ORIGINAL

Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: the BREATHE criteria

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Abstract

Purpose: Breath stacking dyssynchrony generates higher tidal volumes than intended, potentially increasing lung injury risk in acute respiratory distress syndrome (ARDS). Lack of validated criteria to quantify breath stacking dyssynchrony contributes to its under-recognition. This study evaluates performance of novel, objective criteria for quantifying breath stacking dyssynchrony (BREATHE criteria) compared to existing definitions and tests if neuromuscular blockade eliminates high-volume breath stacking dyssynchrony in ARDS.

Methods: Airway flow and pressure were recorded continuously for up to 72 h in 33 patients with ARDS receiving volume-preset assist-control ventilation. The flow–time waveform was integrated to calculate tidal volume breath-by-breath. The BREATHE criteria considered five domains in evaluating for breath stacking dyssynchrony: ventilator cycling, interval expiratory volume, cumulative inspiratory volume, expiratory time, and inspiratory time.

Results: The observed tidal volume of BREATHE stacked breaths was 11.3 (9.7–13.3) mL/kg predicted body weight, significantly higher than the preset volume [6.3 (6.0–6.8) mL/kg; $p < 0.001$]. BREATHE identified more high-volume breaths ($\geq$2 mL/kg above intended volume) than the other existing objective criteria for breath stacking [27 (7–59) vs 19 (5–46) breaths/h; $p < 0.001$]. Agreement between BREATHE and visual waveform inspection was high (raw agreement 96.4–98.1 %; phi 0.80–0.92). Breath stacking dyssynchrony was near-completely eliminated during neuromuscular blockade [0 (0–1) breaths/h; $p < 0.001$].

Conclusions: The BREATHE criteria provide an objective definition of breath stacking dyssynchrony emphasizing occult exposure to high tidal volumes. BREATHE identified high-volume breaths missed by other methods for quantifying this dyssynchrony. Neuromuscular blockade prevented breath stacking dyssynchrony, assuring provision of the intended lung-protective strategy.

Keywords: Acute respiratory distress syndrome, Acute lung injury, Ventilator-induced lung injury, Respiratory mechanics, Mechanical ventilation, Patient–ventilator dyssynchrony

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Introduction

Low tidal volume ventilation limits ventilator-induced lung injury (VILI) and improves survival from acute respiratory distress syndrome (ARDS) [1, 2]. However, restricting tidal volume (V_T) may contribute to patient–ventilator dyssynchrony [3].

Breath stacking dyssynchrony (BSD) is a patient–ventilator interaction in which consecutive machine inspiratory cycles occur in close succession with incomplete exhalation between them (Fig. 1), typically owing to inspiratory muscle effort early during the machine expiratory phase. As a result, higher V_T than intended may be delivered [3–9], likely increasing VILI risk. Prevention of BSD-mediated lung overdistension has been suggested to be a mechanism by which early neuromuscular blockade (NMB) improves survival in ARDS [10, 11].

BSD-mediated overdistension may not be recognized reliably by monitoring conventional metrics of VILI risk. Plateau pressure requires absence of respiratory muscle effort during measurement and thus excludes BSD breaths. Peak airway pressures may not change sufficiently to trigger alarms during BSD if inspiratory muscle effort is sustained throughout the second machine inspiratory cycle. The incorrect, widely held view that the clinician sets V_T in the volume assist-control mode [12–14] further impedes recognition of BSD. The clinician sets only the machine inspiratory cycle volume in volume assist-control. Patient inspiratory muscle effort can dictate the number and timing of machine inspiratory cycles (as in any assist-control mode), including whether complete exhalation occurs between them [3, 6, 9, 15]. Thus, in the setting of BSD, the patient can determine the true V_T delivered regardless of assist-control mode employed.

Lack of a gold standard measure likely contributes to under-recognition of BSD. Chanques et al. [3] define BSD as "inspiratory flow triggered before complete expiration." Such clinical definitions [3, 6, 16] offer face validity but are subject to inter-rater discordance and preclude automated measurement required for scalability. Thille et al. [5] define double triggering as "two [inspiratory] cycles separated by a very short expiratory time, defined as less than one-half the mean inspiratory time, the first cycle being patient-triggered." Several subsequent investigations have adopted the Thille definition [7, 17, 18], although it too has limitations when applied to BSD. When most/all of the previous inspiratory cycle volume is exhaled, breaths are not "stacked" according to the literal meaning of the term, regardless of the proximity of inspiratory cycles. Similarly, if the preset inspiratory time is comparatively short, the Thille definition may fail to identify breaths that produce incomplete exhalation and result in overdistension, i.e., "stacked" breaths.
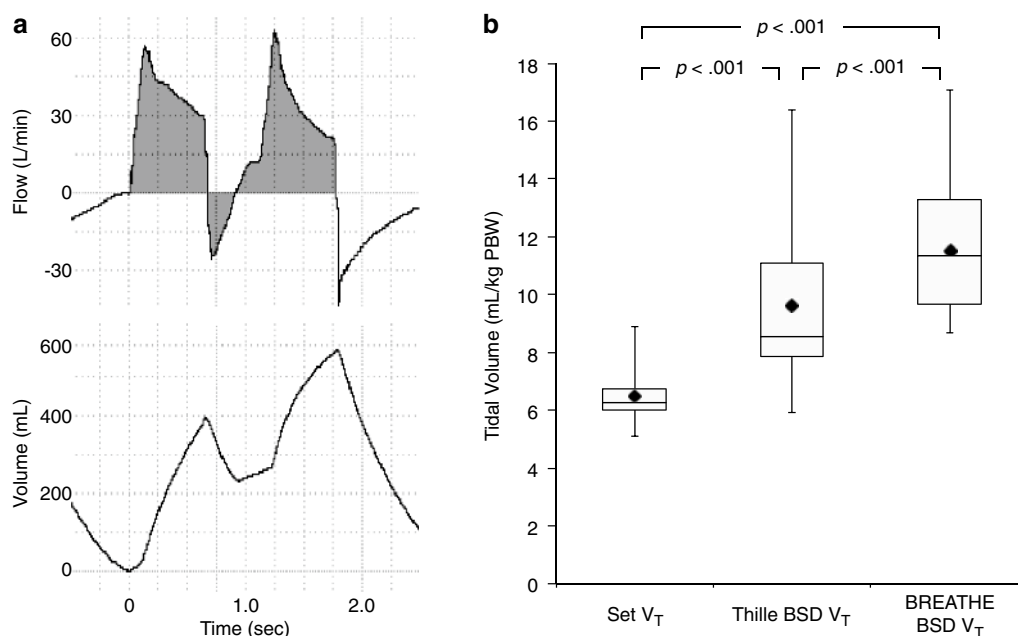

Fig. 1 Tidal volume delivered during breath stacking dyssynchrony. **a** Integration of the flow–time waveform during consecutive inspiratory cycles with incomplete interval exhalation (*shaded area* under the flow–time curve) was used to calculate the true tidal volume delivered. **b** Comparison of preset tidal volume with actual volume delivered during breath stacking dyssynchrony according to the Thille and BREATHE criteria. *Box plots* illustrate median and interquartile range (*boxes*), mean (*diamond*), and maximum and minimum values (*whiskers*). *BSD* breath stacking dyssynchrony, *PBW* predicted body weight, V_T tidal volume

Table 1 BREATHE criteria for quantifying breath stacking dyssynchrony (BSD)

	Criterion	Rationale for inclusion
1. Ventilator cycling	Consecutive inspiratory cycles	Preserve historical meaning of terminology
2. Expiratory time threshold	<1 s	Face validity
		Lay definition: inspiratory cycles "in close proximity"
		Duration sufficient to be inclusive if volume criteria met
3. Expiratory volume threshold	Expiratory volume between inspiratory cycles at least 2 mL/kg PBW less than first inspiratory cycle volume	Lay definition: "incomplete exhalation"
		Exclude false positives from rapid brief inspiratory flow followed by near-complete exhalation
4. Inspiratory time threshold	$\geq$120 % set inspiratory time *(Pressure-targeted breaths only)*	Distinguish BSD from high-volume breaths due to patient effort within normal inspiratory cycle
5. Inspiratory volume threshold	BSD $V_T \geq$ 2 mL/kg PBW above intended V_T	Translate literal meaning of term "stacked" breaths
		Biological relevance to lung injury risk

Application of criteria: consecutive machine inspiratory cycles that met the expiratory time and expiratory volume thresholds (criteria 1–3) were treated as a single breath in evaluating remaining criteria. For pressure-targeted breaths (in pressure assist-control and volume-targeted pressure control modes), the inspiratory time criterion was then applied (criterion 4). Finally, inspiratory cycle pairs that met the prior criteria were classified as BREATHE BSD only if the cumulative inspiratory volume (first inspiratory cycle volume + second inspiratory cycle volume − interval expiratory volume) met the inspiratory volume threshold (criterion 5)

To address these issues, we developed the BREATHE criteria (*B*reathing *R*ecognizing *E*xpected vs. *A*ctual *T*idal volume for lung *H*ealth *E*nhancement) (Table 1), an objective BSD definition emphasizing unintentional high V_T exposure that may contribute to lung injury. In this study, we (1) compared performance of the BREATHE criteria to other BSD definitions, (2) described the incidence of BSD in early ARDS, and (3) validated prior reports [3, 6] that BSD increases V_T in volume-preset assist-control modes. (4) We also tested whether NMB eliminates BSD-mediated high V_T in volume-preset assist-control modes.

Methods

Study population

Eligible patients were adults age at least 18 years with Berlin definition ARDS [19] for whom mechanical ventilation was initiated within the previous 24 h. Use of an assist-control mode at time of screening was required for eligibility. Patients were excluded for chronic mechanical ventilation, neuromuscular disease compromising spontaneous ventilation, or impending withdrawal of full supportive care. Patient enrollment was pursued regardless of whether dyssynchrony was evident at study screening. The study was approved with waiver of informed consent by the hospitals' institutional review boards.

Study procedures

Airway flow and pressure were recorded continuously for the first 72 h after enrollment or until discontinuation of mechanical ventilation. Waveforms were measured by an inline pressure/flow sensor (NM3/NICO Philips Respironics) connected to an analog–digital converter (Dataq Instruments). Visual inspection of raw waveforms, blinded to clinical outcomes, was performed for quality control and to code exclusion times during circuit disconnect, endotracheal suctioning, or water condensation in the recording circuit (Fig. E1). The resulting coded waveform files were read directly into Matlab (MathWorks) for analysis using an automated program developed by two of the authors (JRB, SAS) that applies the BREATHE criteria to quantify BSD.

Ventilator management, sedative titration, use of NMB, and all other clinical care were directed by the ICU team, led by an intensivist attending physician, without input from research staff. NMB, when prescribed, was initiated only after achieving deep sedation (RASS −4 or −5) and titrated at the treating physician's instruction without input from research staff; train of four was not universally monitored. Clinical team members were blinded to waveform recordings and analysis throughout the study but had access to any waveform graphics displayed on the ventilator screen per usual care.

BREATHE criteria for BSD

The BREATHE criteria were developed a priori by consensus with input from all authors. The criteria were intended to apply to patients receiving ventilatory support in assist-control modes (volume assist-control, pressure assist-control, and volume-targeted pressure control), in which preset ventilator parameters alone determine machine inspiratory cycle duration. Included were five domains of patient–ventilator interaction thought to be characteristic of BSD during assist-control ventilation: ventilator cycling, interval expiratory volume, cumulative inspiratory volume, expiratory time, and inspiratory time (Table 1). To apply these criteria, the flow–time waveform was integrated to calculate

cumulative volume change over consecutive machine inspiratory cycles that met the expiratory volume and expiratory time criteria. For pressure-targeted breaths (in pressure assist-control and volume-targeted pressure control modes), the inspiratory time criterion was then applied. Finally, eligible inspiratory cycle pairs for which cumulative inspiratory volume (first inspiratory cycle volume + second inspiratory cycle volume − any interval expiratory volume) met the inspiratory volume threshold were classified as BSD. Consecutive inspiratory cycles classified as BSD were counted as a single breath throughout the analysis.

Three clinically intuitive variables were created to summarize BSD-associated VILI risk. BSD V_T (mL/kg PBW) is calculated by integrating the flow waveform over consecutive ventilator cycles (Fig. 1a). BSD frequency is calculated as number of breaths meeting BSD criteria divided by the total time included in analysis. BSD minute-volume is the product of BSD V_T and BSD frequency.

Alternative criteria for BSD

The Thille method, described above, was applied using automated analysis with one modification to the original definition. To account for both double triggering and reverse triggering [9] as contributors to BSD, all breaths meeting the Thille expiratory time criterion were labeled as Thille BSD irrespective of whether the patient or machine initiated the first inspiratory cycle.

Clinical detection of BSD was performed by visually inspecting airway flow and pressure waveforms. Three hours per subject (99 h study-wide) were randomly selected for evaluation. When data were available for all three study days (e.g., no extubation or early death), 1 h/day was selected. Evaluation was performed independently by two attending intensivist physicians with expertise in mechanical ventilation. Evaluators were blinded to results of automated analyses applying BREATHE or Thille criteria and to clinical outcomes. Evaluators were asked to identify stacked breaths in the specified period by applying the following definition: "consecutive breaths occurring in close proximity with incomplete exhalation between them."

Statistical analysis

Results are presented as number (%), mean ± SD, median (interquartile range), estimated mean (95 % confidence interval), or range as appropriate. Two-sided alpha threshold of 0.05 was set for statistical significance. BSD summary statistics were calculated from individual patient-level results, thus accounting for between-patient differences in time recorded or excluded.

Performance of the BREATHE criteria vs. Thille criteria was analyzed using the proposed variables for quantifying VILI risk: BSD V_T, BSD frequency, and BSD minute-volume. Results were compared using the paired t test or one-sample Wilcoxon signed rank sum test as appropriate. To compare BREATHE and Thille to manual waveform inspection, raw and chance-independent agreement for identifying BSD breaths were calculated. Raw agreement was defined as the proportion of breaths that both raters concluded were or were not stacked. Chance-independent agreement was quantified using the phi statistic [20, 21], calculated as $\text{phi} = (\sqrt{\text{odds ratio}} - 1)/(\sqrt{\text{odds ratio}} + 1)$ and with range from −1.0 (complete disagreement) to 1.0 (perfect agreement). To evaluate physician ability to recognize occult high V_T from BSD, the proportion of breaths meeting BREATHE criteria that physicians failed to identify as BSD was also considered.

The effect of NMB on BSD frequency and BSD minute-volume was evaluated among participants in whom waveforms were recorded both during NMB and without NMB, allowing within-subject comparison. Linear mixed-effects models were used to study the longitudinal evolution of BSD frequency and BSD minute-volume accounting for between-subject variability (random subject effects) and evaluating fixed effects of NMB.

Results

Patient characteristics

Thirty-three patients were enrolled over 8 months at two academic US hospitals. Most participants had pneumonia (82 %) and shock (91 %). No patients had a history of chronic obstructive pulmonary disease. PaO_2/FiO_2 at enrollment was 107 (73–132) mmHg. All participants were ventilated in a volume-preset assist-control mode of ventilation at enrollment; over three-fourths received volume-targeted pressure control and the remainder traditional volume assist-control. Set V_T was 6.4 (6.0–7.0) mL/kg PBW and PEEP 10 (10–14) cmH$_2$O. Nine patients (27.3 %) died before hospital discharge or day 28 of enrollment. Additional patient characteristics are summarized in Table 2.

Recording characteristics

Time from onset of mechanical ventilation to initiating waveform recording was 15.9 ± 6.7 h. Study-wide, a total of 1841 h of waveform data [66 (44–72) h/patient] were recorded out of a possible 2171 h during which patients were alive, receiving mechanical ventilatory support, and thus eligible for recording. During manual coding, 413 h were excluded [22 % of total study-wide recorded time; 5.8 (2.4–19.0) h/patient], primarily for equipment disconnect (361 h for procedure, patient transporting, or accidental by clinical staff). Only 87 h [4.7 % of all recorded time; 0.8 (0.2–2.0) h/patient] were manually excluded

Table 2 Characteristics of study participants

Characteristic	All subjects ($n = 33$)
Age (years)	57 ± 17
Female	15 (45.5 %)
APACHE II	33 ± 7
Shock[a]	30 (90.9 %)
Risk factor for lung injury	
Pneumonia	27 (81.8 %)
Sepsis	24 (72.7 %)
Aspiration	9 (27.3 %)
Acute pancreatitis	2 (6.1 %)
Duration of mechanical ventilation prior to enrollment (h)	15.9 ± 6.7
Respiratory parameters at enrollment	
Volume-preset assist-control mode of ventilation[b]	33 (100 %)
Volume assist-control with ramp flow pattern	7 (21.2 %)
Volume-targeted pressure control	26 (78.8 %)
Set tidal volume (mL/kg PBW)	6.4 (6.0–7.0)
Set respiratory rate (breaths/min)	25 ± 5
Observed respiratory rate (breaths/min)	27 ± 5
Positive end-expiratory pressure (cmH_2O)	10 (10–14)
Plateau pressure (cmH_2O)	24 ± 4
Driving pressure (cmH_2O)	13 ± 4
Inspiratory time (s)	0.76 ± 0.11
FiO_2 (%)	50 (50–70)
Respiratory system compliance (mL/cmH_2O)	35 ± 11
PaO_2/FiO_2	107 (73–132)
Trigger type and sensitivity	
Flow trigger	30 (90.9 %)
Flow trigger threshold (L/min)	2.0 (2.0–3.0)
Pressure trigger	3 (9.1 %)
Pressure trigger sensitivity (cmH_2O)	2 (2–2)
ARDS severity, Berlin definition	
Mild	3 (9.1 %)
Moderate	15 (45.5 %)
Severe	15 (45.5 %)
Sedation level, RASS at enrollment	−3 (−4 to −1)
Any neuromuscular blockade during recording	10 (30.3 %)
Clinical outcomes	
Death before discharge or day 28	9 (27.3 %)
Ventilator-free days through day 28	14 ± 10
Non-pulmonary organ failure-free days through day 28	13 ± 9
Hospital-free days through day 28	9 ± 7

PBW predicted body weight, *FiO₂* fraction of inspired oxygen, *PaO₂* arterial blood oxygen tension, *RASS* Richmond agitation–sedation scale

[a] Shock was defined as systolic blood pressure ≤90 mmHg for at least 2 h or any vasopressor use

[b] Includes volume assist-control and mixed modes that deliver pressure-targeted breaths to achieve a preset tidal volume

for waveform quality control issues (Fig. E1; Table E1). A total of 2,166,076 breaths were analyzed study-wide (65,639 $\pm$ 32,590 breaths/patient), of which 1,737,473 (80 %) occurred without NMB.

BREATHE BSD characteristics

BSD frequency differed considerably between patients (Fig. 2). Averaged over the entire recording period, the observed BSD frequency was 27 (7–59) breaths/h without NMB. Peak hourly BSD frequency, calculated as the maximum BSD frequency averaged over a 1-h period for each patient, was 170 (55–394) breaths/h. BSD frequency was sustained for more than 60 breaths/h during 18 (1–37) % of hours recorded without NMB. At least one BSD breath occurred during 72 (60–94) % of hours recorded without NMB.

Within patient variability in hourly BSD frequency also was substantial (Fig. 2b, c). The median within-patient range in hourly BSD frequency was 168 (55–394) breaths/h without NMB.
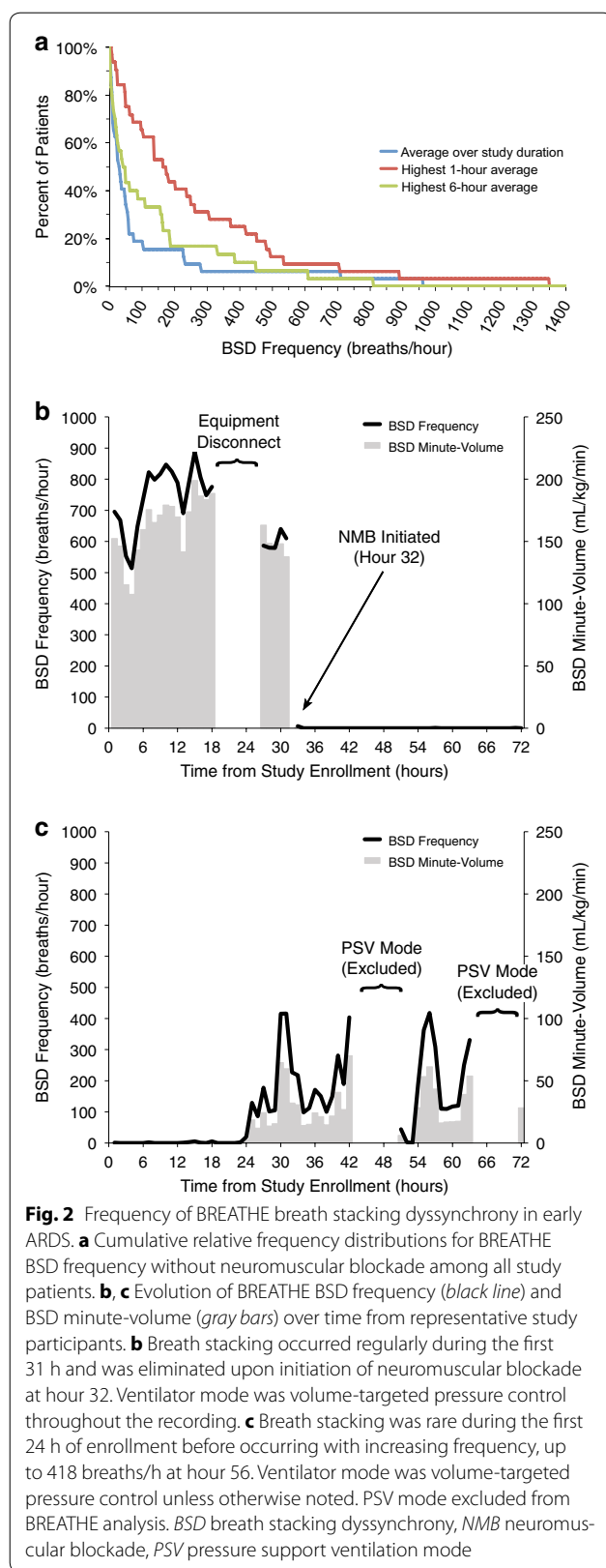
The observed BSD V_T was 11.3 (9.7–13.3) mL/kg PBW, which was significantly higher than the preset V_T of 6.3 (6.0–6.8) mL/kg PBW during those breaths ($p < 0.001$) (Fig. 1b). The resulting BSD minute-volume, defined as the product of BSD frequency (in breaths/min) and BSD V_T (in mL/kg PBW), was 5.4 (1.3–12.6) mL/kg/min.

Peak airway pressure increased minimally with BSD. Average peak airway pressure of BSD breaths was 30 ± 8 cmH_2O, compared with 28 ± 5 cmH_2O of non-BSD breaths (difference, 2 ± 4 cmH_2O; $p = 0.011$).

Performance of BREATHE vs. Thille criteria

BSD frequency averaged over the recording period was 43 (18–92) breaths/h applying the Thille criteria, significantly higher than found using the BREATHE criteria [difference, Thille vs. BREATHE frequency 9 (−2 to 27) breaths/h; $p = 0.012$] (Table 3). However, compared to the Thille approach, BREATHE detected significantly more high-volume breaths, defined as BSD $V_T \geq 2$ mL/kg PBW above the preset V_T [623 (235–2805) vs. 494 (127–1885) high-volume breaths/patient; $p < 0.001$] (Fig. E2). Twenty-eight percent of Thille BSD breaths were less than 2 mL/kg PBW above the preset V_T.

Thille BSD V_T of 8.6 (7.9–11.1) mL/kg PBW was higher than the preset V_T [6.3 (6.0–6.8) mL/kg PBW] but significantly lower than BREATHE's V_T of 11.3 (9.7–13.3) mL/kg PBW ($p < 0.001$ for all comparisons). BSD minute-volume did not differ significantly between approaches [BREATHE 5.4 (1.3–12.6) vs. Thille 6.6 (2.5–13.5) mL/kg/min; $p = 0.109$]. However, considering only high-volume

Fig. 2 Frequency of BREATHE breath stacking dyssynchrony in early ARDS. **a** Cumulative relative frequency distributions for BREATHE BSD frequency without neuromuscular blockade among all study patients. **b**, **c** Evolution of BREATHE BSD frequency (*black line*) and BSD minute-volume (*gray bars*) over time from representative study participants. **b** Breath stacking occurred regularly during the first 31 h and was eliminated upon initiation of neuromuscular blockade at hour 32. Ventilator mode was volume-targeted pressure control throughout the recording. **c** Breath stacking was rare during the first 24 h of enrollment before occurring with increasing frequency, up to 418 breaths/h at hour 56. Ventilator mode was volume-targeted pressure control unless otherwise noted. PSV mode excluded from BREATHE analysis. *BSD* breath stacking dyssynchrony, *NMB* neuromuscular blockade, *PSV* pressure support ventilation mode

breaths, BSD minute-volume was significantly higher when applying the BREATHE criteria [BREATHE 5.4 (1.3–12.6) vs. Thille 3.6 (0.8–9.2) mL/kg/min; $p < 0.001$].

Performance of automated criteria vs. visual waveform inspection

Two intensivist physicians evaluated 143,199 breaths acquired over 99 h to identify BSD breaths applying the aforementioned clinical definition without automated support. The physician pair's visual inspection demonstrated high raw and chance-independent interobserver agreement overall (raw agreement, 97.5 %; phi, 0.89; Table E2), including near-perfect agreement during volume assist-control (raw agreement, 99.7 %; phi, 0.98) with slightly less agreement during volume-targeted pressure control (raw agreement, 96.9 %; phi, 0.87). When one physician classified a breath as stacked, the other physician agreed on 67–84 % of breaths overall, including 90–96 % of breaths during volume assist-control and 64–83 % of breaths during volume-targeted pressure control.

Each physician also demonstrated reasonably high raw and chance-independent agreement with BREATHE BSD (raw agreement, 98.1 and 96.4 %; phi, 0.92 and 0.80, respectively for each physician rater). When BREATHE identified a breath as stacked, at least one physician agreed on 59–90 % of breaths, comparable to between-physician agreement on BSD classification by visual inspection (Tables E3, E4; Fig. E2). Agreement between visual waveform inspection and BREATHE was near-perfect during volume assist-control (raw agreement, 99.8 and 99.7 %; phi, 0.99 and 0.99), during which blinded manual inspection concurred with 98–99 % of BREATHE BSD breaths. Agreement was poorer during volume-targeted pressure control (raw agreement, 97.6 and 95.5 %; phi, 0.91 and 0.76), during which blinded manual inspection identified 55–89 % of BREATHE BSD breaths (Fig. E3).

Compared to their agreement with BREATHE, agreement of each physician's visual inspection with the Thille criteria was slightly less (raw agreement, 97.4 and 95.3 %; phi, 0.88 and 0.76; Tables E5 and E6). This pattern held true for chance-independent agreement both during volume assist-control (raw agreement, 97.7 and 97.5 %; phi, 0.87 and 0.84) and volume-targeted pressure control (raw agreement, 97.4 and 94.7 %; phi, 0.89 and 0.74). When Thille identified a breath as stacked, at least one physician agreed on 48–74 % of breaths overall, including just 48–49 % of breaths during volume assist-control and 48–78 % of breaths during volume-targeted pressure control.

Table 3 Performance of criteria for breath stacking dyssynchrony

	BREATHE criteria	Thille et al. criteria	*p* value
Number of breaths per patient			
No. breaths analyzed[a]	54,296 ± 31,500	55,085 ± 32,232	0.018
No. breaths meeting stacked criteria	623 (235–2805)	1147 (726–2930)	0.034
No. stacked ≥2 mL/kg PBW	623 (235–2805)	494 (127–1885)	<0.001
BSD frequency			
No. stacked per hour	27 (7–59)	43 (18–92)	0.012
No. stacked per hour ≥2 mL/kg PBW	27 (7–59)	19 (5–46)	<0.001
Tidal volume			
Set V_T (mL/kg PBW)	6.3 (6.0–6.8)	6.2 (6.0–6.8)	0.204
BSD V_T (mL/kg PBW)	11.3 (9.7–13.3)	8.6 (7.9–11.1)	<0.001
V_T difference, BSD minus set (mL/kg PBW)	4.8 (3.5–6.3)	2.4 (1.7–4.3)	<0.001
Minute-volume			
BSD minute-volume (mL/kg/min)	5.4 (1.3–12.6)	6.6 (2.5–13.5)	0.109
BSD minute-volume, breaths with $V_T \geq 2$ mL/kg PBW only	5.4 (1.3–12.6)	3.6 (0.8–9.2)	<0.001

During assist-control modes without neuromuscular blockade

No. number, *BSD* breath stacking dyssynchrony, V_T tidal volume, *PBW* predicted body weight

[a] Number of breaths analyzed differs because BSD criteria differ: when consecutive inspiratory cycles met criteria for BSD, they were counted as a single breath

Table 4 Breath stacking dyssynchrony applying BREATHE criteria among recipients of neuromuscular blockade

Stacked breath characteristic	During paralysis	Absent paralysis	*p* value
No. breaths analyzed	42,860 ± 24,057	46,677 ± 31,697	0.811
No. stacked breaths	5 (2–15)	576 (53–1332)	0.004
No. stacked per hour	0 (0–1)	23 (7–31)	0.004
Set V_T of stacked breaths (mL/kg PBW)	6.0 (5.8–6.3)	6.3 (6.0–6.8)	0.125
BSD V_T (mL/kg PBW)	11.8 (11.1–14.1)	11.5 (10.5–13.3)	0.461
V_T difference, BSD minus set (mL/kg PBW)	5.5 (3.9–8.5)	5.1 (4.4–5.9)	0.313
BSD minute-volume (mL/kg/min)	0.0 (0.0–0.2)	4.4 (1.1–7.3)	0.004

No. number, *BSD* breath stacking dyssynchrony, V_T tidal volume, *PBW* predicted body weight

Effect of neuromuscular blockade

Ten patients received NMB during waveform recording: seven received cisatracurium [infusion rate 0.12 (0.08–0.14) mg/kg/h] and three received rocuronium [infusion rate 8 (8–10) µg/kg/min]. Applying the BREATHE criteria, BSD frequency during NMB was 0 (0–1) breaths/h and BSD minute-volume 0.0 (0.0–0.2) mL/kg/min. No BSD breaths occurred during 88 % percent of hours recorded during NMB. BSD frequency exceeded five breaths/h only 1 % of the time during NMB (Table 4). BSD frequency did not differ by paralytic administered.

Among the nine patients who received paralytics for only a portion of the recording period, BSD minute-volume was significantly lower during NMB vs. non-NMB independent of time (β = −22.5, 95 % CI −27.7 to −17.3 mL/kg/min for change in BSD minute-volume during NMB vs. no NMB; *p* < 0.001). BSD frequency similarly was significantly lower during NMB independent of time (β = −103.5, 95 % CI −126.9 to −80.1 stacked breaths/h; *p* < 0.001) (Fig. 2). Ventilator settings, including preset V_T, inspiratory time, and trigger sensitivity, did not differ significantly during NMB vs non-NMB.

Discussion

The BREATHE criteria were developed specifically to quantify occult high V_T exposure from breath stacking dyssynchrony (BSD) and address the lack of a gold standard for BSD objective measurement. The term "breath stacking" implies higher-than-intended V_T due to incomplete exhalation between consecutive inspiratory cycles. The Thille definition, intended by its authors to describe double triggering (not BSD per se), emphasizes expiratory time and does not incorporate a V_T threshold. It is not surprising therefore that BREATHE, by excluding low-volume breaths, overall classified fewer breaths as stacked than the Thille method. Yet, BREATHE also consistently identified high-volume inspiratory cycle pairs not deemed to be stacked by the Thille method. Thus,

BREATHE is both a more sensitive and more specific method than Thille for detecting high-volume inspiratory cycle pairs, with resultant V_T at least 2 mL/kg PBW above the preset value. Indeed, visual waveform inspection concurred with BREATHE more often than with Thille, indicating the BREATHE criteria offer a truer translation of the lay definition of BSD.

BREATHE also outperformed visual waveform inspection at identifying occult high-volume insufflation from BSD. This finding highlights the potential for automated analyses to enhance detection of important patient–ventilator interactions. Near-perfect agreement was found between BREATHE and visual inspection during the volume assist-control mode, conferring face validity to BREATHE and validating prior reports [3, 6] that relied on visual identification of BSD during volume assist-control ventilation. Yet, during volume-targeted pressure control, physician waveform inspection regularly missed several high-volume BSD breaths detected by BREATHE. In this mode, individual breaths are pressure-targeted and time-cycled; the machine varies the target inspiratory pressure breath-to-breath to approximate the preset volume. With sufficient inspiratory muscle effort during a machine inspiratory cycle, driving pressure may approach zero. Consistent visual detection of BSD from airway flow and pressure waveforms therefore becomes exceedingly difficult without measuring breath-by-breath inspiratory time, using the flow waveform, to determine whether more than one inspiratory cycle occurred (Fig. E3). Interobserver agreement between physicians was lowest during volume-targeted pressure control and was comparable to agreement between each physician and the BREATHE criteria.

This study validates prior reports that occult high V_T exposure from BSD can occur commonly during volume-preset lung-protective ventilation for ARDS. Building on these findings, we found that, by preventing BSD, NMB lowers the V_T delivered during volume-preset assist-control ventilation. These results suggest one plausible causal pathway for the ACURASYS trial's finding that NMB prevents barotrauma even during protocolized volume-preset lung-protective ventilation [11]. In addition to BSD, cyclic opening/collapse of lung units, pendelluft, and differences in regional ventilation may play important roles in propagating VILI during active respiratory muscle effort [22]. Cisatracurium also may attenuate lung and systemic inflammation directly, e.g., via inhibition of nicotinic acetylcholine receptor α1 expressed by endothelial and epithelial cells and macrophages involved in proinflammatory signaling [23].

Certain limitations to this study should be noted. First, while the preponderance of literature supports our assumption that frequent high V_T from BSD increases VILI, we did not test this association directly. We speculate that this association may not be linear but J-shaped. Frequent BSD that causes most breaths to be high volume almost certainly induces VILI. Yet, infrequent high-volume breaths may be protective by promoting sustained alveolar recruitment [24–27] and endogenous surfactant release [28]. The dose–response curve between intermittent high-V_T breaths and VILI, including the importance of exposure intensity [29], remains to be described.

Second, the BREATHE criteria require the observed BSD V_T exceed intended V_T by at least 2 mL/kg PBW. This threshold was chosen to reflect the literal meaning of breath "stacking" while considering the clinically permissible V_T range routinely adopted in ARDS clinical trials and practice. The original ARDSNet low-V_T protocol targeted V_T of 6 mL/kg PBW but permitted increasing V_T by as much as 2 mL/kg PBW for severe dyspnea, dyssynchrony, or acidemia [1]. Importantly, BREATHE BSD breaths were not clustered around this volume threshold, indicating that inspiratory cycle pairs of comparable volume were not excluded arbitrarily. Mean BSD V_T was at least 3.5 mL/kg PBW above preset V_T in 75 % of patients and 2.6 mL/kg PBW or more above preset V_T in all patients. Still, the biologically safe V_T range to avoid VILI is unclear and likely depends on multiple factors, including ARDS baby lung volume [30, 31], stress concentration from regional inhomogeneity of lung parenchyma [32], frequency of exposure to intermittent high-volume breaths [33], and extent of immunological priming [34], among other factors.

Finally, this study did not distinguish underlying mechanisms that lead to BSD. At least two distinct BSD endotypes exist: double and reverse triggering. Double triggering occurs when a single sustained patient inspiratory effort persists beyond the end of a patient-initiated machine inspiratory cycle, triggering a second inspiratory cycle with incomplete interval exhalation [3, 6, 18, 35]. Reverse triggering describes rhythmic passive ventilator-initiated insufflations that induce diaphragm entrainment (periodic muscle contraction phase-locked with an extrinsic oscillator), resulting in BSD if out of phase with the machine [9, 36, 37]. These two endotypes likely respond differently to therapeutic interventions given their distinct underlying mechanisms, even though their clinical phenotype (BSD) and relevance to overdistension-mediated VILI may be similar. Autotriggering, in which oscillations in the ventilator circuit (e.g., sloshing water in tubing, transmitted cardiac oscillations) trigger machine inspiratory cycles independent of respiratory muscle effort, rarely also may produce stacked breaths.

In conclusion, frequent BSD can result in regular exposure to potentially injurious high V_T despite ventilator settings consistent with a lung-protective strategy. NMB

was associated with near-complete elimination of BSD, assuring provision of the intended low-V_T strategy. The BREATHE criteria offer the first objective definition of BSD that emphasizes occult, unintended exposure to high tidal volumes, and identified several high-V_T breaths missed by previously proposed methods for BSD quantification.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4423-3) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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