred to as respiratory entrainment or the phase-locking phenomenon.[2,3] Reverse triggering was recently described in a small series of deeply sedated mechanically ventilated patients with acute respiratory distress syndrome (ARDS) in the intensive care unit (ICU) and also in two brain-dead subjects.[4,5] In these series, all patients presented reverse triggering, often with a 1:1 or 1:2 ratio with mechanical insufflations. Such a regular entrainment is not always present, however, and the pattern can be irregular or modified by the consequences of the "reverse breaths," such as incomplete expiration and air trapping or double cycling.

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Patient ventilator asynchronies may contribute to poor prognosis. The effects of reverse triggering on lung and diaphragm function and its impact on outcome remain uncertain. This asynchrony may potentially aggravate lung injury through multiple mechanisms: during pressure control ventilation reverse triggering can increase tidal volume; during volume control, it can overstretch dependent regions by abrupt diaphragmatic efforts resulting in pendelluft phenomena as evidenced by imaging[6]; in all modes, it can induce double-cycling with breath-stacking.[4] The impact on diaphragm function could go in opposite directions: On one hand, this reflex mechanism could help prevent diaphragm disuse and atrophy; on the other hand, reverse triggering may cause potentially injurious eccentric contractions (*i.e.*, contraction during lengthening of the muscle in the expiratory phase).[7–9] The clinical impact of these effects probably depends on their incidence, magnitude, and duration.

Accurate detection of this patient–ventilator interaction is challenging at the bedside. Visual inspection of flow and airway pressure waveforms is not very sensitive.[10] Esophageal pressure or electrical activity of the diaphragm recordings facilitates detection by directly assessing the timing of the onset of esophageal pressure or electrical activity of the diaphragm relative to the onset of inspiration in the airway pressure and flow-time waveforms at each ventilator cycle. Automated methods are needed, but no dedicated software is currently available specifically for reverse triggering.[11,12] We aimed to characterize the incidence of reverse triggering in recently intubated patients under assist-control ventilation in the ICU.

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Materials and Methods

Data Collection

The current study uses data collected in a study conducted at St. Michael's Hospital in Toronto, Canada, to detect the timing of resumption of diaphragm activity after intubation.[13] Patients were enrolled between June 2015 and August 2017. Electrical activity of the diaphragm was measured by using an esophageal catheter (neurally adjusted ventilator assist catheter and feeding tube) placed within 12 h after endotracheal intubation and initiation of mechanical ventilation. The catheter was positioned according to a formula based on the measurement from nose to ear lobe to xiphoid process of the sternum, and the position was carefully adjusted based on the electrocardiogram tracings (making sure the QRS amplitude decreased from top to bottom traces and checking for the disappearance of the P wave on the bottom tracing, indicating that the last electrode was below the diaphragm). This approach ensures a standardized placement and homogeneous electrical activity of the diaphragm electrical amplitude, as previously described.[14,15] Patients were selected as being likely to remain under mechanical ventilation for at least 24 h. Minute-by-minute trends in electrical activity of the diaphragm were recorded. A 1-h recording of airway pressure, flow, and electrical activity of the diaphragm (neurally adjusted ventilator assist catheter) tracings were obtained at 24 h postintubation in every patient. The goal of the current study was to determine the incidence of reverse triggering in patients who were on assist-control mode (volume or pressure) at the time of this first recording and to study whether there were differences in demographics, sedative depth (clinically monitored), and ventilatory management among patients displaying frequent reverse triggering and those who did not. The research ethics board of St. Michael's Hospital (Toronto, Canada) approved the protocol, and patients were included by waiver of consent (Research Ethics Board No. 15-073, St. Michael's Hospital). Some of the information has been presented previously in abstract form.[16]

Derivation of the Automated Detection of Reverse Triggering

For the first 10 included patients in assist/control mode, a period of 200 breaths with recordings of airway pressure, flow, and electrical activity of the diaphragm was randomly selected and visually reviewed for overall signal quality. Then, three independent trained reviewers (R.M.A., L.F.D., and T. Piraino) visually assessed these tracings breath by breath and classified each breath for the presence of reverse triggering: first, by analyzing airway pressure and flow waveforms only, and again (blind to the first assessment) also analyzing the same breaths with electrical activity of the diaphragm tracings. Definitions and criteria are shown in table 1 and figure 1A. Briefly, based on previous work,[10] the presence of reverse triggering was first established by the presence of an electrical activity of the diaphragm waveform starting after the

Table 1. Definitions and Criteria Used for Visual and Automated Detection

Criterion	Definition
Visual inspection	
Mandatory breath	No deflection in airway pressure curve at the initiation of the breath
Peak expiratory flow	Reduced expiratory peak flow compared with other breaths
Plateau pressure	Variation in plateau pressure compared with other breaths (volume control) in absence of airflow leak
Flow and pressure	Drops in pressure and flow during ventilator inspiratory time (pressure control)
Peak of electrical activity of the diaphragm	Peak greater than 1 μV
Delay of electrical activity of the diaphragm	Electrical activity of the diaphragm onset after pressurization start
Neurosync	
Mandatory breath	Airway pressure drop less than 0.33 cm H_2O at the beginning of insufflations
Electrical activity of the diaphragm breath	Sum of consecutive electrical activity of the diaphragm sample differences exceed the trigger level of 0.5 μV and time integral greater than 0.5 μV after cycling off at 70% of its peak
Delay of electrical activity of the diaphragm	Electrical activity of the diaphragm onset after pressurization start either during inspiratory or expiratory phase of respiratory cycle
Peak of electrical activity of the diaphragm	Peak greater than 1 μV Peak greater than 3 μV Peak greater than 5 μV

For visual inspection, the presence of at least electrical activity of the diaphragm, delay of electrical activity of the diaphragm, and mandatory breath criteria were needed. For Neurosync, the presence of all criteria was needed.

beginning of a mandatory mechanical insufflation and reaching more than 1 μV. Visual assessment with electrical activity of the diaphragm tracing was considered as the reference, and the definitive presence of reverse triggering was considered when a breath was labeled the same among all three reviewers (accepted standard). In addition, to estimate the accepted standard uncertainty, a sensitivity analysis using different definitions was performed (Supplemental Digital Content 1, appendix 1, http://links.lww.com/ALN/C542). Double cycling was also assessed and considered to be present when a second breath occurred, causing breath stacking (fig. 1B). In the primary analysis, we wanted to describe the phenomenon of reverse triggering and tried to be as sensitive as possible using a threshold of greater than 1 μV to declare that there was a reverse-triggered breath. Selecting a higher electrical activity of the diaphragm threshold suggesting a stronger contraction, however, might detect reverse triggering with a more clinically relevant impact, either on the diaphragm or on the lung. We thus also calculated the prevalence of reverse triggering using a greater than 3 μV and a greater than 5 μV peak electrical activity of the diaphragm cutoff.

To calculate the prevalence of reverse triggering, an algorithm was constructed to automatically detect reverse triggering using the Neurosync software (Neurovent Research Inc., Canada). Neurosync is an automatized and validated method based on electrical activity of the diaphragm that detects timing of electrical activity of the diaphragm activity and compares it to the ventilator timing (inspiratory and expiratory valves). The software has been designed to detect dyssynchrony.[12] To detect reverse triggering, we designed a simple algorithm consisting in a combination of four criteria coming from Neurosync output (table 1): (1) mandatory breath with no negative deflection in airway pressure (*i.e.*, not triggered by the patient); (2) electrical activity of the diaphragm present; (3) electrical activity of the diaphragm starting after the ventilator insufflation; and (4) electrical activity of the diaphragm greater than 1 μV. This algorithm was tested on a combined cohort consisting of 10 patients on assist-control (2,000 breaths) and 10 patients on pressure support ventilation (2,000 breaths); the latter group (triggered breaths) was used to rule out the presence of false positive detection. See Supplemental Digital Content 1, appendix 1, http://links.lww.com/ALN/C542, for further details.

Validation of the Automated Detection of Reverse Triggering

We validated the constructed algorithm with two different approaches: First, we wanted to be sure that the efforts labeled as reverse triggering always occurred during a mandatory breath delivered by the ventilator and not during a patient-triggered breath; we used the expiratory time distribution to classify a breath as either machine- or patient-triggered (*i.e.*, a machine-triggered breath is preceded by a fixed, preset, expiratory time; Supplemental Digital Content 1, fig. S1, http://links.lww.com/ALN/C542) and compared it with our definition.

Second, a validation was performed on 1,000 different additional breaths recorded in five different patients in assist-control mode. Visual detection of reverse triggering by three reviewers was considered as the accepted standard and performed during the derivation phase. The algorithm sensitivity, specificity, positive predictive value, and negative predictive value were calculated in the derivation and the validation cohorts.

Incidence of Reverse Triggering

After the algorithm had been developed and validated, for all patients on assist-control mode at the time of the

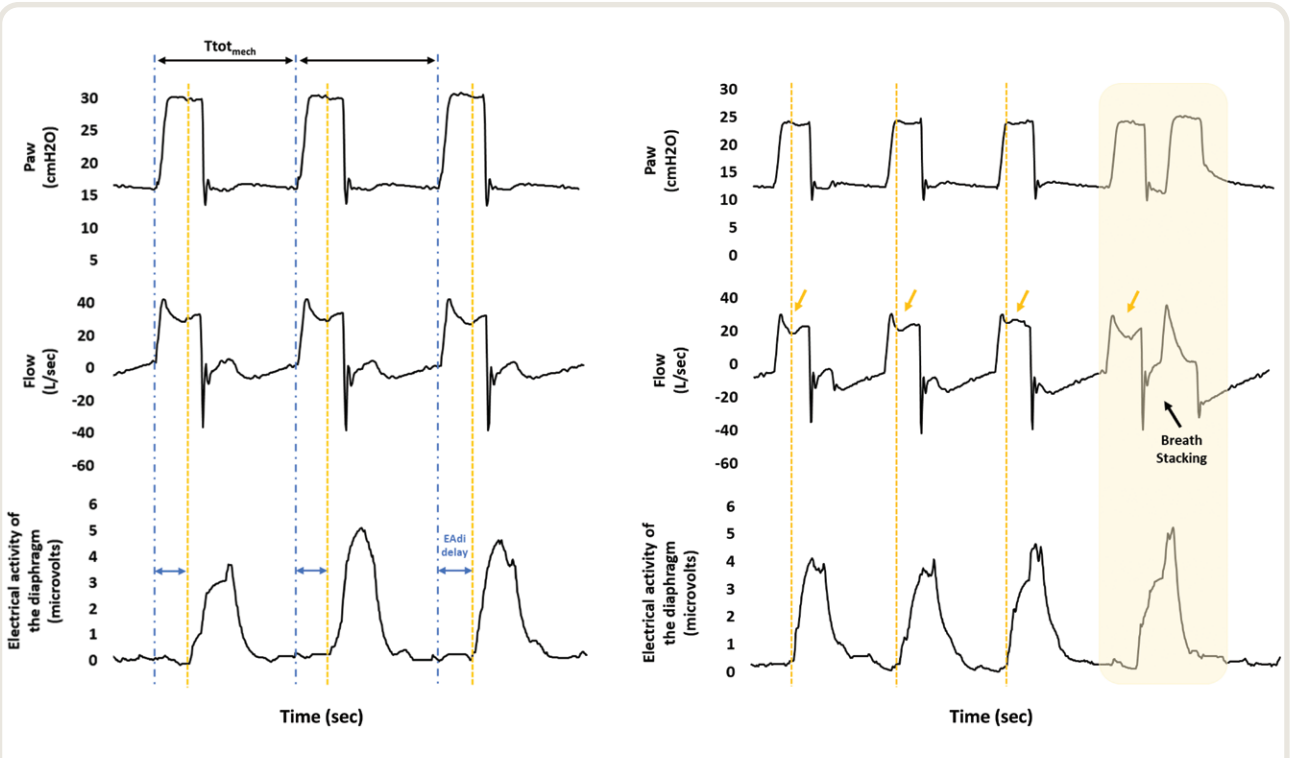

Fig. 1. (*A*) Reverse triggering was defined as an electrical activity of the diaphragm waveform starting after pressurization onset of mandatory breaths. *Blue lines* indicate onset of mechanical breath. *Yellow dashed lines* indicate the electrical activity of the diaphragm onset. (*B*) Double-cycling was defined as reverse triggering causing a patient-triggered breath with breath stacking. *Yellow dashed lines* indicate the electrical activity of the diaphragm onset. P_{aw}, airway pressure.

recording (*i.e.*, 24 h after intubation), we analyzed the complete 1-h tracings. Incidence was analyzed as the number of cycles with this asynchrony over the total number of breaths for each patient, and its distribution was calculated in the whole population as median and interquartile range and expressed in percentage of breaths. We also assessed the presence of different entrainment patterns: Entrainment pattern was defined as the number of reverse triggering breaths (patient respiratory effort) within each ventilator breath. Thus, during 1:1 entrainment pattern, one reverse-triggered breath is associated with one machine breath; during 1:2 pattern, one reverse-triggered breath occurs every two machine breaths, and so on. Here, we defined that a 1:1 entrainment pattern occurred when reverse triggering was present over three or more consecutive breaths. A 1:2 entrainment pattern was identified when reverse triggering was present in every other mandatory breath for at least six events. Then, the cohort was divided in two groups, one above the median rate and one equal to or below the median rate. In these two groups, we looked for differences in demographic data, ventilatory parameters, sedation scores, and medications used at the time of the recording.

Finally, because reverse triggering breaths were not all associated with a clear entrainment pattern, we performed a patient-level analysis of the first quintile of patients with the higher number of reverse-triggered breaths to compare electrical activity of the diaphragm and phase angles of entrained and nonentrained reverse-triggered events. The question was whether entrained or nonentrained reverse-triggered events have the same characteristics. Phase angles were calculated as the phase delay between the onset of a mechanical breath and the onset of neural activity divided by the duration of a mechanical ventilation cycle (Ttot), and all multiplied by 360°: ([onset of pneumatic event − onset of neural event]/[Ttot]) × 360.

Statistical Analysis

No statistical power and sample size calculations were conducted before the study. As a secondary analysis of an observational study, we aimed to include all patients based on our inclusion criteria. We arbitrarily selected the first 10 included patients for the derivation phase and five different patients for the validation phase.

Descriptive statistics (frequencies, median, interquartile range, or mean ± SD) were used considering whether variables had a normal or nonnormal distribution assessed by the Shapiro–Wilk test. Interobserver agreement was assessed by using a Fleiss' kappa statistic. Agreement is generally considered to be excellent if kappa is greater than 0.80, substantial if kappa ranges from 0.61 to 0.80, moderate if kappa

ranges from 0.41 to 0.60, fair if kappa ranges from 0.21 to 0.40, and slight if kappa is less than 0.20.[17] To calculate the diagnostic accuracy of the algorithm based on Neurosync, 2 × 2 tables, sensitivity, specificity, and positive and negative predictive value were calculated. Breaths were the unit of analysis, and they were assumed to be independent. Sensitivity and specificity greater than 80% were defined as acceptable. For comparison of demographic and ventilatory variables between patients above or below the reverse triggering median value, a chi-square test was used for categorical variables. and a two-sample *t* test or Mann–Whitney U test was used for continuous data. Outliers were defined as values below the first quartile minus 1.5 times the interquartile range or above the third quartile plus 1.5 times the interquartile range. However, no action was needed because these values were clinically plausible. In addition, correlations between the amount of reverse triggering breaths and the percentage of breaths with entrainment, other ventilatory variables, and sedation doses were calculated using Pearson's linear correlation coefficient r^2. A two-sided *P* value of <0.05 was considered statistically significant.

Results

Detection of Reverse Triggering

For the derivation phase using a total of 2,000 breaths from 10 patients in assist-control mode, interrater agreement showed a Fleiss' kappa of 0.5 when only flow and airway pressure were used but increased to 0.84 when electrical activity of the diaphragm tracing was added. Diagnostic accuracy of the automatic method and sensitivity analysis with different definitions compared with expert agreements are shown in Supplemental Digital Content 1, table S1, http://links.lww.com/ALN/C542.

Validation of the Automated Detection

Using a total of 1,000 breaths from five patients in assist-control mode, diagnostic accuracy of the algorithm for detection was sensitivity 0.86 (0.80 to 0.91), specificity 0.95 (0.93 to 0.96), positive predictive value 0.74 (0.67 to 0.81), and negative predictive value 0.97 (0.96 to 0.98). The event rate was 15.4% in the validation cohort. The ratio of reverse breaths using expiratory time *versus* our automated algorithm (expiratory time method/automated algorithm) was 1.02 (Supplemental Digital Content 1, fig. S2, http://links.lww.com/ALN/C542).

Incidence of Reverse Triggering above 1 μV

Of the 75 patients included in the original observational study, 30 patients were under a partial mode of ventilation and were not used for the analysis; additionally, six patients were excluded for technical problems with the recording (Supplemental Digital Content 1, flow chart, http://links.lww.com/ALN/C542). Finally, the 39 remaining patients ventilated in assist-control mode were all included in the current study to calculate the incidence of reverse triggering (table 2). The tracings were recorded at a median time (interquartile range) of 24 (21 to 26) h after intubation: A total of 66,296 breaths with an average ± SD breaths of 1,699 ± 567 per patient was analyzed. Patients had a mean age of 57 yrs and an Acute Physiology and Chronic Health Evaluation Score II of 21, and 22 of 39 (56%) subjects had a primary pulmonary reason for intubation (table 2). Regarding sedation, 32 patients (82%) were on a continuous infusion, and 34 received any sedative during the recording (87%), with propofol being the most commonly used drug (continuously in 21 and bolus only in two). Twenty-one patients were sedated with more than one continuous infusion (table 2). The median Riker Sedation-Agitation Scale score was 2, indicating very sedated patients (table 2). One patient was receiving neuromuscular blocking agents at the time of recording. No other patients had

Table 2. Baseline Patient Characteristics

Variable	n = 39
Age, yr	57 ± 17
Male, no. (%)	23 (59)
Body mass index, median (interquartile range)	27 (23 to 34)
Number of breaths studied	1,700 ± 588
Time to recording after intubation, h	24 (21 to 26)
Acute Physiology and Chronic Health Evaluation Score II	21 (18 to 29)
Pao_2/Fio_2 ratio, mmHg	156 (107 to 282)
Reason for intubation, no. (%)	
Pulmonary	22 (56)
Pneumonia	8/22 (36)
COPD exacerbation	5/22 (23)
Chest trauma	2/22 (9)
Other	7/22 (32)
Nonpulmonary	17 (44)
Sepsis	3/17 (18)
Seizures	5/17 (29)
Trauma	5/17(29)
Postcardiac arrest	3/17 (18)
Stroke	1/17 (6)
Sedation score (Riker Sedation-Agitation Scale)	2 (1 to 3)
Continuous sedation, No. (%)	32 (82)
Propofol	21 (65)
Midazolam	11 (34)
Both propofol and midazolam	4 (12)
Any opioid	21 (65)
Either propofol or midazolam plus opioid	17 (53)
Sedatives during recording (mg × kg of ideal body weight × h)	
Propofol	2.98 (0.90 to 4.79)
Midazolam	0.09 (0.05 to 0.25)
Equipotent fentanyl	1.32 (0.81 to 2.74)
Mechanical ventilation days	5 (2 to 9)
ICU mortality, No. (%)	11 (28)
Total number of patients	39

Values are presented as mean ± SD, n (%), or median (25th to 75th interquartile range). In "reason for intubation," the percentages of each cause refer to the main categories (pulmonary and nonpulmonary). For "continuous sedation," categories are not mutually exclusive. Riker Sedation-Agitation Scale ranges from 1 to 7, with lower values indicating deeper sedation. COPD, chronic obstructive pulmonary disease; Fio_2, fractional inspired oxygen tension; ICU, intensive care unit.

received neuromuscular blocking agents in the previous hours. Depth of paralysis was not recorded on the chart.

More than 90% of patients had at least a few reverse breaths detected using the threshold of 1 μV, and 17 of 39 (44%) of them had greater than or equal to 10% of reverse breaths. The median rate for the whole group was 8% of the breaths (range, 0.1 to 75%; fig. 2A). No reverse triggering was observed for the patient who received neuromuscular blockade agents. The number per minute for each patient is presented in figure 2B.

Incidence of Reverse Triggering with 3 and 5 μV

When using thresholds of 3 μV above baseline or 5 μV above baseline to define a diaphragm contractile event, the median value of reverse triggering was 2% (range, 0 to 48%) and 0.1% (range, 0 to 29%), respectively. The percent of patients with greater than or equal to 10% of reverse breaths was 26% (10 patients) using a 3-μV and 13% (five patients) using a 5-μV electrical activity of the diaphragm threshold (fig. 3).

Entrainment

The 1:1 and 1:2 entrainment patterns were observed in 27 (69%) and 24 (62%) of the patients over this 1-h recording, respectively; 30 (77%) of the subjects presented at least one of these two patterns. Overall, entrainment was present from 1 to 69% of all studied breaths per patient; 1:1 entrainment was more common with a higher percentage of reverse-triggered breaths (r^2 coefficient of 0.73; $P < 0.001$).

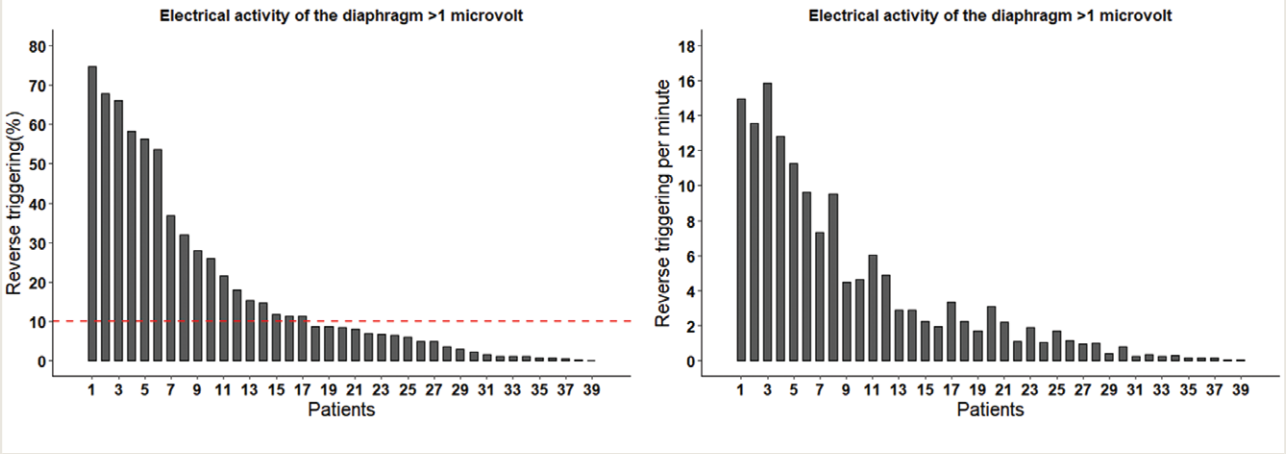

Fig. 2. Incidence of reverse triggering dyssynchrony by patient during the 1-h recording. (*A*) Percentage of reverse-triggered breaths over the total number of breaths. (*B*) Amount of reverse-triggered breaths per minute. Each *bar* represents an individual patient in our cohort.

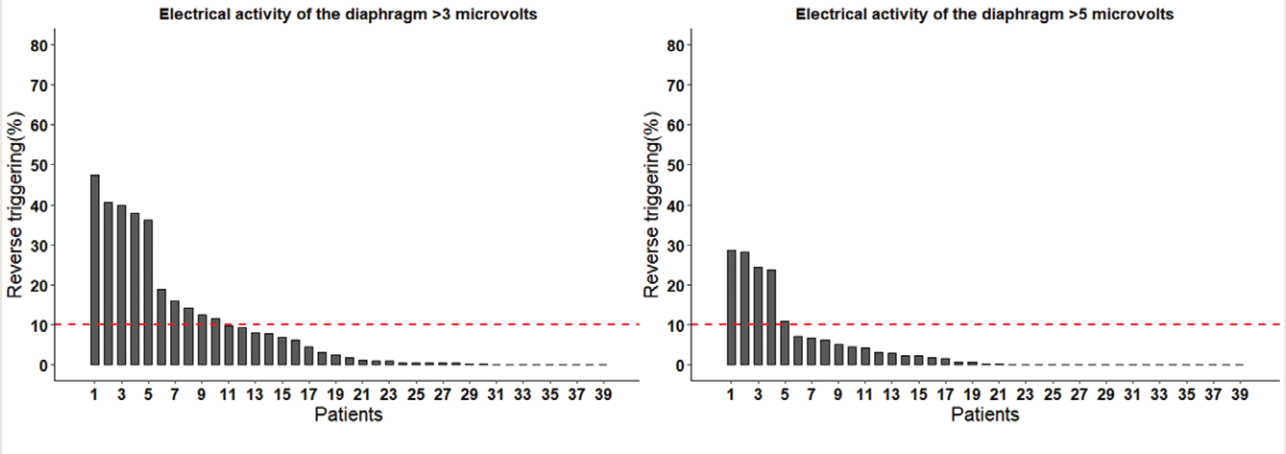

Fig. 3. (*A*) Percentage of reverse triggering using an electrical activity of the diaphragm cutoff of more than 3 μV. (*B*) Percentage of reverse triggering using an electrical activity of the diaphragm cutoff of more than 5 μV. Each *bar* corresponds to a patient.

Within-subject Analysis

Patient-level analysis found no differences (except for one patient) in either electrical activity of the diaphragm or phase angles when comparing entrained and nonentrained reverse-triggered breaths in the eight patients displaying the most frequent reverse triggering (table 3).

Factors Associated with a High Incidence of Reverse Triggering

Table 4 shows the characteristics and ventilatory parameters of patients with higher *versus* lower frequencies of reverse triggering. There was no difference in baseline characteristics and ventilatory parameters, except for the baseline arterial oxygen tension/fractional inspired oxygen tension ratio, which was higher in the group with more reverse triggering (200 *vs.* 124 mmHg; $P = 0.020$), and set respiratory rate, which was lower in the group of patients with more reverse triggering (20 *vs.* 28 breaths per minute; $P = 0.041$). Most patients received continuous sedative infusions regardless of the presence of reverse triggering, and sedation scores showed that most patients were deeply sedated in both groups (table 2). Use of propofol, midazolam, and either fentanyl or hydromorphone did not differ between groups (table 4). The group with higher incidence exhibited more frequent patient-triggered breaths during the 1-h recording (12% *vs.* 1%; $P < 0.001$) and were more likely to be ventilated in an assisted mode of ventilation (pressure support or neurally adjusted ventilator assist) or extubated within 24 h after the recording (68% *vs.* 35%; $P = 0.039$). Similar results were obtained when using 3 and 5 μV because 68% and 63% of patients above the median rate (2% and 0.1%, respectively) were either extubated or switched to supported mode within 24 h ($P = 0.039$ and $P = 0.153$, respectively). The rate of double-cycling was very low (median, 0%; interquartile range, 0 to 0.11%; 0 breaths per hour; interquartile range, 0 to 2).

Discussion

An automated method to detect reverse triggering based on airway pressure and electrical activity of the diaphragm waveforms proved feasible and accurate. Using the most sensitive threshold of 1 μV, 44% of patients under assist-control 24 h after intubation had greater than or equal to 10% of their breaths presenting reverse triggering, whereas the median rate per patient was 8%, with a wide variability among subjects (range, 0.1 to 75%). This variability could not be explained by patient demographics, cause of intubation, disease severity, or depth or type of sedation.

The presence of reverse-triggering dyssynchrony in ICU patients was recently reported by Akoumianaki *et al.*[4] to be present in eight of eight patients with ARDS studied at time of deep sedation. In the current study, we report the incidence in a larger group of mechanically ventilated patients, all requiring mechanical ventilation and sedation for critical illness. Our study population comprised mostly medical patients including a wide array of admission diagnoses with more than 50% of patients having a pulmonary cause of admission but not necessarily ARDS.

To evaluate the prevalence in our tracings, we needed to develop an automatic method of detection. The assessment performed by the three reviewers showed a good agreement between themselves when using electrical activity of the diaphragm associated with ventilator waveforms. Given the time-consuming task of visually analyzing ventilator waveforms and given that dyssynchrony may occur in clusters,[18] dedicated software seems necessary.[12,19–21] Our algorithm using Neurosync showed a good sensitivity (0.86) with excellent specificity (0.95) to automatically calculate the incidence of this phenomenon at 24 h after intubation. The algorithm was further validated by checking that all breaths labeled with reverse triggering were identified as being mandatory breaths and not patient-triggered breaths.

The high incidence of reverse triggering reported in this study (44% of patients with greater than or equal to 10%

Table 3. Within-subject Analysis of Entrainment Incidence in Eight Patients with the Highest Rate of Reverse Triggering

	Electrical Activity Entrained (μV)	Electrical Activity Nonentrained (μV)	*P* Value	Angles Entrainment (Degrees)	Angles Nonentrainment (Degrees)	*P* Value
Patient 1 (n = 921)	3.4 (2.6–4.1)	3.4 (2.6–4.3)	0.528	48 (27–65)	37 (15–64)	0.001
Patient 2 (n = 845)	3.8 (2.7–11.9)	8.7 (3.1–6.2)	< 0.001	50 (36–62)	46 (23–63)	0.004
Patient 3 (n = 579)	2.0 (1.6–2.3)	1.8 (1.5–2.2)	0.004	36 (25–50)	40 (21–53)	0.564
Patient 4 (n = 450)	6.3 (5.4–7.5)	6.2 (5.1–7.1)	0.147	37 (26–57)	33 (21–55)	0.142
Patient 5 (n = 183)	4.1 (2.1–6.6)	4.1 (2.8–6.2)	0.465	11 (5–30)	9 (3–21)	0.112
Patient 6 (n = 982)	4.8 (3.3–8.0)	3.7 (2.3–6.0)	< 0.001	100 (31–286)	82 (31–230)	0.02
Patient 7 (n = 622)	2.4 (1.8–3.5)	2.3 (1.7–3.2)	0.045	104 (71–126)	121 (101–140)	0.056
Patient 8 (n = 1,096)	3.7 (2.8–5.1)	2.6 (2.1–3.5)	< 0.001	43 (35–52)	43 (35–57)	< 0.001
All (n = 5,672)	3.5 (2.4–5.3)	3.0 (2.0–5.0)	< 0.001	49 (31–73)	48 (29–79)	0.274

Values are presented as median (interquartile range). Group comparison between entrained and nonentrained breaths for electrical activity of the diaphragm and angles was performed using the Mann–Whitney U test. n depicts the numbers of reverse-triggered breaths assessed in each patient.

Table 4. Outcomes and Demographic and Respiratory Variables Grouped by Incidence of Reverse Triggering

Variable	Reverse Triggering: Greater than 8% (n = 19)	Reverse Triggering: Less than or Equal to 8% (n = 20)	*P* Value
Age, yr	53 ± 17	62 ± 16	0.118
Male, no. (%)	10 (53)	13 (65)	0.432
Number of breaths studied	1,601 ± 601	1,794 ± 567	0.216
Time to recording from intubation, h	26 (21–28)	24 (22–26)	0.989
Acute Physiology and Chronic Health Evaluation Score II	20 (16–27)	24 (21–30)	0.171
Pulmonary cause of intubation, no. (%)	9 (47)	13 (65)	0.267
Riker Sedation-Agitation Scale score	2 (1–3)	2 (1–3)	0.229
Propofol, mg · kg^{-1} · h^{-1}	3.4 (2.7–4.7)	2.3 (0.9–4.0)	0.156
Midazolam, mg · kg^{-1} · h^{-1}	0.09 (0.05–0.09)	0.11 (0.04–0.36)	0.831
Fentanyl, mcg · kg^{-1} · h^{-1}	1.9 (1.3–4.3)	0.9 (0.6–2.5)	0.423
Mechanical ventilation, days	5 (2–9)	6 (4–10)	0.252
Switch to a partial support mode or extubation the next day, no. (%)	13 (68)	7 (35)	**0.039**
Pao_2/Fio_2 ratio, mmHg	200 (148–353)	124 (96–229)	**0.020**
Respiratory rate, breaths per minute	20 (19–26)	28 (21–30)	**0.041**
V_T, ml/kg predicted body weight	6.8 ± 1.3	6.5 ± 1	0.598
PEEP, cm H_2O	8 (5–11)	9 (6–12)	0.271
Median peak of electrical activity of the diaphragm, μV	1.7 (0.8–4.3)	0.7 (0.7–0.8)	**< 0.001**
Patient-triggered breaths over the 1-h recording, %	12 (8–26)	1 (0–3)	**< 0.001**
Double cycling, %	0 (0–0.4)	0 (0–0.0)	0.172

All numeric variables are presented as median (interquartile range) except for age, number of breaths studied, and V_T, which are expressed as mean ± SD. Groups were defined as those patients above the median and below or equal to the median. Riker Sedation-Agitation Scale ranges from 1 to 7, with lower values indicating deeper sedation. Boldface indicates significant differences for *P* values. Fio_2, fractional inspired oxygen tension; PEEP, positive end-expiratory pressure; V_T, tidal volume.

reverse triggering) suggests that this is a very frequent phenomenon in deeply sedated mechanically ventilated ICU patients. This high frequency of reverse triggering may justify exploring further the potential consequences for the lung and the diaphragm. In a recent study by de Haro *et al.*,[22] 34% of the double cycling breaths were caused by this interaction. Goligher *et al.*[23] showed that eccentric contractions of the diaphragm were caused by reverse triggering and that 52% of reverse-triggered breaths met criteria for eccentric contractions. Conversely, we did not find increased double cycling rate in our study when reverse triggering rate was higher, likely because many diaphragmatic contractions were not strong enough to trigger the ventilator. Overall, double cycling was uncommon in our cohort (median less than 0.5%), representing a lower incidence than published reports from patients with ARDS[24,25] and suggesting that patients enrolled in this study presented with an overall low respiratory drive. An observational study aiming to investigate the relationship between asynchronies and patient-centered outcomes in ARDS or acute respiratory failure is currently ongoing (Incidence of Dyssynchronies in Early ARDS [BEARDS] study, NCT03447288) and will hopefully provide more insight about this phenomenon.

In the current study, reverse breaths were often associated with a 1:1 entrainment phenomenon for up to three or more consecutive breaths. The entrainment phenomenon or respiratory phase locking has been previously described in sedated patients as well as healthy individuals and patients after lung transplantation. The mechanisms generating entrainment are poorly understood and could be multiple, including stretching of the slowly adapting receptors and a sustained activation of the vagally mediated Hering–Breuer reflex.[2–4,26] Graves *et al.*[2] showed that the temporal relationship between mechanical inflation and patient effort was highly dependent of the ratio of the ventilator set rate to patient neural rate. In that study, a stable 1:1 entrainment pattern would develop only when patients' intrinsic neural rate was close to the ventilator set rate. In our study, ventilator set rate was lower in patients presenting with more reverse triggering, which could be explained by a ventilator-to-patient neural rate ratio closer to 1. Additionally, although most reverse-triggered breaths exhibited an entrainment pattern, others were isolated or irregular without clear entrainment. Modifications in drive with the use of sedation can have dramatic effects on the development of respiratory-phase locking,[2] and different brain states might change the range of ventilator-to-patient rate ratios to result in entrainment.[27] To determine whether breaths qualified as reverse triggering without having entrainment might represent signal artefact or activity of the patients simply nonsynchronized with the ventilator, we compared reverse-triggered breaths with or without entrainment. We found similar electrical activity of the diaphragm amplitude and, importantly, similar phase angles between entrained and nonentrained breaths, suggesting that these isolated reverse-triggered breaths were still related to the same mechanism.

Many of our patients were deeply sedated at the time of the recording, and it seemed that reverse triggering was especially frequent in patients who later resumed spontaneous activity. In our study, the group of patients with a higher incidence

of reverse triggering presented with more patient-triggered breaths and showed a higher probability of either being ventilated on a partial mode or extubated the day after the initial recording. These data, in line with those of Graves *et al.*,[2] suggest that the appearance of reverse triggering may represent the point where patient's drive is starting to recover, and it could be interpreted as a phenomenon susceptible to happen during a transition phase from deep sedation to patient-triggered breaths.

Our study has limitations. This is a single-center study, and we only assessed 1-h recordings at 24 h, which may not adequately represent the true prevalence of dyssynchrony in the ICU population. Second, we assessed diaphragm electromyography with a neurally adjusted ventilator assist catheter that uses a filtered electromyograph instead of the raw signal. This may delay the apparent electrical activity of the diaphragm onset. This forced us to create an additional step in our algorithm, which assessed the presence of a decrease in airway pressure to detect patient-triggered breaths and avoid false positives.

This study has also strengths. We created an automatic method to detect reverse triggering with a high sensitivity and tested the model during supported modes and, hence, present an algorithm with an excellent specificity. Finally, we performed an internal validation of our model confirming the accuracy of the algorithm.

Conclusions

Detection of reverse triggering based on electrical activity of the diaphragm is feasible with a good diagnostic accuracy. It is very frequent early after intubation, but the incidence depends on the amplitude of the detected electrical activity of the diaphragm. Reverse triggering seems to be occurring during the transition phase between deep sedation and ventilator triggering, and it could represent the first step to recovering neural drive.

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Competing Interests

Dr. Brochard has indicated the following financial relationships: grants from Medtronic Covidien (Boulder, Colorado), Fisher Paykel (Auckland, New Zealand); equipment from Air Liquide (Antony, France), Philips (Nashville, Tennessee), Sentec (Saint Gal, Switzerland); and consulting with Baxter (Deerfield, Illinois). T. Piraino has indicated the following financial relationships: Dräger (Montreal, Canada), Philips, and Fisher & Paykel. Dr. Telias has indicated the following financial relationships: MBMed SA (Argentina); and Covidien (Argentina). Dr. Sinderby has indicated the following financial relationships: reimbursement by Maquet Critical Care (Solna, Sweden) for attending several conferences; participation as a speaker in scientific meetings or courses organized and financed by Maquet Critical Care; and through Neurovent Research, consultation to Maquet Critical Care. Dr. Sinderby has made inventions related to neural control of mechanical ventilation that are patented. The patents are assigned to the academic institution(s) where inventions were made. The license for these patents belongs to Maquet Critical Care. St. Michael's Hospital has a research agreement with Maquet Critical Care and receives royalties and overhead from this agreement. Dr. Heunks reports financial relationships with Vent free (U.S.); Orion Pharma (United Kingdom); and Maquet Critical Care. The other authors declare no competing interests.

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