Impact of Ventilator Adjustment and Sedation–Analgesia Practices on Severe Asynchrony in Patients Ventilated in Assist-Control Mode*

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Objectives: Breath-stacking asynchrony during assist-control-mode ventilation may be associated with increased tidal volume and alveolar pressure that could contribute to ventilator-induced lung injury. Methods to reduce breath stacking have not been well studied. The objective of this investigation was to evaluate 1) which interventions were used by managing clinicians to address severe breath stacking; and 2) how effective these measures were.

Setting: Sixteen-bed medical ICU.

Patients and Interventions: Physiological study in consecutively admitted patients without severe brain injury, who had severe breath stacking defined as an asynchrony index greater than or equal to 10% of total breaths. During 30 minutes before (baseline) and after any intervention employed by the managing clinician, the ventilator flow, airway pressure, and volume/time waveforms were continuously recorded and analyzed to detect normal and stacked breaths. The initial approach taken was assigned to one of three categories: no intervention, increase of sedation–analgesia, or change of ventilator setting. Nonparametric Wilcoxon-Mann-Whitney tests and multiple regression were used for statistical analysis. Quantitative data are presented as median [25–75].

Main Results: Sixty-six of 254 (26%) mechanically ventilated patients exhibited severe breath-stacking asynchrony. A total of 100 30–minute sequences were recorded and analyzed in 30 patients before and after 50 clinical decisions for ongoing management (no intervention, $n = 8$; increasing sedation/analgesia, $n = 16$; ventilator adjustment, $n = 26$). Breath-stacking asynchrony index was 44 [27–87]% at baseline. Compared with baseline, the decrease of asynchrony index was greater after changing the ventilator setting (–99 [–92, –100]%) than after increasing the sedation–analgesia (–41 [–66, 7]%, $p < 0.001$) or deciding to tolerate the asynchrony (4 [–4, 12]%, $p < 0.001$). Pressure-support ventilation and increased inspiratory time were independently associated with the reduction of asynchrony index.

Conclusions: Compared with increasing sedation–analgesia, adapting the ventilator to patient breathing effort reduces breath-stacking asynchrony significantly and often dramatically. These results support an algorithm beginning with ventilator adjustment to rationalize the management of severe breath-stacking asynchrony in ICU patients. (*Crit Care Med* 2013; 41:2177–2187)

Key Words: acute lung injury; acute respiratory distress syndrome; mechanical ventilation; patient–ventilator asynchrony; respiratory insufficiency; sedation

A lung-protective ventilation strategy reduces mortality in patients mechanically ventilated for acute respiratory distress syndrome (ARDS) or mild ARDS (1). In patients with ARDS ventilated in assist-control-volume (ACV) mode, tidal volumes of 4–6 mL/kg of predicted body weight (PBW) have been recommended to reduce ventilator-induced lung injury (2, 3), and it is believed larger tidal volumes may increase the risk of ARDS development in patients ventilated

*See also p. 2240.

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for other reasons (4, 5). Thus, ventilation practices have been changing worldwide (6), many intensivists have embraced low tidal-volume ventilation broadly for mechanically ventilated patient (7). Unfortunately, simply setting low tidal volumes does not always achieve this goal because patients may have breath-stacking asynchrony development that results in higher tidal volumes than set by the physician (8). Breath-stacking asynchrony, also called *double triggering*, occurs when patient inspiratory effort continues during the ventilator exhalation. This can result in the delivered tidal volume being up to twice the set value (9, 10) (**Fig. 1**). Although measures to reduce other forms of ventilator asynchrony have been reported (11–14), approaches to reduce breath stacking in ACV have not been well studied. The objective of this investigation was to evaluate 1) which interventions were employed in cases of severe breath stacking in ACV; and 2) what was their success in reducing patient–ventilator asynchrony. The overall hypothesis was that patients with breath-stacking asynchrony are treated with a variety of different strategies to reduce asynchrony, and these strategies could be associated with more or less success regarding reduction of asynchrony.

MATERIALS AND METHODS

Ethics and Consent

The protocol was approved by the Institutional Review Board, and written consent was obtained from the patient or surrogate decision maker.

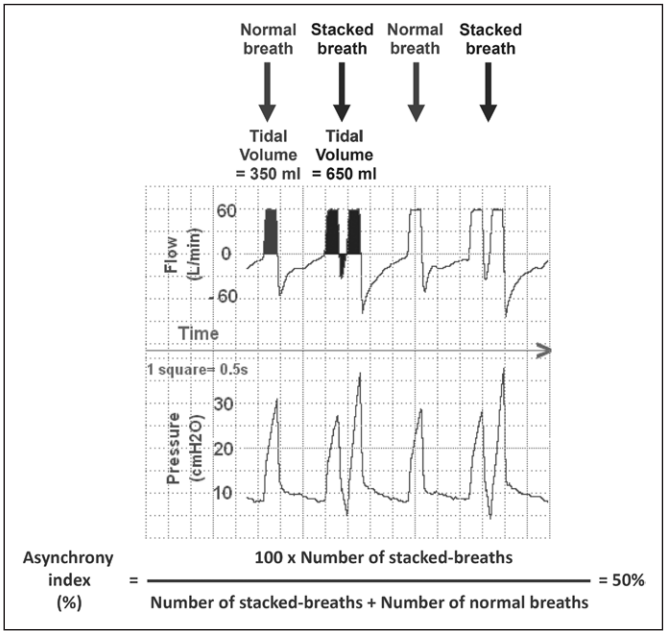

Figure 1. Measurement of breath-stacking asynchrony index (AI) and tidal volume. Ventilator flow/time and pressure/time waveforms were recorded and analyzed to detect breath-stacking asynchrony. A stacked breath was defined as a subsequent inspiratory flow triggered before any complete expiration. AI was calculated as the ratio between the sum of stacked breaths divided by the sum of stacked breaths and normal breaths recorded during the same period, expressed in percentage. In this example, AI was 50%. Tidal volume was measured using the computer software as the calculation of area under the flow/time waveform.

Population

The study took place in the 16-bed medical ICU of the University of Chicago Hospitals, an academic tertiary care hospital, from August 2011 through February 2012 (7 mo). All consecutive patients 18 years old or older receiving mechanical ventilation in ACV were eligible for enrollment if they demonstrated severe breath stacking defined as an asynchrony index (AI) ≥ 10% (see below for method of calculation). Exclusion criteria were brain injury, decision to withdraw life support, planned extubation at the time of enrollment, mechanical ventilation greater than or equal to 7 days, and technical issues such as unavailability of the dedicated computer or ventilator.

Study Design

Investigators were contacted by the primary care team when breath stacking was noted. In addition, the research team screened every patient admitted to the ICU daily to detect any breath-stacking asynchrony by a 5-minute inspection of the ventilator flow and pressure/time waveforms displayed on the machine interface. The primary care team was informed of the objective of the study, specifically that it was an observational study aimed at evaluating their strategy to reduce asynchrony or not. After enrollment, a personal computer was connected to the ventilator (Esprit ventilator, Philips/Respironics, Philips Healthcare, Andover, MA). Ventilator flow, airway pressure, and volume/time waveforms provided by the ventilator were recorded using a computer software program (Windaq, Dataq Instruments, Akron, OH). The software was calibrated as previously described (8). Waveforms were recorded from enrollment until the last decision made by the primary care team regarding breath-stacking asynchrony. Ventilator settings, sedation/analgesia scores, and dosing were evaluated over two different sequences of 30 minutes each: 1) before (baseline) any intervention decided by the primary care team; and 2) after the intervention. The initial approach taken was determined and characterized in three categories: no intervention, increase of sedation–analgesia, and change of ventilator setting. No-intervention decisions were decided only by the attending physician. The 30-minute postintervention sequence started: 1) just after the first sequence (baseline) in case of no intervention decided; 2) after 5 minutes in case of decision to change the ventilator setting to allow for patient's breathing pattern adaptation; 3) after either 5 or 30 minutes in case of decision to increase sedation/analgesia if the increase was a bolus IV injection or an increase in infusion continuous rate, to allow achievement of a steady state after dose adjustment.

Evaluated Variables

Breath-Stacking Asynchrony and Ventilator Variables. Waveform recordings were analyzed to detect breath-stacking asynchrony.

A stacked breath was defined as an inspiratory flow triggered before complete expiration (9, 10) (Fig. 1). AI was calculated as the ratio between the sum of stacked breaths divided by the sum of stacked breaths and normal breaths recorded during the same period, expressed in percentage, that is, AI (%) =

100 × number of stacked breaths/(number of stacked breaths + number of normal breaths) (15). Severe AI was defined as an AI greater than or equal to 10% (15).

Tidal volume was measured by the computer software as the calculation of area under the flow/time waveform (Fig. 1) as previously described (8). Minute ventilation was calculated as follows: (normal breath's tidal volume × number of normal breaths during 30 min/30) + (stacked breath's tidal volume × number of stacked breaths during 30 min/30). Peak, plateau, mean, and end-expiratory airway pressures were measured from pressure waveforms. Plateau pressure was measured after application of an inspiratory hold of 0.5 seconds for at least five reproducible breath cycles. Dynamic compliance (L/cm H_2O) was calculated as the tidal volume (L) divided by the difference between plateau pressure and positive end-expiratory pressure (PEEP) (cm H_2O). Airway resistance (cm H_2O/L/s) was calculated as the difference between peak and plateau airway pressures (cm H_2O) divided by inspiratory flow (L/s). Intrinsic PEEP and total PEEP were not measured because inspiratory efforts in patients with severe breath stacking prevent an accurate measurement of these variables (16). Arterial blood gases were obtained before enrollment. Initial ventilator setting was performed by a respiratory therapist according to unit policy: ACV with a tidal volume of 6 mL/kg of ideal body weight, inspiratory flow of 60 L/min, inspiratory trigger of −2 cm H_2O, FIO_2, and PEEP according to the ARDS Network protocol (1). Further changes were done by the individual nurse and physician team. Pressure support level in pressure-support ventilation (PSV) was adjusted for a tidal volume between 6 and 10 mL/kg and a respiratory rate between 10 and 35 breaths/min. Expiratory trigger was set at 25% of the maximal inspiratory flow.

Sedation and Analgesia Variables. Sedation and pain levels were measured by the investigator at the beginning of the baseline sequence before any intervention and at the end of the postintervention sequence. Sedation level was assessed by the Richmond Agitation-Sedation Scale (RASS) (17). RASS levels above, equal to, or below 0 described a patient sedated, awake, or agitated, respectively. Pain was assessed using the behavioral pain scale (18). Pain intensity was also self-reported by patients if they were able to communicate, using the visually enlarged numeric rating scale from 0 (no pain) to 10 (maximum imaginable discomfort(19)). The presence of at least moderate pain intensity was defined by either a behavioral pain scale score > 4 or a numeric rating scale level greater than 3 (18–20). Sedation and analgesia were routinely managed by critical care nurses according to an observed RASS level and subjective assessment of pain, as previously described (21, 22). The sedation–analgesia protocol began with an assessment for the presence of pain by asking the patient directly during the sedative interruption. If the patient was experiencing pain, the opiate (e.g., fentanyl) was bolused (50–100 μg increments), and the infusion rate was increased by 50%. A similar strategy was used for sedation, first targeting a RASS score of 0 to −2. Boluses of sedatives were required only in case of severe agitation (RASS > 2). Targeting a deeper level of sedation was made upon medical prescription according to clinical condition (respiratory mechanics, failure to achieve a light sedation without intermittent agitation). Doses of sedatives (propofol or midazolam) and analgesic drugs (fentanyl) were collected throughout the evaluated sequences. For statistical analysis, midazolam dose was converted to a propofol equivalent dose assuming that 1 mg of midazolam would equal 10 mg of propofol (23).

Demographic and Medical Data. Age, gender, height and weight, comorbidities, and reason for admission to the ICU were recorded. Acute Physiology and Chronic Health Evaluation II score was calculated with 24 hours of admission, and Sequential Organ Failure Assessment score was calculated within 24 hours of enrollment (24). PBW was calculated according to usual formulas (1). Body mass index was calculated as the ratio (kg/m^2) between weight (kg) and height squared (m^2).

Statistical Analysis

The primary endpoint was the impact of the different types of decisions (increase of sedation/analgesia or ventilator setting change) on AI reduction. Considering that one to two interventions could be employed by the primary care team for each patient with severe asynchrony, analyzing $n = 45$ interventions in $n = 30$ patients was predicted to detect a 30% difference in AI reduction between two strategies assuming one to be highly effective (90% reduction in stacked breaths), with an SE of 0.30, alpha of 0.05, and beta of 0.10.

Quantitative data were shown as medians and 25th–75th percentiles. Nonparametric Mann-Whitney-Wilcoxon test (quantitative data) and chi-square test or Fisher exact test (qualitative data) were used to compare evaluated variables regarding the type of intervention employed by the primary care team. A multivariate analysis using a logistic regression model was performed to identify factors associated with the type of intervention that was decided by the primary care team ("sedation/analgesia intervention" or "ventilator intervention"). To identify factors associated with the percent decrease in AI, a multivariate analysis was performed using a multiple regression model. In multivariate analyses, variables were selected if their p value was less than 0.20 in univariate analysis or if explicative variables have been described in the literature. A stepwise procedure was used to select the final model. Significant variables were sequentially entered (forward procedure). After entering into the model, variables were checked and possibly removed if became nonsignificant (backward procedure). A p value of less than or equal to 0.05 was considered statistically significant. Data were analyzed using the SAS software version 9.1 (SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients Upon Enrollment

During the study period, $n = 66$ (26%) of the 254 mechanically ventilated patients who were screened by the research team experienced at least one episode of severe breath-stacking

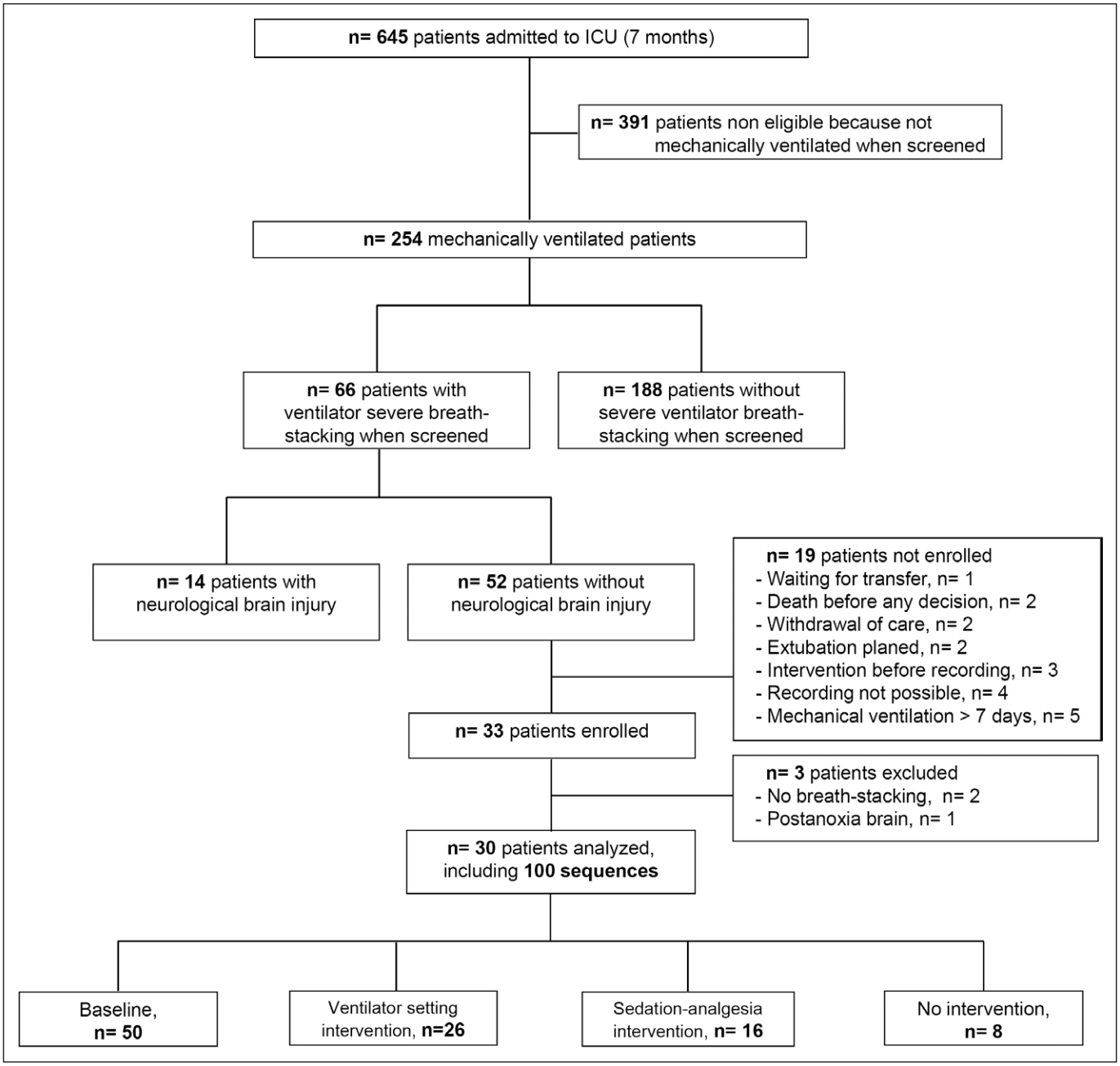

Figure 2. Study flow chart identifying the number of patients screened, eligible, enrolled, and analyzed.

asynchrony. Thirty patients were included for analysis. A consort flow chart of patient enrollment is shown in **Figure 2**.

Table 1 summarizes patients' demographic and medical characteristics. Duration of mechanical ventilation prior to enrollment was 22 hours (15–37). Primary reasons for admission to the ICU were acute respiratory failure (57%) and severe sepsis or septic shock (30%). ARDS or mild ARDS was present in 30% of patients upon enrollment. Respiratory characteristics are shown in **Table 2**. All patients were ventilated in ACV (**Table E1**, Supplemental Digital Content 1, http://links.lww.com/CCM/A677) upon enrollment. Median set tidal volume and respiratory rate were 6.7 (6.2–7.4) mL/kg of PBW and 18 (14–22) breaths/min, respectively. Breath-stacking AI was 44 (27–87) % in this cohort upon enrollment. Sedation and analgesia characteristics are shown in Table E1 (Supplemental Digital Content 1, http://links.lww.com/CCM/A677). Sustained infusion of sedatives and fentanyl were used in 57% and 70% of patients, respectively. Thirty percent of patients were aware or agitated and 27% were with at least moderate pain (Table E1, Supplemental Digital Content 1, http://links.lww.com/CCM/A677).

Decisions Made by the Primary Care Team

In total, 100 30-minute sequences were analyzed before and after 50 decisions made by the managing physicians: no intervention employed, $n = 8$; increasing sedation/analgesia, $n = 16$;

TABLE 1. Demographic and Medical Characteristics of the 30 Patients Included for Analysis

Variable	All Patients *n* = 30
Age (yr)	58 (40–67)
Sex (female/male)	16/14
Actual weight upon admission (kg)	79 (63–88)
Predicted body weight (kg)	61 (54–68)
Body mass index (kg/m^2)	26 (23–31)
Chronic lung disease, *n* (%)	10 (33)
Chronic obstructive pulmonary disease, *n* (%)	6 (20)
Asthma, *n* (%)	3 (10)
Interstitial lung disease, *n* (%)	1 (3)
Reason for admission to the ICU	
Acute respiratory failure, *n* (%)	18 (60)
Severe sepsis/septic shock, *n* (%)	8 (27)
Gastrointestinal bleeding, *n* (%)	3 (10)
Hepatitis fulminans, *n* (%)	1 (3)
Acute Physiology and Chronic Health Evaluation II score within 24-hr after admission to ICU	24 (17–27)
Sequential Organ Failure Assessment score upon enrollment	9 (5–14)
Time between admission to ICU and enrollment (hr)	36 (18–56)
Time between intubation and enrollment (hr)	22 (15–37)
Diffuse pulmonary edema upon enrollment, *n* (%)	11 (36)
Acute respiratory distress syndrome, *n* (%)	7 (23)
Mild acute respiratory distress syndrome, *n* (%)	3 (10)
Cardiogenic pulmonary edema, *n* (%)	1 (3)

Sequential Organ Failure Assessment (24).
Continuous data are expressed in median [25th–75th percentiles].

adjusting ventilator setting, $n = 26$ (Fig. 2). In univariate analysis, the decision to increase sedation/analgesia was significantly associated with awareness or agitated state and a decision made by the first-line primary care team, that is, the bedside nurse or the resident (**Table E2**, Supplemental Digital Content 1, http://links.lww.com/CCM/A677). Multivariate analysis included these two significant variables, as well as variables with a *p* value of less than 0.20 (presence of pain, chronic lung disease, ARDS, and Sequential Organ Failure Assessment score) and possible explicative data (AI and order of decision). In this analysis, only the first-line primary care team was independently associated with decision to increase sedation/analgesia (odds ratio, 8.4 [1.9–35.8], $p = 0.004$).

When a sedation/analgesia intervention was decided, the dose of sedatives and analgesics was increased by 50–60% and the magnitude of agitation or pain decreased after these interventions (**Table E3**, Supplemental Digital Content 1, http://links.lww.com/CCM/A677). Among the 16 patients

TABLE 2. Respiratory Characteristics Upon Enrollment in the 30 Patients Included for Analysis

Variable	All Patients *n* = 30
Mechanical ventilator setting	
Assist-control ventilation, *n* (%)	30 (100)
Tidal volume (mL)	400 (380–450)
Tidal volume (mL/kg of predicted body weight)	6.7 (6.2–7.4)
Respiratory rate (breath/min)	18 (14–22)
Minute ventilation (L/min)	8.0 (6.0–9.3)
Minute ventilation (mL/min/kg predicted body weight)	120 (106–158)
Inspiratory flow (L/min)	60 (50–60)
Inspiratory time (s)	0.5 (0.4–0.8)
F_{IO_2} (%)	58 (50–60)
Positive end-expiratory pressure (cm H_2O)	5 (5–8)
Inspiratory pressure trigger (cm H_2O)	–2 (–2, –2)
Software calculated variables	
Breath-stacking asynchrony index (%)	44 (27–87)
Stacked-breath variables	
Tidal volume (mL)	804 (668–862)
Tidal volume (mL/kg of predicted body weight)	12.9 (11.4–13.4)
Respiratory rate (breath/min)	10 (4–15)
Non-stacked-breath variables	
Tidal volume (mL)	400 (360–444)
Tidal volume (mL/kg of predicted body weight)	6.6 (6.1–7.2)
Respiratory rate (breath/min)	9 (2–13)
All (stacked and nonstacked breaths) variables	
Total respiratory rate (breath/min)	18 (15–25)
Minute ventilation (L/min)	12.1 (8.8–14.1)
Minute ventilation (mL/min/kg predicted body weight)	196 (137–241)

(*Continued*)

TABLE 2. (*Continued*). Respiratory Characteristics Upon Enrollment in the 30 Patients Included for Analysis

Variable	All Patients *n* = 30
Lungs mechanics measurements	
Stacked breaths	
Peak airway pressure (cm H_2O)	37 (33–44)
Mean airway pressure (cm H_2O)	12 (9–15)
Nonstacked breaths	
Peak airway pressure (cm H_2O)	28 (22–32)
Mean airway pressure (cm H_2O)	9 (7–11)
Plateau airway pressure (cm H_2O)[a]	16 (14–19)
Dynamic compliance (mL/cm H_2O)[a]	38 (32–48)
Airway resistance (cm H_2O/L/s)[a]	14 (10–18)
Arterial blood gases[b]	
pH	7.34 (7.29–7.37)
$Paco_2$ (mm Hg)	37 (31–45)
HCO_3^- (mEq/L)	19 (17–24)
Base excess (mEq/L)	–5 (–8–0)
Sao_2 (%)	95 (93–97)
Pao_2 (mm Hg)	101 (76–141)
Pao_2/Fio_2 ratio (mm Hg)	185 (127–342)

Continuous data are expressed in median [25th–75th percentiles].
[a]Dynamic compliance and resistance were calculated in 18 patients in whom the plateau pressure could be measured.
[b]Arterial blood gases were obtained in 26 patients, 2 (1–3) hr before enrollment.

for whom sedation/analgesia was increased, the proportion of those with agitation and/or pain decreased from 8 patients (50%) to 1 patient (6%; $p < 0.01$).

Regarding ventilation interventions, switching from ACV to PSV and increasing the inspiratory time in ACV were the most frequently employed interventions (62% and 35%, respectively; **Table E4**, Supplemental Digital Content 1, http://links.lww.com/CCM/A677). In ACV, increasing the inspiratory time in ACV was done adding an inspiratory hold (plateau pressure) to obtain a total inspiratory time up to 1 second, without any change in inspiratory flow. When ACV was switched to PSV, the PSV level was titrated to obtain, if possible, a tidal volume close to the value which was previously set in ACV. However, compared with interventions in ACV mode (increasing the inspiratory time or increasing tidal volume), switching to PSV was associated with a significant increase in tidal volume and a significant decrease in mean airway pressure (Table E4, Supplemental Digital Content 1, http://links.lww.com/CCM/A677). Inspiratory time increased in all ventilator interventions (Table E4, Supplemental Digital Content 1, http://links.lww.com/CCM/A677). Also, ventilator interventions diminished agitation ($n = 1$), pain behavior ($n = 1$), and reported discomfort associated with mechanical ventilation ($n = 1$) in some patients.

Impact of Interventions on Breath-Stacking AI Reduction

AI decreased significantly after both sedation/analgesia and ventilator setting interventions. **Figure 3** shows the individual change in AI according to the type of intervention. AI decreased significantly from 41% (16–64%) to 27% (5–52%) after sedation/analgesia interventions ($p = 0.01$) and from 38% (25–83%) to 2% (0–7%) after ventilator interventions ($p < 0.001$). Breath-stacking AI was reduced more by ventilator interventions than by increasing drug dosing (**Fig. 4**).

Multivariate analysis showed that among all interventions, switching to PSV and increasing the inspiratory time in ACV were the two factors independently associated with decrease of breath-stacking AI (**Table 3**). **Figure 5** shows the impact of these two kinds of ventilator setting on breath-stacking asynchrony on the recording from two patients with severe breath-stacking asynchrony.

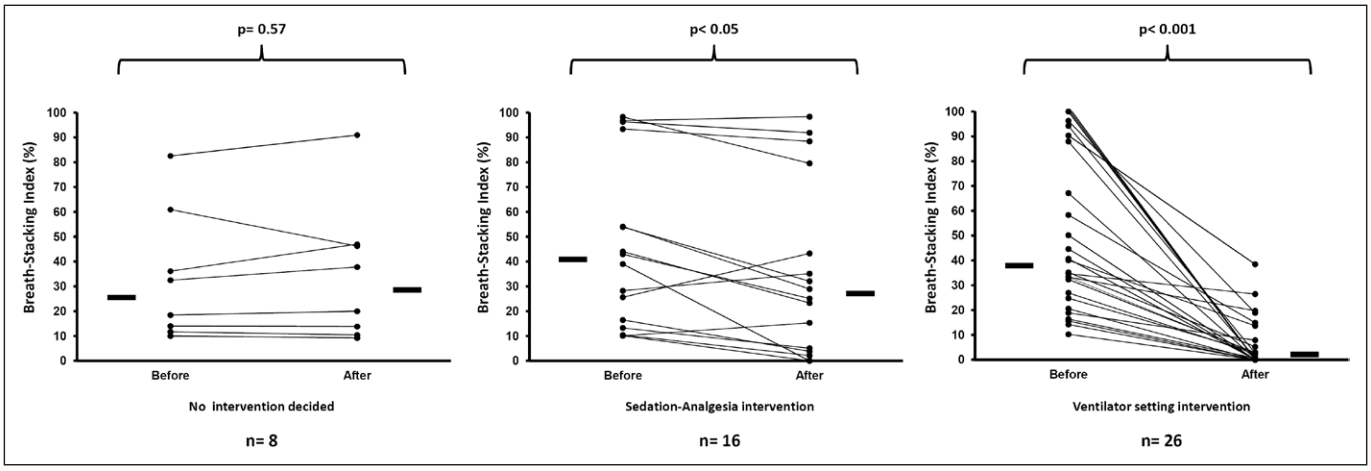

Figure 3. Individual change of breath-stacking index compared with baseline according to interventions decided by the primary care team. This figure shows individual changes in breath-stacking asynchrony index according to interventions decided by the primary care team (Wilcoxon test). The breath-stacking asynchrony index was calculated as the ratio between the sum of stacked breaths, which was divided by the sum of stacked breaths and normal breaths recorded during the same period, expressed in percentage.

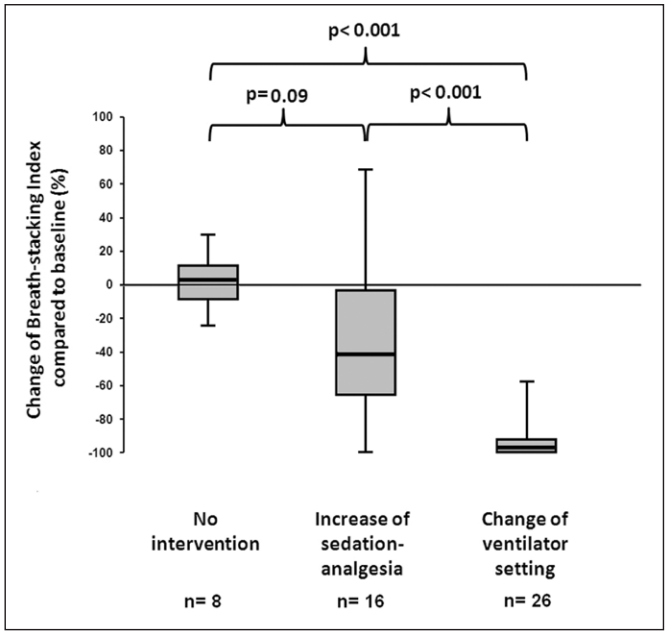

Figure 4. Percent change of breath-stacking index compared with baseline according to interventions decided by the primary care team. This figure shows that the breath-stacking index decrease was significantly more important when the primary care team decided to change the ventilator setting instead of either increasing sedatives and/or opioids or doing no change (Mann-Whitney-Wilcoxon test). The breath-stacking index was calculated as the ratio between the sum of stacked breaths divided by the sum of stacked breaths and normal breaths recorded during the same period, expressed in percentage.

TABLE 3. Multiple Regression Analysis Assessing Predictors of Breath-Stacking Decrease After Intervention

Regression Equation				
Independent Variables	**Coefficient**	**SE**	***T***	***p***
(Constant)	31.1			
Increase of inspiratory time	50.7	20.3	2.5	0.01
Pressure-support ventilation	46.4	13.6	3.4	0.001

Analysis of Variance

Source	**Degrees of Freedom**	**Sum of Squares**
Regression	2	37496
Residual	35	48946
F-ratio		13.4
Significance level		$p < 0.001$

Multiple regression stepwise analysis identified factors associated significantly with the magnitude of decrease of breath-stacking asynchrony (calculated in percentage of decrease according to baseline). Selected factors associated with breath-stacking asynchrony were previously published or clinically selected, based on the nature of intervention decided by the primary care team: Chronic lung disease (Yes/No); acute respiratory distress syndrome or mild acute respiratory distress syndrome (yes/no); Acute Physiology and Chronic Health Evaluation II score upon admission to ICU; Sequential Organ Failure Assessment score at baseline; Pao_2/inspired fraction of oxygen ratio at baseline (mm Hg); base excess at baseline (mEq/L); change in dose of sedatives calculated as propofol equivalents (µg/kg/min); change in dose of fentanyl (µg); effective treatment of agitation and/or pain syndrome if present at baseline (yes/no); change in tidal volume from baseline (mL/kg ideal body weight); change in inspiratory time from baseline (s); use of pressure-support ventilation (yes/no). Only the change in inspiratory time and the use of pressure-support ventilation were included in the regression equation model using stepwise analysis.

DISCUSSION

The main findings of this study are that 1) in routine practice severe breath-stacking is addressed half of the time by ventilator adjustments; 2) it is almost equally likely for the bedside nurse or junior physician to increase sedation/analgesia in response to this finding; 3) ventilator adjustment is a much more effective intervention to reduce breath stacking than drug-dose adjustment; and 4) switching ACV to PSV mode and increasing the inspiratory time in ACV are both effective strategies that could support a bedside decision-making algorithm aimed at reducing breath-stacking asynchrony (**Fig. 6**). Pending further studies aimed at evaluating this strategy on outcome and while checking for any worsening in lung mechanics (air trapping, wasted efforts), this could be tried by clinicians to achieve the goals of both limiting the risk of ventilator-induced lung injury and limiting the risk of over use of sedatives and analgesics.

Only a few studies have evaluated breath-stacking asynchrony. A study in 20 patients deeply sedated and ventilated in ACV with a lung-protective ventilation strategy for an acute lung injury reported a percentage of stacked breaths of 9.7% ± 15.2% and a median volume of stacked breaths of 10 mL/kg (9–11) PBW (8). A multivariate analysis showed that only a greater tidal volume was associated with less breath-stacking asynchrony. A study in 62 patients included as soon as they were able to trigger all the ventilator breaths showed that stacked breaths were 12 times more frequent in the 11 patients ventilated in ACV than in the 51 patients ventilated in PSV (15). In all, despite a number of well-conducted randomized trials that showed the benefits of reduced tidal-volume ventilation on patient outcome in patients with (1, 3) and without (4, 5) ARDS, breath-stacking asynchrony has been inadequately evaluated as a risk factor causing lung injury or as a confounding factor diminishing the benefits of low tidal-volume ventilation. Future randomized trials should evaluate if breath stacking might diminish the benefits of low tidal-volume lung-protective ventilation strategies. This kind of asynchrony is the opposite result of targeting small tidal-volume strategy on the one hand but could also be a possible recruitment maneuver on the other hand.

In case of severe breath-stacking asynchrony, clinicians have the options of adjusting ventilator settings or increasing sedation/analgesia. In the present study, increasing sedation/analgesia was decided mostly by nurses and residents but was relatively ineffective to abolish severe breath-stacking asynchrony. Furthermore, increasing the dose of sedatives and analgesics could be associated with adverse effects and an increased duration of mechanical ventilation and length of stay in ICU

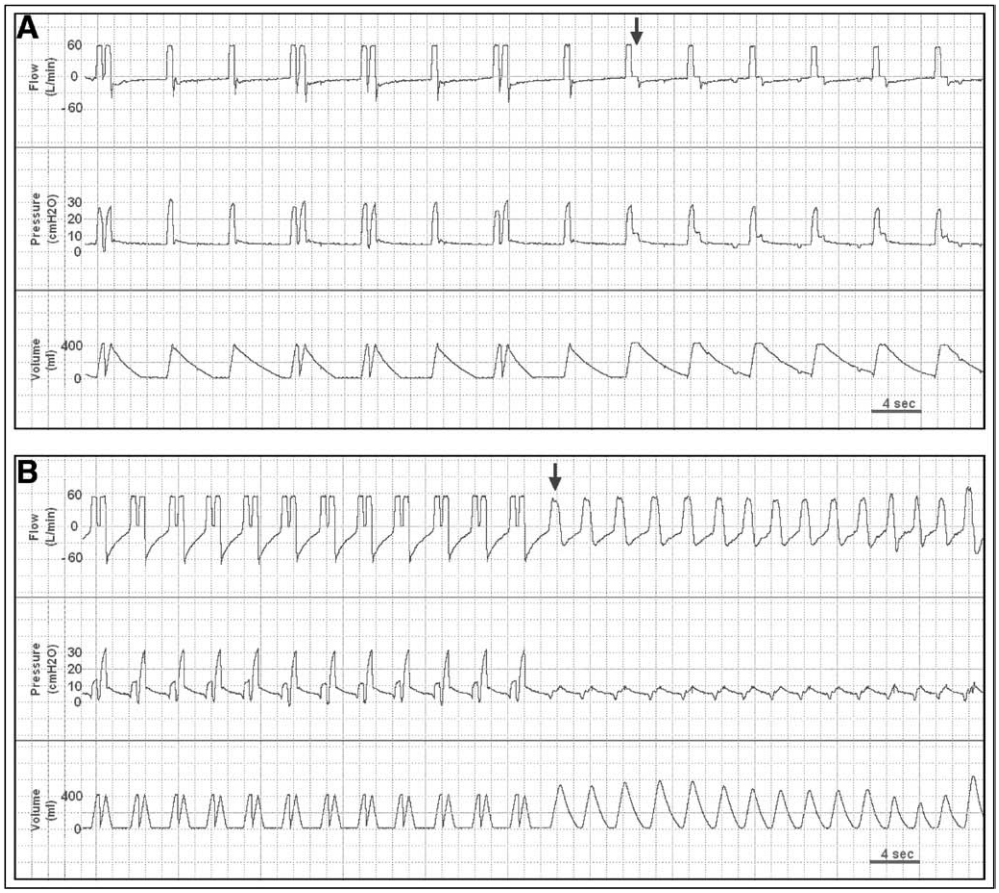

Figure 5. Impact of ventilator setting on breath-stacking asynchrony in two patients. **A**, Increasing inspiratory time from 0.4 s to 1 s (*arrow*) was associated with a decreased double-stacking asynchrony index from 50% to 0% in a 66-yr-old male patient with chronic obstructive pulmonary disease mechanically ventilated in assist-control volume (ACV) for acute respiratory failure. Tidal volume set at 400 mL increased to 800 mL while double stacking and then remained constant at 400 mL after having increased the inspiratory time. **B**, Switching from ACV to pressure-support ventilation (PSV) (*arrow*) was associated with a decreased double-stacking asynchrony index from 100% to 0% in a 38-yr female patient mechanically ventilated for a fulminans hepatitis. Tidal volume set at 400 mL in ACV increased to a mean of 550 mL in PSV, which was smaller than the 800 mL measured during every breath while double stacking in ACV.

and hospital. A number of studies over the past decade have shown that strategies aimed at reducing the dose of sedatives or analgesics are associated with a better outcome, including the use of a nurse-driven sedation/analgesia algorithms (25–27), daily awakening trials (21, 28), and formal protocols regarding agitation, delirium, and pain management in ICU patients (29–31). In these studies, ventilator management was not described in detail. This is important because adjustment of ventilator settings may be more effective than increases in sedation/analgesia in cases of ventilator asynchrony. Furthermore, increasing the inspiratory time to 1 second may help to prevent patient's double triggering when patient's inspiratory effort is prolonged without any increase in tidal volume (9). Increasing the inspiratory time may increase the risk of developing auto-PEEP while reducing the expiratory time in ACV. Although it was not possible to measure auto-PEEP in all patients with severe breath stacking in our study, visual inspection of the flow waveform did not show any obvious increase in auto-PEEP. Finally, contrary to increasing inspiratory time in ACV while tidal volume remained constant, switching to PSV was associated with an increased tidal volume compared with that which was set in ACV. However, tidal volume in PSV was less than that of a stacked breath and less than 12 mL/kg, which was the large tidal volume used in the standard group of the first ARDS Net study. Because it is likely necessary to keep to the recommended low tidal-volume strategy, switching to PSV may have adverse effects mediated by larger tidal volumes. Further studies are needed to evaluate this new strategy.

Switching to PSV was associated with a significant and drastic decrease in mean airway pressure. Because we did not measure transpulmonary pressure, it is not possible to provide details as to whether PSV might alter the risk for barotrauma compared with the baseline of stacked breaths in our patients (32). Supported spontaneous ventilation could be preferable to control modes for other reasons. Diaphragmatic motion is more physiological during spontaneous breathing with motion of posterior portions of the diaphragm leading to aeration of dependent regions of the lungs in patients ventilated in the supine position (33). Compared with ACV, activation of the diaphragm during expiration, activation of abdominal muscles, and mismatch in timing and amplitude of endogenous respiratory activity with the mechanical ventilator could be less in PSV. This could explain in part the decrease in airway pressure observed with a better patient–ventilator synchrony. This may improve ventilation/perfusion matching, reduced histologic damage, and better gas exchange (34, 35). Besides changes in lung ventilation/perfusion, venous return to the heart and cardiac output is greater in PSV compared with a control mode (36). Spontaneous ventilation could conceivably result in improved organ perfusion and lesser degrees of organ dysfunction or failure in the mechanically ventilated patient (37). For these reasons, PSV has been increasingly used not only in patients being weaned from mechanical ventilation (6) but also in more severe patients with mild ARDS (38).

Using a ventilatory mode facilitating spontaneous breathing early in the course of respiratory failure may also decrease ventilator-induced diaphragmatic dysfunction. This complication is observed rapidly after the beginning of mechanical ventilation

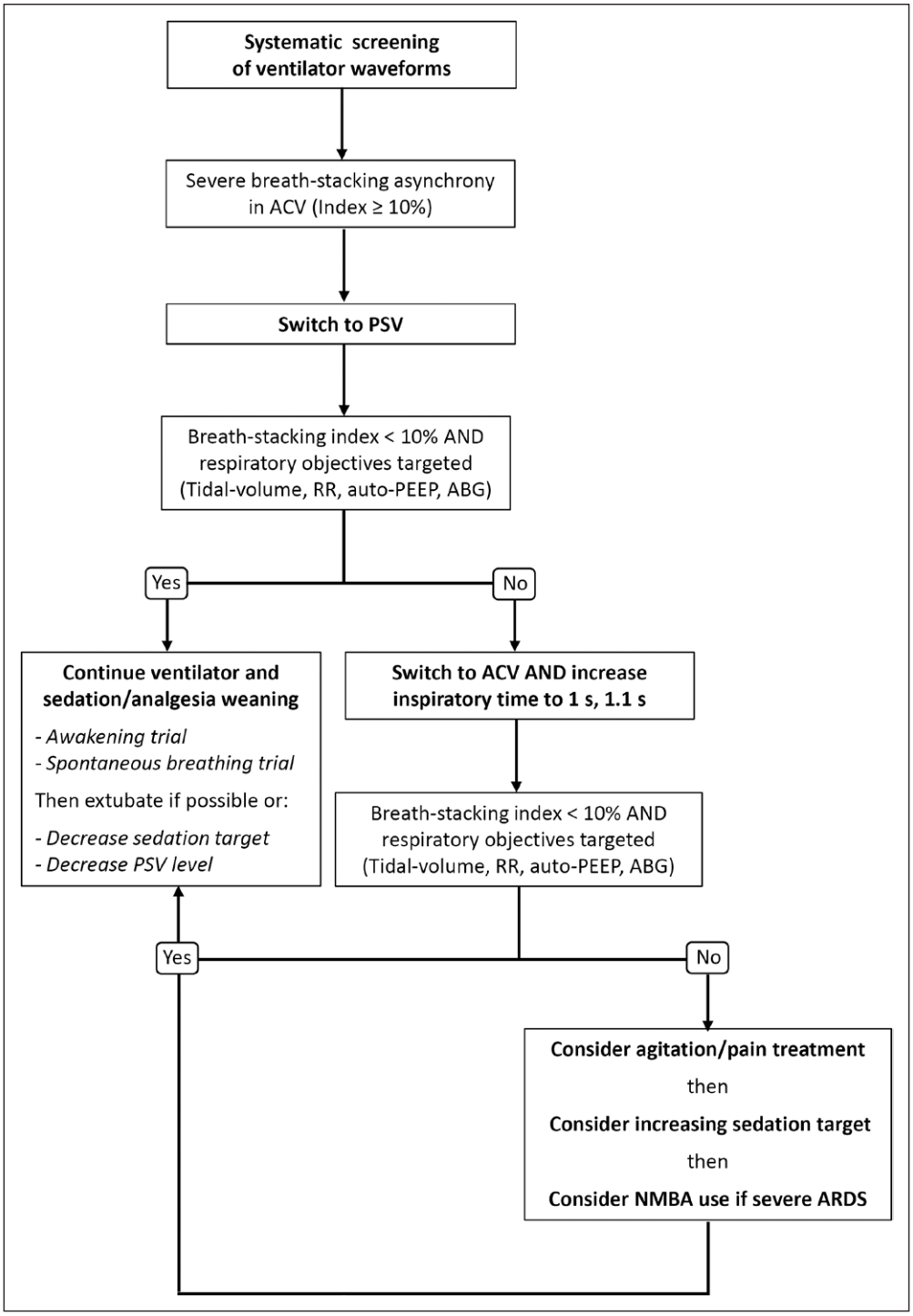

Figure 6. Proposition of a bedside decision-making algorithm to treat breath-stacking asynchrony. ACV = assist-control volume, PSV = pressure-support ventilation, RR = respiratory rate, PEEP = positive end-expiratory pressure, ABG = arterial blood gas, NMBA = neuromuscular blocking agent, ARDS = acute respiratory distress syndrome.

(39, 40). An experimental study in piglets showed that maintaining diaphragmatic contractile activity results in less decrease in diaphragmatic strength and atrophy compared with fully controlled mechanical ventilation (41). In this study, sedative and analgesic doses were reduced to allow spontaneous breathing, and hence, it was not possible to completely differentiate the drug effects from those related to the ventilatory mode. Indeed, in the clinical realm, mechanical ventilation and sedation/analgesia are often intricately intertwined, particularly when controlled modes are used, as shown by the response of clinicians in our study to often increase drug doses in response to asynchrony.

Our study has several limitations. As mentioned above, we did not use an esophageal manometer. Thus, we were not able to measure transpulmonary pressure and work of breathing. However, the primary endpoint of the study was to measure the impact of clinical interventions on breath-stacking asynchrony. Although an esophageal catheter might have use in future studies aimed at investigating lung mechanics with different ventilator settings used to reduce double stacking, it was not possible to use such a device for this first observational study. Indeed, the insertion procedure might have been associated with pain or agitation and a possible need to increase sedation that was against the purpose of the study. Also, an esophageal catheter, although essential to determine all forms of patient effort in interacting with the ventilator, is not required to assess breath stacking, which is the easiest recognizable type of patient/ventilator asynchrony, measured by bedside inspection of ventilator waveforms (8, 42). Other types of asynchrony such as wasted efforts are less readily detected using waveform analysis without a measurement of diaphragmatic electrical activity (13). Second, the inspiratory time in our study was much shorter at baseline than that used in the ARDS network protocol (inspiration to expiration duration ratio between 1:1 and 1:3, leading to set an inspiratory time between 0.83 and 1.66 s for a respiratory rate of 18 breaths/min) (1). This could explain the high prevalence of severe breath-stacking in our population and that the increase

in inspiratory time to 1 second drastically improved this kind of asynchrony. Even if the ARDS network protocol is recommended in patients with ARDS and with minimal spontaneous breathing, it could be preferable to set the ventilator in the general population to maintain an inspiratory time around 1 second, avoiding too short or too long timings, in order to limit the risk of breath stacking and auto-PEEP. Contrary to control modes, only PSV or new modes (Neurally Adjusted Ventilatory Assist or Proportional Assist Ventilation Plus) allow patients to determine their own inspiratory time. Also, the impact of the type of delivered mode, that is, volume versus pressure mode on the pressure and severity of double stacking was not specifically evaluated. The degree of freedom for patient–ventilator interaction in ACV which is a constant-flow mode is limited. This might be different in other modes such as pressure-control ventilation. Similarly, the type of trigger delivering assistance, that is, flow versus pressure, was not evaluated. Third, the increases in sedation/analgesia by the primary care team in this study may not have been sufficient to abolish patients' inspiratory effort and asynchrony although sufficient to treat pain and agitation in almost all the cases. Furthermore, further increases in sedation/analgesia would likely have been associated with adverse hemodynamic effects and/or increased duration of awakening and weaning from mechanical ventilation. Finally, because interventions were not randomized, a multivariate analysis was performed to deal with factors that might have influenced the primary care team strategy to reduce breath stacking. However, subjective factors, overall strategy, and Hawthorne effect influencing the primary care team decision could not be evaluated.

Because mechanical ventilation and sedation/analgesia are so intertwined and considering the limitations of this physiological observational study, we nonetheless propose a simple rationale that should help clinicians manage severe breath-stacking asynchrony (**Fig. 6**). Objectives of this algorithm are to avoid unnecessary increases in the dosing of sedation/analgesia while promoting spontaneous breathing whenever it is possible (Fig. 6).

In conclusion, severe breath-stacking asynchrony is treated mostly by bedside nurses and residents by increasing sedation/analgesia. Although effective to treat pain and agitation if present, increasing sedation/analgesia is less effective on breath stacking than adjusting the ventilator setting. The latter intervention may require more specialized skill and is therefore mostly done by senior physicians. Simple adjustments such as switching ACV to PSV, or increasing inspiratory time to 1 second in ACV, are independently associated with breath-stacking reduction. Whether these strategies could improve patient outcomes compared with increased sedation/analgesia or to simply tolerate breath stacking will require further investigations.

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