

Frequency and Risk Factors for Reverse Triggering in Pediatric ARDS During Synchronized Intermittent Mandatory Ventilation

Tatsutoshi Shimatani (✉ tatsutoc@gmail.com)

Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan 2. Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Los Angeles 4650 Sunset Boulevard, Los Angeles, CA 90027 <https://orcid.org/0000-0002-0148-2924>

Benjamin Yoon

Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Los Angeles

Miyako Kyogoku

Department of Intensive Care Medicine, Osaka Women's and Children's Hospital

Michihito Kyo

Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University

Shinichiro Ohshimo

Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University

Christopher JL Newth

Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Los Angeles

Justin C. Hotz

Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Los Angeles

Nobuaki Shime

Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University

Robinder G. Khemani

Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Los Angeles

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Abstract

[BACKGROUND]

Reverse triggering (RT) occurs when respiratory effort begins after a mandatory breath is initiated by the ventilator. RT may exacerbate ventilator-induced lung injury and lead to breath stacking. We sought to describe the frequency and risk factors for RT amongst ARDS patients and identify risk factors for breath-stacking.

[METHODS]

Secondary analysis of physiologic data from children on Synchronized Intermittent Mandatory pressure control ventilation enrolled in a single center RCT for ARDS. When children had a spontaneous effort on esophageal manometry, waveforms were recorded and independently analyzed by two investigators to identify RT.

[RESULTS]

We included 81,990 breaths from 100 patient-days and 36 patients. Overall, 2.46% of breaths were RTs, occurring in 15/36 patients (41.6%). Higher tidal volume and a minimal difference between neural respiratory rate and set ventilator rate were independently associated with RT ($p = 0.001$) in multivariable modeling. Breath stacking occurred in 534 (26.5%) of 2017 RT breaths, and 14 (93.3%) of 15 RT patients. In multivariable modeling, breath stacking was more likely to occur when total airway delta pressure (Peak Inspiratory Pressure-PEEP) at the time patient effort began, Peak Inspiratory Pressure, PEEP, and Delta Pressure were lower, and when patient effort started well after the ventilator initiated breath (higher phase angle) (all $p < 0.05$). Together these parameters were highly predictive of breath stacking (AUC 0.979).

[CONCLUSIONS]

Patients with higher tidal volume and who have a set ventilator rate close to their spontaneous respiratory rate are more likely to have RT, which results in breath stacking over 25% of the time.

Trial registration: NIH/NHLBI R01HL124666, Clinical Trials.gov NCT03266016, Registered 29 August 2017, <https://clinicaltrials.gov/ct2/show/NCT03266016>

[background]

Patient-ventilator asynchrony (PVA) is increasingly recognized as a serious complication of mechanical ventilation. A number of investigators have proposed definitions for PVA and many types of PVA have been associated with prolonged length of mechanical ventilation¹, ICU and hospital mortality².

In recent years, reverse triggering (RT) has been identified as an underrecognized form of PVA. RT occurs when the patient has respiratory effort after a mandatory breath is initiated by the ventilator. RT can lead to unintended consequences with mechanical ventilator breaths, including double-triggering, breath stacking, and higher than desired driving pressure³ which may exacerbate ventilator-induced lung injury. This is particularly important when it leads to breath stacking⁴.

RT likely occurs from respiratory entrainment, in which the patient's respiratory control system resets the respiratory rhythm such that the neural respiratory activity corresponds to machine inflations. This concept of entrainment has been described for years, and a variety of animal studies⁵⁻⁷ suggest more entrainment seems to occur when machine delivered tidal volume is higher, and flow is low. Animal data also suggests entrainment to the ventilator is mediated by the Hering-Breuer reflex, as it is lost after bilateral vagotomy. Respiratory entrainment is secondarily mediated by rapidly adapting receptors and vagal C fibers, along with cortical and subcortical influence⁴. Human data corroborates the importance of the Hering-Breuer reflex in the physiology of respiratory entrainment, and highlights that sustained entrainment with machine breaths is most common when the ventilator rate is set just above the spontaneous neural respiratory rate⁸.

While the concept of entrainment has been described for decades, contemporary data is lacking regarding the frequency with which RT occurs in critically ill patients with lung injury, the risk factors for RT, and the frequency with which RT results in potentially injurious ventilator settings. This data is crucial to better understand the magnitude of the problem, identify high risk patients, and ultimately devise effective strategies to prevent RT. We sought to describe the frequency with which RT occurs in pediatric ARDS patients, describe differences in characteristics between patients who have RT and those who do not, and identify factors which make it more likely for RT breaths to result in breath stacking.

[methods]

We performed secondary analysis of physiologic data from esophageal pressure, airway pressure and flow from ventilated children enrolled in an ongoing single center randomized clinical trial testing a lung and diaphragm protective ventilation strategy (REDvent, NIH/NHLBI R01HL124666, ClinicalTrials.gov NCT03266016)⁹ in the intensive care units at Children's Hospital Los Angeles. Based on previous literature and animal studies, we hypothesized that higher tidal volume and a set ventilator rate close to neural respiratory rate would be risk factors for RT, and that breath stacking would be very common when RT occurred.

All patients were enrolled in the parent REDvent study, which included children between 1 month and \leq 18 years of age who are within 48 hours of initiation of invasive mechanical ventilation with Pediatric Acute Respiratory Distress Syndrome (PARDS) with Oxygen Saturation Index (OSI) \geq 5 or Oxygenation Index (OI) \geq 4). Children were excluded if they had a contraindication to use of an esophageal catheter or respiratory inductance plethysmography bands, or had conditions that precluded conventional methods of weaning (i.e., severe lower airway obstruction, critical airway, intracranial hypertension, Extra Corporeal

Life Support (ECLS), do-not resuscitate, severe chronic respiratory failure, spinal cord injury, cyanotic heart disease (unrepaired or palliated).

As part of the parent trial, children were randomized to usual care ventilation versus ventilator management which uses a computerized decision support tool to achieve lung and diaphragm protective ventilation. Esophageal catheters were placed in all children in the study and were used to measure effort of breathing continuously for titration of ventilator support in the intervention arm and were used for once a day monitoring and data collection in the control arm. SIMV Pressure Control/Pressure support is the mode of ventilation used in both arms. Physiologic waveforms of esophageal pressure (Pes), flow, and airway pressure (Paw) were recorded daily for patients in both intervention and control arms. For this secondary analysis, we included the subset of children who had evidence of spontaneous respiratory effort on a given day, as determined by esophageal manometry. Data was recorded for 30 minutes, and no specific interventions (such as changes to ventilator settings etc.) were performed during this time.

Hardware and Software

Airway pressure was measured with a proximal sampling line placed just after the endotracheal tube, along with a self-calibrating pneumotachometer (Viasys Variflex 51000 – 40094). One of 3 esophageal pressure catheters were used, based on the size of the patient (Carefusion, Avea SmartCath 6,7, or 8Fr). The amount of air to be inflated into the esophageal balloon was determined prior to each measurement using a previously validated calibration algorithm¹⁰. All sensors were connected to a custom build hardware device (New Life Box, Applied Biosignals, Germany), which recorded data at a frequency of 200 Hz. Data was subsequently post-processed in a custom-built software program for analysis (designed in C# language).

Other clinical data included: demographics, risk factors and severity of lung injury, respiratory parameters (observed respiratory rate, ventilator rate (RRvent), spontaneous i.e. neural respiratory rate (RRneural), peak inspiratory pressure (PIP), PEEP, Δ Pes (the change in esophageal pressure), transpulmonary pressure (Ptp: airway pressure – esophageal pressure), Pressure Time product, Pressure Rate product, blood gas data), sedation and analgesia (cumulative dose of drugs, State Behavioral Scale (SBS), Face, Legs, Activity, Cry, Consolability (FLACC) scale). All doses of opioids were converted to fentanyl equivalents, represented as the cumulative dose per day^{11,12}. We also categorized each patient day as “spontaneous breathing present” when at least 10% of the minute ventilation resulted from patient triggered breaths. Because these patients are in pressure control modes of ventilation, tidal volume will vary from breath to breath, and will also be affected by asynchrony and reverse triggering. For this reason, we separated tidal volume into one of four groups for analysis: 1. Mandatory ventilator breath without reverse triggering, 2. Synchronous patient triggered breath, 3. Asynchronous patient triggered breath, 4. Reverse triggered breath.

PVA Definitions

All recordings were independently analyzed by two investigators (TS, BY) and each breath was labeled as synchronous or asynchronous using definitions modified from previously validated definitions^{13,14} but which also incorporate esophageal pressure (eTable1). If a breath was labeled asynchronous, then it was categorized into one of 8 possible Patient ventilator Asynchrony (PVA) events: 1) Reverse Triggering (RT), 2) ineffective triggering, 3) double triggering, 4) auto triggering, 5) trigger delay, 6) flow asynchrony, 7) delayed termination, 8) premature termination. Disagreements in the classification of breaths were adjudicated through discussion between the two investigators (TS, BY), and when disagreements could not be resolved, a third investigator (RK) cast a deciding vote. The focus of this investigation was on Reverse Triggering (RT), defined as patient effort which occurs after a mandatory breath from the ventilator¹⁵. Patient effort was determined using the Esophageal Pressure (Pes) waveform, mandating a minimum negative deflection of Pes of 2 cm H₂O. In addition, if the RT breath resulted in delivery of an additional breath from the ventilator, it was labeled as breath stacking, using previously published criteria (Fig. 1)¹⁶. For analysis, files which contained at least 3 RTs in the 30-minute recording were classified as having "RT." The pattern of RT was classified as 1:1, 1:2, 1:3 or "other" based on the ratio of breaths to RT breaths. A 1:1 pattern, for example, indicates that every mandatory ventilator breath resulted in a RT.

Any patient who had a daily file which met these criteria was classified as a RT patient.

Additional indices which were calculated included the asynchrony index (total asynchrony events / total breaths*100) and reverse triggering index (RTI, total reverse triggering / total breaths*100). Neural respiratory rate was defined as the time between consecutive patient inspiratory efforts (negative deflection of the esophageal pressure signal) divided by 60 seconds. In addition, to compare the relationship between the time the ventilator initiated a breath and neural respiratory activity, we calculated the phase angle, defined as (time of ventilator initiated breath minus time of esophageal trigger)/ventilator cycle duration $\times 360^{\circ}$ ^{4,8,17}. Furthermore, we labeled Paw_{init} and $flow_{init}$ as the values for airway pressure and flow when the spontaneous negative effort (from esophageal manometry) was initiated. (Fig. 1,2).

Statistical analysis

Normality of the data was tested by the Shapiro–Wilk test, and medians between groups were compared with the Mann-Whitney's *U* test. Correlation between variables was calculated using the spearman rank correlation coefficient. Coefficient of variation was calculated as the standard deviation/mean * 100. Comparisons were made between patients based on classification of the patterns of RT: none, irregular RT (no clear entrainment pattern), regular RT (clear entrainment pattern of 1:1, 1:2, 1:3). Additional analysis was stratified by the Reverse trigger index. Mixed logistic regression models were created to first control for patient level effects with repeated measurements per patient, evaluating variables which retained an independent association with RT or breath stacking. R version 3.5.0 (2018 The R Foundation for Statistical Computing Platform) was used for statistical analysis and all tests were considered to be

statistically significant when p-value was < 0.05. Due to the ongoing nature of the parent clinical trial, outcomes such as mortality are not reported.

[results]

Risk factors for RT (Table 1)

Table 1
The demographics of RT patients and Non-RT patients

	Non Reverse Triggering Patients	Reverse Triggering Patients	p value
Patients	21 (58.4%)	15 (41.6%)	
Age (months)	79.2 [27.1–193.0]	86.5 [23.5-174.1]	0.87
Male	11 (52.3%)	7 (46.6%)	0.62
Body weight (kg)	18.7 [10.8–39.5]	24.5 [11.0-47.8]	0.55
Length of mechanical ventilator (day)	7.0 [4.0–9.0]	6.0 [4.5-8.0]	0.68
Total number of breaths analyzed	59323	22667	
Patient-ventilator Asynchrony			
Reverse triggering (%)	0.0 [0.0–0.0]	9.5 [2.4–15.8]	< 0.0001
Asynchrony Index (%)	3.3 [0.4–38.4]	38.8 [16.8–60.2]	0.019
ARDS severity and triggers			
Risk Factor for lung injury			
Pneumonia	15 (71.4%)	11 (73.3%)	
Sepsis	1 (4.7%)	3 (20.0%)	
Other	5 (23.9%)	1 (6.7%)	0.40
Severity (PALICC)			
Mild	4 (19.1%)	4 (26.7%)	
Moderate	9 (42.8%)	4 (26.7%)	
Severe	8 (38.1%)	7 (46.6%)	0.83
PALICC: Pediatric Acute Lung Injury Consensus Conference			

The parent REDvent trial is ongoing and has enrolled approximately 115 of the target 276 patients to date. This analysis was conducted on a sub-sample of 36 of the first 60 patients in the study who had evidence of spontaneous breathing, but were still on SIMV PC-PS. Patients on pressure support only were not included, since reverse triggering is not possible on pressure support breaths. This yielded 81,990 breaths from 100 patient-days (eFigure1). In the entire cohort, 2.4% of breaths were reverse triggers, and 15/36 patients (41.6%) had at least 1 day in which RT occurred. All patients met diagnostic criteria for Pediatric ARDS¹⁸, and the most common ARDS risk factor was pneumonia (Table 1).

To adjust for multiple days of data recorded per patient, we selected the day when RT occurred most frequently from RT patients, and randomly selected one day from non-RT patients for comparison of ventilator settings and physiologic parameters (Table 2). RT patients had a lower median respiratory rate than non-RT patients (20.0 [15.5–24.0] vs 27.0 [24.0–34.0], $p < 0.0001$), higher tidal volume (ml)/kg on spontaneous synchronous breaths (8.1 [7.7–9.8] vs 6.9 [5.3–7.8], $p = 0.017$), higher tidal volume (ml)/kg on spontaneous asynchronous breaths (9.8 [8.4–11.6] vs 6.9 [5.4–8.5], $p = 0.001$), and spontaneous (or neural) respiratory rate closer to set ventilator rate (difference of 5.1 [0.1–8.3] bpm vs 13.5 [8.4–24.3], $p < 0.0001$) (Table 2). Patient demographics, ARDS severity, ARDS risk factors, blood gas results, effort of breathing, and other ventilator settings did not appear to be different between RT and non-RT patients. There was a trend that RT patients received higher doses of opioids ($p = 0.08$), although they had a trend of being less sedated ($p = 0.06$) than non-RT patients, although this was not statistically significant (Table 2). In multivariable modelling, a smaller difference between neural respiratory rate and set ventilator rate (OR 0.87 [0.82–0.94], $p = 0.0002$) and higher tidal volume/kg during spontaneous synchronous breaths (OR 1.52 [1.1–2.1], $p = 0.015$) remained independently associated with a patient having a day with RT.

Table 2
Each parameter of RT patients and Non-RT patients on representative day

	Non Reverse Triggering Patients	Reverse Triggering Patients	p value
Observed Respiratory Rate	27.0 [24.0–34.0]	20.0 [15.5–24.0]	< 0.01
Set Ventilator Rate	16.0 [12.0–22.0]	14.0 [12.0-15.5]	0.38
RRneural - RRvent	13.5 [8.4–24.3]	5.1 [0.1–8.3]	0.02
Tidal volume of spontaneous synchronous breath/pbw	6.9 [5.4–8.5] (n = 14824 breaths, 18 patients)	8.1 [7.7–9.8] (n = 4401 breaths, 13 patients)	0.017
Tidal volume of spontaneous asynchronous breath/pbw	6.9 [5.3–7.8] (n = 4685 breaths, 17 patients)	9.8 [8.4–11.6] (n = 2579 breaths, 13 patients)	0.001
Tidal volume of Ventilatory mandatory breath/pbw	7.5 [7.2–7.8] (n = 3460 breaths, 4 patients)	9.9 [8.2–11.6] (n = 2052 breaths, 2 patients)	0.32
Tidal volume of reverse triggering breath/pbw	NA	9.4 [8.5–13.7] (n = 1142 breaths, 15 patients)	NA
Coefficient of variation in phase angle (%)	NA	12.4 [4.3–13.7]	NA
Pplateau-PEEP	13.5 [10.5–18.4]	12.5 [7.8–15.0]	0.30
PEEP	8.4 [7.2–10.1]	8.8 [8.1–10.7]	0.27
Δ Pes	8.0 [4.5–10.0]	8.0 [4.5–12.5]	0.67
PRP	207 [152–297]	150 [110.5–271]	0.34
PTP	85.0 [50.5–109.0]	77.0 [52.0-145.5]	0.54
pH	7.43 [7.38–7.49]	7.41 [7.35–7.45]	0.50
PaCO ₂	52.0 [38.7–63.0]	45.0 [40.5–52.0]	0.37
HCO ₃ ⁻	33.0 [29.7–36.5]	28.0 [26.0-29.5]	0.06
Sedation and Pain			

RRneural: spontaneous or neural respiratory rate, RRvent: ventilator rate, pbw: predicted body weight

	Non Reverse Triggering Patients	Reverse Triggering Patients	p value
Cumulative Dexmedetomidine dose/kg/day	21.8 [12.3–40.2]	21.3 [7.3–36.5]	0.82
Cumulative Fentanyl dose/kg/day	25.0 [23.7–53.8]	55.3 [35.1–69.1]	0.08
State Behavioral Scale	-1.0 [-1.0- -1.0]	0.0 [-1.0- 0.5]	0.06
Face, Legs, Activity, Cry, Consolability	1.0 [0.0–5.0]	1.0 [0.0-2.5]	0.49
RRneural: spontaneous or neural respiratory rate, RRvent: ventilator rate, pbw: predicted body weight			

We further explored patterns of RT (eTable 2,3). RT occurred with a 1:1 pattern of entrainment in 1/15 RT patient, accounting for 10.5% of the RTs. No other clear discernable pattern of RT (i.e. 1:2, 1:3) occurred. Hence, 89.5% of RT breaths in 14/15 RT patients were classified as having an irregular pattern of RT, yet these patients had a median of 9.2% of breaths being Reverse Triggers, and nearly 39% of breaths were asynchronous. The patient who had a regular pattern of RT had 73% of breaths being Reverse Triggers and 94% of breaths being asynchronous.

To understand the dose response, we evaluated the RTI daily for the observed 30 minutes of breathing for each patient. Including all patients, as the RTI increased, the median tidal volume during spontaneous synchronous breaths and spontaneous asynchronous breaths also increased (Spearman's rank correlation coefficient 0.435 and 0.336, $p < 0.0001$ and $p = 0.003$)(Fig. 4c,4d), with a similar trend for mandatory breaths (correlation = 0.453, $p = 0.068$). In addition, as RTI increased, the difference between neural respiratory rate and set ventilator rate decreased (Spearman's rank correlation coefficient - 0.574, $p < 0.0001$)(Fig. 4a). There was less of a dose response, although still a clear relationship, between RTI and respiratory rate (Spearman's rank correlation coefficient - 0.418, $p < 0.0001$)(Fig. 4b).

Restricting the analysis to the 15 patients who had a day with reverse triggering, RTI appeared to be highest on the first day or day before patients had at least 10% spontaneous breathing (Fig. 5).

Table 4
Mixed effect Logistic regression model (Dependent Variable: Breath stacking)

	odds ratio	lower 95%CI	upper 95%CI	p.value
PawInit-PEEP	0.83	0.71	0.96	0.01
Set Peak Inspiratory Pressure	0.84	0.80	0.89	< 0.01
Set PEEP	0.62	0.53	0.71	< 0.01
Set Delta Pressure (PIP-PEEP)	0.83	0.74	0.92	< 0.01
Phase Angle	1.08	1.08	1.11	< 0.01
(Intercept)	4935.75	73.89	5.51e + 05	< 0.01

Risk factors for breath stacking when RT occurs.

14 (93.3%) of 15 RT patients had at least one episode of breath stacking and breath stacking occurred in 534 (26.5%) of 2017 RT breaths. The median tidal volume when breath stacking occurred as a result of a RT was 12.2 ml/kg, compared to 9.8 ml/kg when RT did not result in breath stacking. In univariable analysis (Table 3), breath stacking was more common when the onset of patient effort occurred well after the ventilator initiated breath (higher phase angle), when flow or inspiratory pressure was lower at the time of patient effort, when inspiratory time was shorter, and when Set Peak Inspiratory Pressure, Set PEEP, and Set Delta Pressure (Peak Inspiratory Pressure-PEEP) were lower. In multivariable modeling, breath stacking was more likely to occur when total airway delta pressure (Peak Inspiratory Pressure-PEEP) at the time patient effort began, Set Peak Inspiratory Pressure, Set PEEP, and Set Delta Pressure were lower and when the onset of patient effort occurred well after the ventilator initiated breath (higher phase angle) (all $p < 0.05$, Table 4). Together these parameters were highly predictive of breath stacking (AUC 0.979) (eFigure 2).

Table 3

The comparison between Breath Stacking and Non Breath Stacking in the breath by breath analysis of RT breaths only

	Non-Breath Stack waveform	Breath Stack waveform	p value
Numbers (%)	1483 (73.5)	534 (26.5)	
Vt / PBW	9.8 [9.1–11.1]	12.2 [9.1–14.0]	< 0.01
Δ Pes	18.4 [15.9–21.2]	17.7 [11.8–22.6]	0.14
Phase Angle	29.1 [21.6–42.8]	75.7 [57.3–98.1]	< 0.01
Flow _{init}	35.7 [35.0–41.0]	9.0 [7.0–15.6]	< 0.01
Paw _{init} -PEEP	13.6 [13.1–16.3]	11.5 [9.5–13.1]	< 0.01
Set PEEP	10.0 [10.0–10.0]	8.0 [8.0–10.0]	< 0.01
Set Peak Inspiratory Pressure	26.0 [18.0–30.0]	22.0 [18.0–22.0]	< 0.01
Set Delta pressure	16.0 [8.0–20.0]	11.0 [10.0–14.0]	< 0.01
Ventilator Inspiratory time	1.0 [1.0–1.0]	0.8 [0.8–0.9]	< 0.01
Paw _{init} and flow _{init} were labeled as the values for airway pressure and flow when the spontaneous negative effort (from esophageal manometry) was initiated.			

[discussion]

We have found that reverse triggering occurs in nearly half of pediatric ARDS patients on SIMV ventilation. Reverse triggering seems to occur more often when patients have their neural respiratory rate close to the set ventilator rate, and in patients who achieve a higher median tidal volume on non-RT breaths. RT results in breath stacking approximately 25% of the time, and in these cases of breath stacking, median tidal volume exceeds 12 ml/kg. Breath stacking was more likely to occur when total airway delta pressure (Peak Inspiratory Pressure-PEEP) at the time patient effort began, Set Peak Inspiratory Pressure, Set PEEP, and Set Delta Pressure were lower, and when the onset of patient effort occurred well after the ventilator-initiated breath began (higher phase angle).

We found that the majority of RT breaths were not associated with a repetitive, predictable pattern of respiratory entrainment (only 10% in our cohort), unlike other reported studies^{4,5,19}. We speculate that these irregular patterns of reverse triggering may be related to the SIMV PC-PS mode used in this study, in which time cycled breaths (pressure control) are mixed with flow cycled breaths (pressure support). This may pre-dispose to an irregular pattern when spontaneous breathing is present because both respiratory cycle duration and tidal volume may differ based on the type of breath delivered. Hence, even if the patient is frequently breathing spontaneously, a mandatory breath may be delivered and this lung insufflation leads to later patient effort, with a reverse trigger. Our findings are consistent with Bryce et al

who reported that SIMV was the most common ventilator mode associated with high asynchrony and breath stacking, particularly when the set ventilator rate was more than 10 breaths/min²⁰. The use of SIMV in our study may also explain the higher proportion of patients with RT in our cohort (40%) than other reported studies, which were conducted on assist controlled modes of ventilation. In fact, we found that only 1 patient (3%) had RT with a reproducible entrainment pattern, which is consistent with other estimates²¹. Nevertheless, it appears as if these patients with irregular patterns of RT have many similarities with patients with regular patterns of RT (eTable 3), and are at high risk for adverse events such as breath stacking.

When thinking about the mechanisms of RT, an important phenomenon relates to entrainment of the patient's respiratory rhythm to periodic lung inflations delivered by mechanical ventilation⁸. Respiratory entrainment has been investigated since the 1970s^{6,8,17} and can occur in wakeful, sleeping, and anesthetized human subjects on mechanical ventilation⁸. Many studies in anesthetized animals have shown that periodic lung inflation during controlled mechanical ventilation may entrain the respiratory rhythm to the ventilation frequency close to the intrinsic respiratory rate^{6,7,22,23}. Entrainment with a mechanical ventilator can occur with negative, zero, or positive phase angles. If the phase angle is zero or negative, we would classify this as synchronous ventilation. RT constitutes entrainment with a "positive" phase angle, where neural respiration occurs after lung inflation from the ventilator. It is therefore not surprising that we found RT is much more common when the patient's neural respiratory rate was close to the set ventilator rate. RT also occurred most on the first day or day before significant spontaneous breathing, when inherently the neural respiratory rate may be less than or equal to the set ventilator rate. We presume that the higher doses of opioids in RT patients (although not statistically significant) may be contributing to this potential for entrainment, given opioids are known to reduce minute ventilation primarily by reducing respiratory rate, rather than tidal volume. Interestingly, although these patients had higher dose of opioids, they had similar if not higher levels of wakefulness on the state behavioral scale. Previous literature highlights differential phase relationships with entrainment as a function of the state of wakefulness of the patient⁸. This illustrates the complex interplay between respiratory control of breathing, sedation, and pain in critically ill patients.

Furthermore, previous work⁸ has identified that a positive phase angle with entrainment (i.e. RT) was more common when the ventilator cycle length was less than the respiratory cycle (i.e. ventilator rate > spontaneous rate). This may be because ventilator inflations begin late during neural exhalation which augments lung inflation during neural inspiration, invoking a Hering-Breuer reflex. Our data seem consistent with this as a potential mechanism, as higher tidal volume, which can augment Hering-Breuer inflation reflexes by facilitating relaxation of respiratory muscles, was a risk factor for RT²⁴. Furthermore, flow and pressure applied by the ventilator activate stretch receptors in the upper airways, lungs, and chest wall. Neural feedback by these receptors through vagal fibers causes the respiratory control center to match the phase and frequency of the external stimulus, producing a repetitive respiratory pattern²⁵. It is plausible that patients who achieve a higher median tidal volume have more stimulation of these stretch receptors²⁶, making it more likely for them to entrain with the set respiratory rate on the ventilator,

leading to RT. These mechanisms may explain our finding that RT patients received 8–10 ml/kg tidal volume, compared to 6–8 ml/kg for non RT patients.

While it is important to describe and understand risk factors for RT for physiologic and academic reasons, RT may contribute to ventilator induced lung injury (VILI), particularly when it results in breath stacking and excessive tidal volume or driving pressure. In fact, we identified that the median tidal volume on breath-stacked RT breaths was 12 ml/kg, which is known to be injurious in ARDS patients. Hence, it is important to understand when RT is likely to lead to breath-stacking, so that we can try to prevent it. From the multivariable model, it seems that in pressure control ventilation breath stacking is more likely in patients in whom the set peak pressure (or delta pressure) is lower. We speculate this may be related to a perception of inadequacy of flow during the ventilator delivered breath, which may prolong the patient's subsequent inspiratory effort to continue beyond the set inspiratory time on the set mandatory breath, resulting in a second breath which is patient triggered. Because this is pressure control ventilation, the speed and magnitude of inspiratory flow is most dependent on the set pressure. Some have reported being able to abolish RT by increasing tidal volume (or increasing the set delta pressure in pressure control ventilation), which may be explained by the Hering-Breuer deflation reflex^{27,28}. However, it is unclear how likely this is true in these ARDS patients, as the tidal volume is already high. We also found, not surprisingly, that when the patient effort occurs late in the course of the mandatory breath (higher phase angle), breath stacking is more common. Therefore, perhaps changes to inspiratory time would be beneficial to prevent breath stacking, or reducing the set ventilator rate (making the set rate less than the spontaneous rate) could prevent RT. Of course, these changes may lead to other forms of asynchrony, which should be monitored. These alterations to settings are speculation, as our study was observational and did not test whether these strategies improve RT or breath stacking. Methods focused on eliminating breath-stacking from RT should be a focus of investigation.

It is unclear whether RT in and of itself is dangerous if it does not lead to breath stacking. In some ways, preservation of some form of spontaneous effort during mechanical ventilation may prevent ventilator induced diaphragm dysfunction (VIDD). What is clear, however, is that tidal volume and overall transpulmonary pressure is higher in RT patients, and is even higher when RT occurs, regardless of whether it leads to breath stacking. This may increase the risk for VILI even without breath stacking, but this risk must be balanced against the potential benefits in preventing VIDD. This should be a focus of future investigation.

Our study has several limitations. First, our patients were pediatric ARDS patients on SIMV PC-PS ventilation from a single center. External validity should be explored in other datasets. Second, this was a sample of patients enrolled in an ongoing RCT on ARDS. This will exclude a subset of patients who may also have RT and have different mechanisms for RT (such as patients with intracranial hypertension which are excluded from the REDvent RCT). Third, because the RCT is ongoing, no outcome analysis or analysis of the potential impact of the intervention on RT was undertaken. This can be done after completion of the RCT. However, we believe our study also has many strengths including the use of esophageal pressure to definitively label reverse triggering events and characterize asynchrony, the

rigorous approach to labeling all breaths, and a sample size of both breaths and patients which is larger than any other reported cohort on reverse triggering.

[conclusions]

Reverse triggering is more likely to occur in pediatric ARDS patients when the set ventilator rate is close to the patient's intrinsic neural respiratory rate and when tidal volume is higher. Moreover, reverse triggering results in breath stacking over 25% of the time, which may make it an important risk factor for ventilator induced lung injury.

[abbreviations]

ARDS: Acute respiratory distress syndrome

RT: Reverse triggering

PVA: Patient-ventilator asynchrony

PARDS: Pediatric acute respiratory distress syndrome

SIMV: Synchronized intermittent mandatory ventilation

PC: Pressure Control

PS: Pressure support

Pes: Esophageal pressure

Paw: Airway pressure

RRvent: Ventilator rate

RRneural: Spontaneous or neural respiratory rate

PIP: Peak inspiratory pressure

Ptp: transpulmonary pressure

SBS: State Behavioral Scale

FLACC: Face, Legs, Activity, Cry, Consolability

PawInit: Airway pressure when the spontaneous negative effort (from esophageal manometry) was initiated.

FlowInit: Flow when the spontaneous negative effort (from esophageal manometry) was initiated.

RTI: Reverse triggering index (defined as the number of reverse triggering/total number of breath *100)

Pbw: predicted body weight

[declarations]

Ethics approval and consent to participate

The protocol has been approved by the Children's Hospital Los Angeles (CHLA) Institutional Review Board, as well as an independent Data Safety and Monitoring Board.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable.

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Author Contributions

T.S, R.G.K.: study conception and design; R.G.K., J.C.H.: acquisition, analysis, and interpretation of data; and all coauthors: manuscript drafting and revision for intellectual content, approval of the final manuscript, and agreement to be accountable for the accuracy and integrity of the work.

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Figures

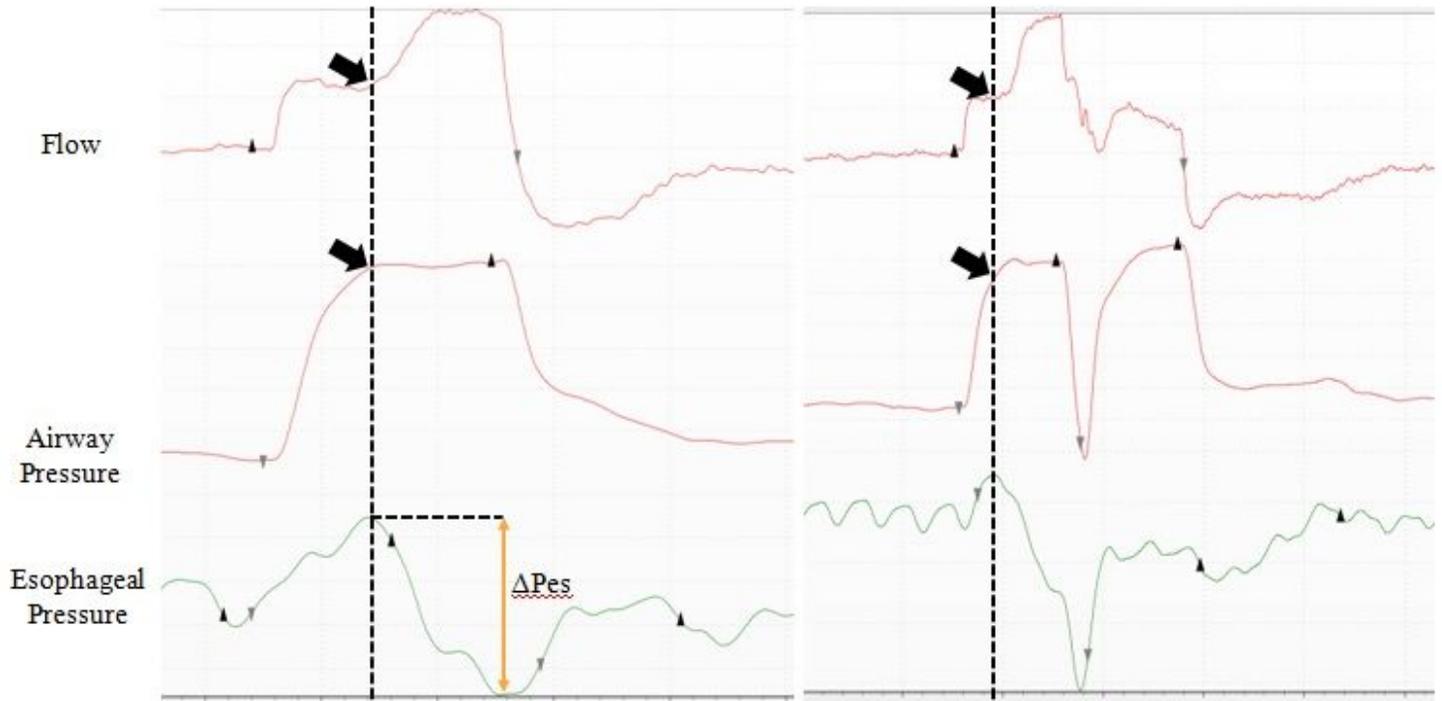


Figure 1

The waveform of non breath stacking (left) and breath stacking (right). Black arrows show airway pressure and flow at initiating spontaneous efforts (flow_{init} and P_{aw}_{init}) ΔP_{es} (Orange arrow) shows the amount of change between peak and minimum esophageal pressure.

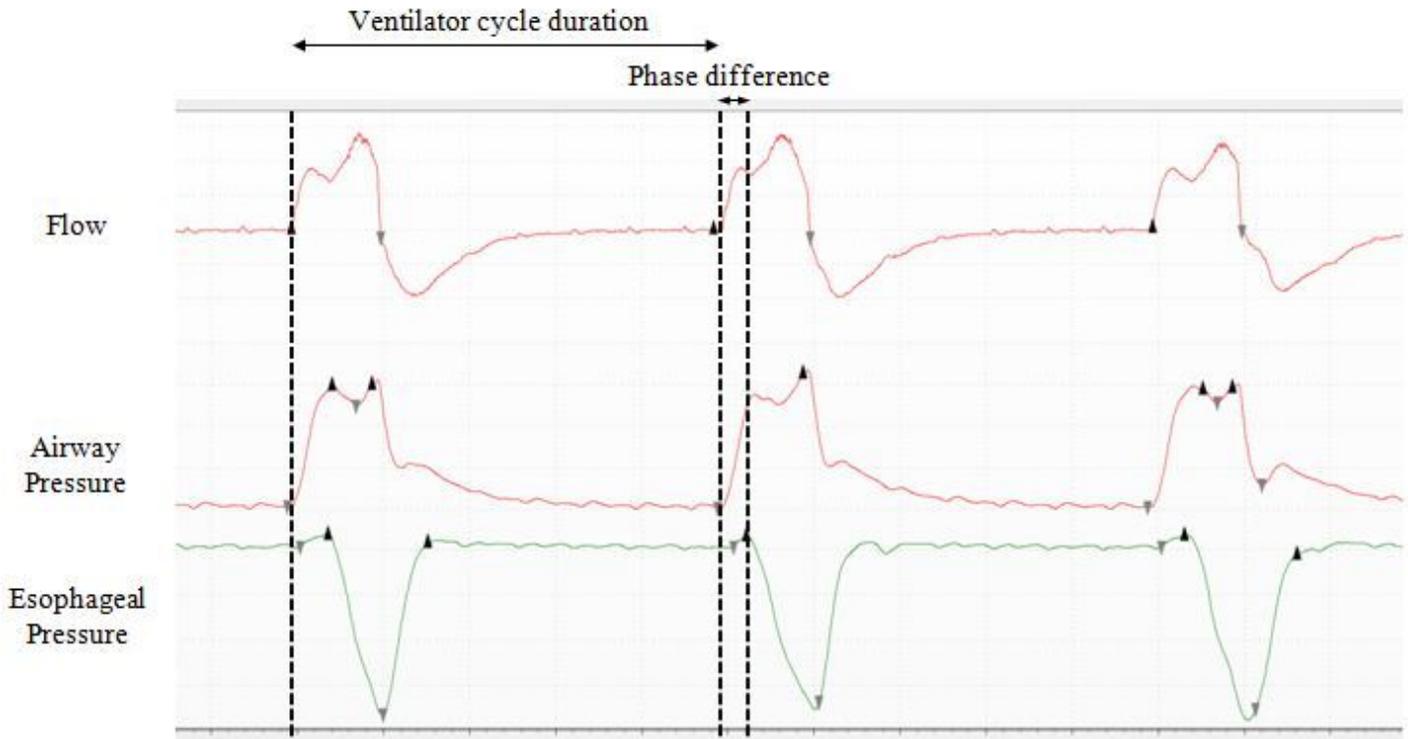
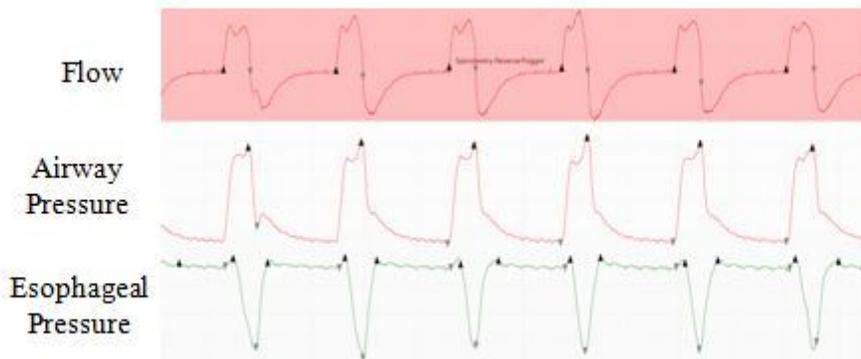


Figure 2

Phase Angle $\text{Phase Angle} = \text{Phase difference} / \text{Ventilator cycle duration} \times 360^\circ$ This is the standard way of expressing the relationship between machine and neural respiratory activity onset.

A: 1:1



B: Irregular

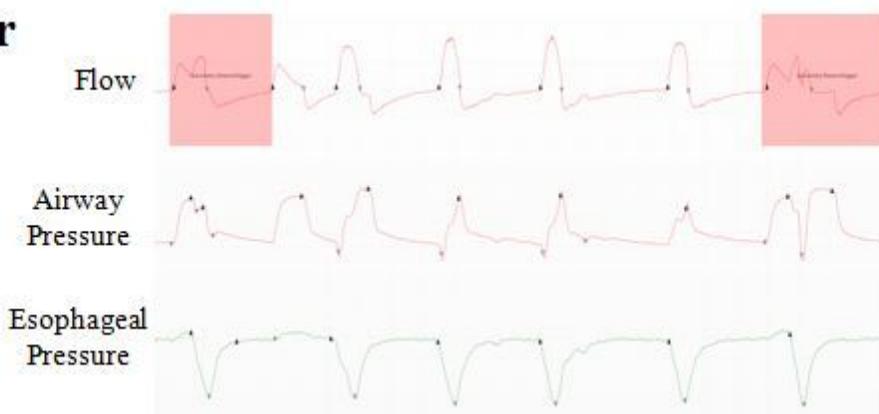


Figure 3

The patterns of RT: irregular RT (no clear entrainment pattern), regular RT (clear entrainment pattern of 1:1) A: Clear entrainment pattern of 1:1 B: Irregular reverse triggering (no clear entrainment pattern) Red shadings show reverse triggerings

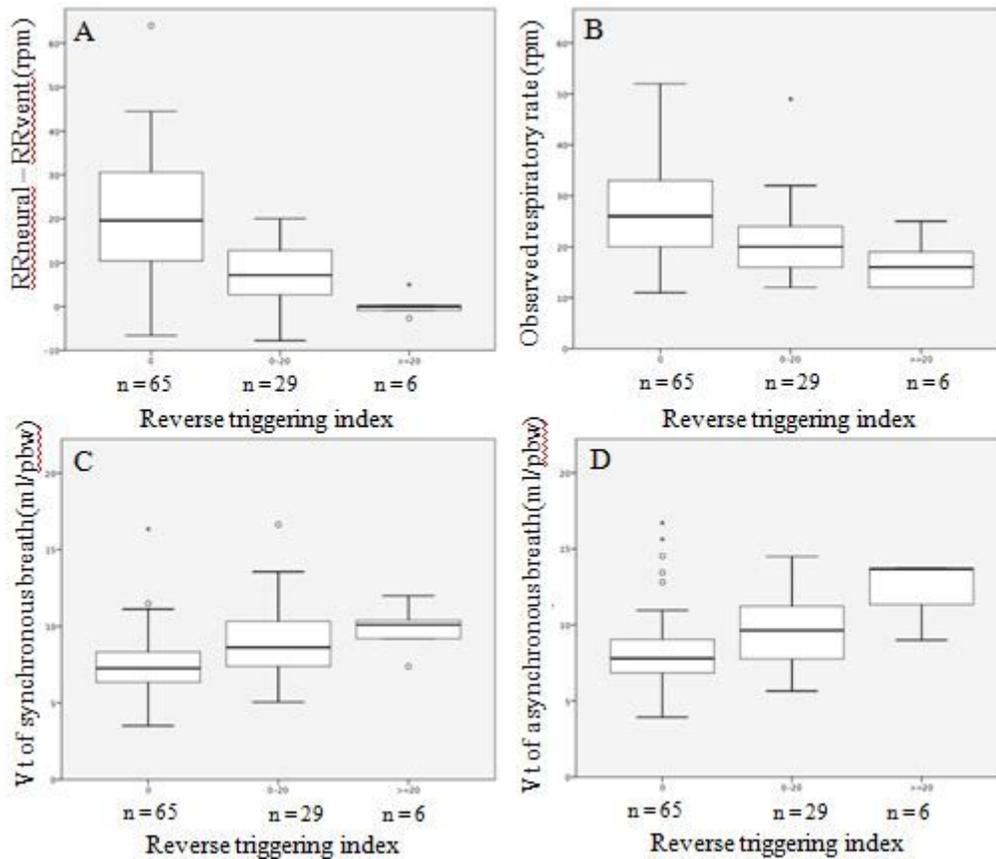


Figure 4

The boxplots of each variable A: Reverse triggering index was higher with neural respiratory rate (RR_{neural}) getting closer to set ventilator rate (RR_{vent}). B-D: The relationship between reverse triggering index and observed respiratory rate (B), V_t/pbw of spontaneous synchronous breath (C) and V_t/pbw of spontaneous asynchronous breath (D). V_t = Tidal volume, pbw = predicted body weight 65files of RTI=0, 29files of $0 < RTI < 20$, 6files of $RTI > 20$

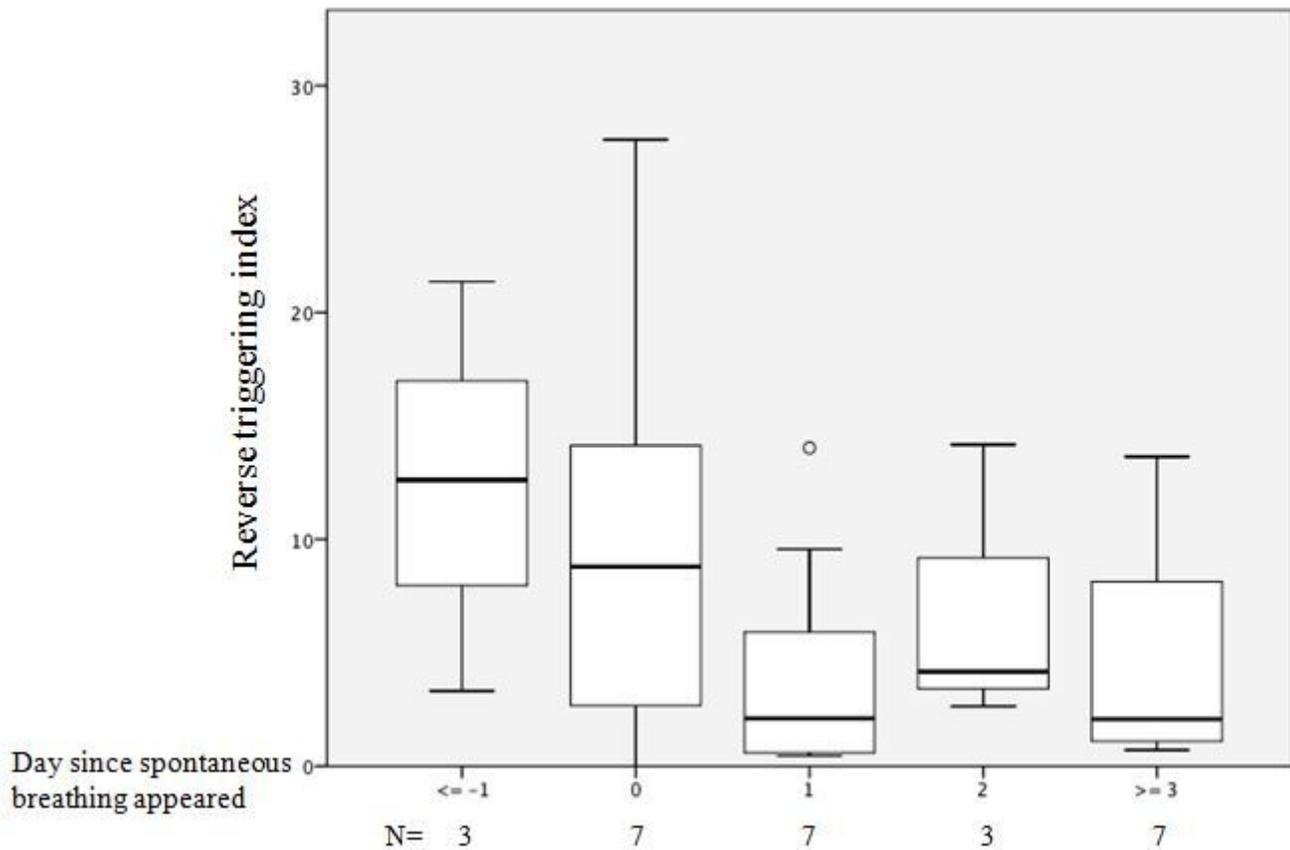


Figure 5

The trend of reverse triggering index and day The X-axis is the day when spontaneous breathing appeared which was defined as minutes volume of triggered breath/total minutes volume > 10%.

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