Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, and Physiologic Implications

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported, in part, by projects PI09/91074 and PI13/02204, integrated in the Plan Nacional de R+D+I, and cofunded by the Instituto de Salud Carlos III Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional, Centro de Investigación Biomédica en Red en Enfermedades Respiratorias, Fundación Mapfre, Fundació Parc Taulí, Plan Avanza TSI-020302-2008-38, Ministerio de Ciencia e Innovación, and Ministerio de Industria, Turismo y Comercio (Spain).

Mr. Montanya and Drs. Blanch, Murias, and Lucangelo own stock options of Better Care SL, which is a research and development spinoff of Corporació Sanitària Parc Taulí (Spain). Dr. Subirà disclosed work for hire. Drs. Murias and Blanch disclosed that they are inventors of one Corporació Sanitaria Parc Taulí owned US patent: "Method and system for managed related patient parameters provided by a monitoring device," U.S. Patent No. 12/538,940. Dr. Kacmarek is a consultant for Medtronic and Orange Medical and has received research grants from Medtronic and Venner Medical. His institution received funding from Medtronic and Venner Medical, and he received funding from Medtronic, Orange Medical, and Teleflex. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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Objectives: Double cycling generates larger than expected tidal volumes that contribute to lung injury. We analyzed the incidence, mechanisms, and physiologic implications of double cycling during volume- and pressure-targeted mechanical ventilation in critically ill patients.

Design: Prospective, observational study.

Setting: Three general ICUs in Spain.

Patients: Sixty-seven continuously monitored adult patients undergoing volume control-continuous mandatory ventilation with constant flow, volume control-continuous mandatory ventilation with decelerated flow, or pressure control-continuous mandatory mechanical ventilation for longer than 24 hours.

Interventions: None.

Measurements and Main Results: We analyzed 9,251 hours of mechanical ventilation corresponding to 9,694,573 breaths. Double cycling occurred in 0.6%. All patients had double cycling; however, the distribution of double cycling varied over time. The mean percentage (95% CI) of double cycling was higher in pressure control-continuous mandatory ventilation 0.54 (0.34–0.87)

than in volume control-continuous mandatory ventilation with constant flow 0.27 (0.19–0.38) or volume control-continuous mandatory ventilation with decelerated flow 0.11 (0.06–0.20). Tidal volume in double-cycled breaths was higher in volume control-continuous mandatory ventilation with constant flow and volume control-continuous mandatory ventilation with decelerated flow than in pressure control-continuous mandatory ventilation. Double-cycled breaths were patient triggered in 65.4% and reverse triggered (diaphragmatic contraction stimulated by a previous passive ventilator breath) in 34.6% of cases; the difference was largest in volume control-continuous mandatory ventilation with decelerated flow (80.7% patient triggered and 19.3% reverse triggered). Peak pressure of the second stacked breath was highest in volume control-continuous mandatory ventilation with constant flow regardless of trigger type. Various physiologic factors, none mutually exclusive, were associated with double cycling.

Conclusions: Double cycling is uncommon but occurs in all patients. Periods without double cycling alternate with periods with clusters of double cycling. The volume of the stacked breaths can double the set tidal volume in volume control-continuous mandatory ventilation with constant flow. Gas delivery must be tailored to neuroventilatory demand because interdependent ventilator setting–related physiologic factors can contribute to double cycling. One third of double-cycled breaths were reverse triggered, suggesting that repeated respiratory muscle activation after time-initiated ventilator breaths occurs more often than expected. (*Crit Care Med* 2018; 46:1385–1392)

Key Words: asynchronies; breath stacking; lung injury; reverse triggering; tidal volume

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Coordinating patient-ventilator interaction is a major clinical challenge during invasive mechanical ventilation (MV). Asynchronies occur when the ventilator's breath delivery does not match the patient's neural ventilatory pattern or is inadequate to meet the patient's flow demand (1–3).

Recent studies highlight the importance of the asynchrony double cycling (DC), also named double triggering or breath stacking. DC consists of a sustained inspiratory effort that persists beyond the ventilator's inspiratory time (Ti), triggering a second ventilator breath, which may or may not be followed by a short expiration, where all or part of the volume of the first breath is added to the second breath. The resulting larger than expected tidal volume (VT) could cause ventilator-induced lung injury (4–10). Whether the incidence and effects of DC differ between pressure-targeted and volume-targeted modes is unknown.

Another recently described phenomenon, reverse triggering, occurs when a periodic diaphragmatic contraction stimulated by a previous passive ventilator breath is strong enough to originate a DC (11, 12).

To assess the relevance of DC in MV patients, we aimed to determine 1) the incidence of DC in volume-targeted and pressure-targeted modes; 2) the effects of DC on delivered VT and airway pressure in each mode; 3) the distribution of DC over time; 4) the proportion of DC due to reverse triggering; and 5) physiologic factors associated with DC in each mode.

MATERIALS AND METHODS

Patients and Software

The study was conducted between October 2011 and January 2013 in three general ICUs equipped with the Better Care platform (Better Care SL; Barcelona, Spain) in patients ventilated with Evita 4 (Dräger, Lübeck, Germany), Puritan Bennet 840 (Covidien, Plymouth, MN), or Servo I (Maquet, Fairfield, NJ, Sweden) ventilators. The institutional review board approved the protocol and waived informed consent because the study was noninterventional, posed no added risk to patients, and did not interfere with usual care. The study prospectively included intubated adult patients expected to undergo invasive MV greater than 24 hours with volume control-continuous mandatory ventilation with constant flow (VCV), volume control-continuous mandatory ventilation with decelerated flow (VCVDF), or pressure control-continuous mandatory ventilation (PCV) (13). Patients who were pregnant, had do-not-resuscitate orders or chest tubes with suspected bronchopleural fistula, or were admitted for organ donation were excluded.

The attending ICU team was aware of the study, and all patients were managed under lung-protective MV strategies. Ventilator mode and alarm settings were set by attending physicians, as part of usual care. Recordings were initiated in the first 24 hours after intubation and were continued until extubation. Better Care platform was used to capture digital outputs from the ventilators (9, 14), detects the ventilator mode (13), determines whether the breath is patient triggered or ventilator delivered, and classifies double-cycled breaths as patient triggered or reverse triggered (**supplemental data 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/D708; **Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/D709; and **Supplemental Fig. 1**, Supplemental Digital Content 3, http://links.lww.com/CCM/D710).

Detection of DC was based on mathematical calculations previously published (8–10, 15, 16). The system identifies DC when 1) expiratory time is 50% shorter than the averaged Ti or 2) when two consecutive inspiratory cycles (positive flow-zero flow-positive flow) are detected with no expiration (negative flow) before the second Ti. We included cycles in which the first cycle was triggered by the patient or time cycled by the ventilator. Once Ti is validated, expiratory time is automatically calculated. **Supplemental Figure 2** (Supplemental Digital Content 4, http://links.lww.com/CCM/D711) shows representative waveforms (flow, airway pressure, and volume) of double-cycled breaths (reverse or patient triggered).

The system measures VT in conventional breaths and calculates the accumulated volume due to absent or incomplete exhalation between consecutive inspiratory cycles. Variables

evaluated were as follows: ventilatory mode, type of trigger, peak airway pressure (P_{peak}), peak inspiratory flow, VT, respiratory rate, Ti, total positive end-expiratory pressure (PEEP), and number of double-cycled breaths. To perform all the analyses, variables were structured and stored (PostgreSQL Berkeley, CA; https://www.postgresql.org/) in two different databases containing: 1) breath-by-breath measures and 2) averaged values per hour. Hours with missing data due to interruptions in the recording related to clinical interventions, out-of-ICU transfers, technical incidents, or other issues were excluded from the analysis. The frequency of DC was computed as a percentage of the total number of breaths each hour. The identification of clusters of DC is described in **supplemental data 2** (Supplemental Digital Content 5, http://links.lww.com/CCM/D712).

Statistical Analysis

Patient's characteristics are reported as median (25th–75th percentiles) for continuous variables, unless otherwise specified. Our study was exploratory in nature, and no sample size calculation was performed. Comparisons of VT and P_{peak} recorded breath-by-breath among ventilatory modes and in DC (reverse-triggered or patient-triggered breaths) are depicted graphically with boxplots.

To assess the association between DC and ventilatory mode, we used a generalized linear mixed-effects model with random effects at the intercept for each patient to account for the intrasubject variability of longitudinal data (17). This model assumed a negative binomial distribution for the rate of DC. To investigate physiologic variables thought to affect DC, we used a multivariate approach, allowing variations of slope (degree of change) for ventilatory modes (**supplemental data 3**, Supplemental Digital Content 6, http://links.lww.com/CCM/D713; **Supplemental Fig. 3**, Supplemental Digital Content 7, http://links.lww.com/CCM/D714).

We used R 3.3.1 (R Core Team, Vienna, Austria; URL: http://www.R-project.org/) with the RPostgreSQL package (Berkeley, CA; https://CRAN.R-project.org/package=RPostgreSQL) for interfacing the database; *p* value less than 0.05 was considered significant for all analyses.

RESULTS

Table 1 reports demographic and clinical data of the 67 patients studied. We analyzed 9,251 hours of MV data comprising 9,694,573 breaths; 59,265 (0.6%) breaths were double-cycled breaths (**Fig. 1**). A single mode of ventilation was used in 43.3% of patients; the single mode was VCV in 89.7% and PCV in 10.3%.

DC rates varied widely among patients and modes (**Supplemental Fig. 4*A***, Supplemental Digital Content 8, http://links.lww.com/CCM/D715). All patients had DC but the distribution of DC differed within patients. Some patients had very few DC during the ventilatory period (**Supplemental Fig. 4*B***, Supplemental Digital Content 8, http://links.lww.com/CCM/D715), others had DC at the beginning or end of ventilation (**Supplemental Fig. 4, *C* and *D***, Supplemental Digital Content 8, http://links.lww.com/CCM/D715), and others had a high incidence of DC throughout the ventilatory period (**Supplemental Fig. 4*E***, Supplemental Digital Content 8, http://links.lww.com/CCM/D715).

TABLE 1. Patients' Demographic and Clinical Data

Variables and Clinical Outcomes	*n*	%	Median (25th–75th Percentiles)
Patients	67	–	–
Age (yr)	–	–	65 (55–77)
Sex (male)	–	62.7	–
Reason for mechanical ventilation			
Acute respiratory failure	51	76.12	–
Cardiorespiratory arrest	7	10.45	–
Trauma	2	2.99	–
Bronchoaspiration	1	1.49	–
Pneumonia	6	8.96	–
Sepsis/septic shock	12	17.91	–
Congestive heart failure	2	2.99	–
Acute respiratory distress syndrome	5	7.46	–
Postsurgical	8	11.94	–
Other	8	11.94	–
Coma	11	16.42	–
Stroke	4	6	–
Intoxication	1	1.19	–
Traumatic brain injury	3	4.48	–
Metabolic	3	4.48	–
COPD	4	5.97	–
Asthma	1	1.49	–
COPD exacerbation	3	4.48	–
Neuromuscular disease	1	1.49	–
Acute Physiology and Chronic Health Evaluation II	–	–	16 (10–23.5)
Sequential Organ Failure Assessment score at admission	–	–	7 (5–10.75)
Length of mechanical ventilation (d)	–	–	6 (3–11.5)
ICU stay (d)	–	–	10 (6–18)
Hospital stay (d)	–	–	26.5 (15.5–68.0)
ICU mortality	–	23.88	–

COPD = chronic obstructive pulmonary disease.

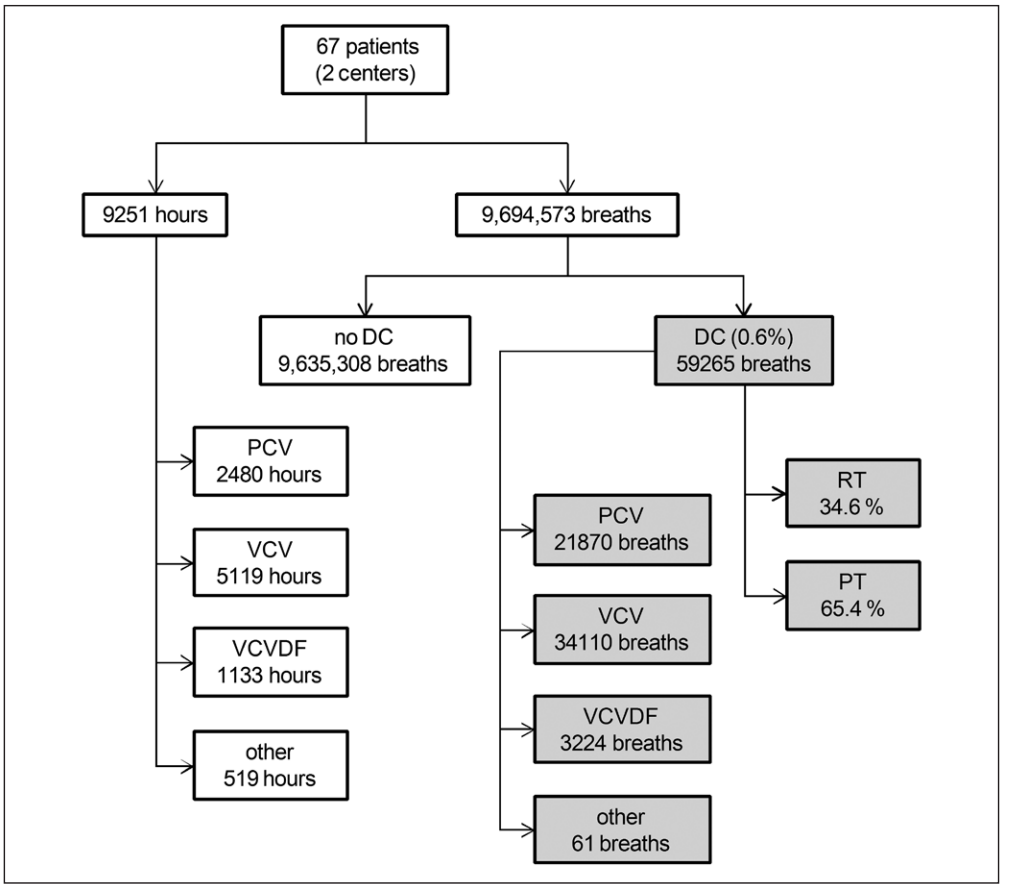

Figure 1. Flow chart representing the distribution of ventilatory modes and frequency of double cycling (DC). PCV = pressure control-continuous mandatory ventilation, PT = patient triggered, RT = reverse triggered, VCV = volume control-continuous mandatory ventilation with constant flow, VCVDF = volume control-continuous mandatory ventilation with decelerated flow.

The distribution of DC among ventilatory modes was evaluated in the 8,732 hours corresponding to PCV (2,480 hr), VCV (5,119 hr), and VCVDF (1,133 hr) (Fig. 1). The mean percentage of DC per hour (95% CI) estimated with the statistical model was 0.54 (0.34–0.87) for PCV, significantly higher than 0.27 (0.19–0.38) for VCV, and 0.11 (0.06–0.20) for VCVDF ($p < 0.05$ and $p < 0.001$, respectively) (**Fig. 2**).

DC due to patient triggering was more common than DC due to reverse triggering (65.4% vs 34.6%) (Fig. 1) overall and in every mode (PCV, 68.1% vs 31.9%; VCV, 62.2% vs 37.8%; VCVDF, 80.7% vs 19.3%, respectively).

Figure 3*A* shows VT in double-cycled and normal breaths. In normal breaths, VT was similar in all three ventilatory modes. In double-cycled breaths, the increase in VT was higher in VCV and VCVDF than in PCV. In patient-triggered breaths, VT was lower in PCV than in both volume-controlled modes. In reverse-triggered breaths, VT was higher in VCV than in PCV or VCVDF (**Fig. 3*B***).

Peak pressure in normal breaths (**Fig. 3**, ***C*** and ***D***) was slightly lower in PCV than in VCV and VCVDF. In patient-triggered breaths, P_{peak} was higher in VCV than in PCV or VCVDF. In reverse-triggered breaths, P_{peak} in volume-targeted modes was higher than in PCV. To describe whether the P_{peak} pattern differed between first and second breaths, we evaluated the two breaths composing DC separately (**Supplemental Table 2**, Supplemental Digital Content 9, http://links.lww.com/CCM/D716). P_{peak} values for the second breath were generally greater than for the first. This difference was greatest in VCV, mainly for patient-triggered breaths (84.7% vs 15.1%), and more balanced in VCVDF (56.0% vs 43.0%).

Table 2 shows estimated coefficients for factors associated with DC in each mode. The statistical model was fitted to the 7,580 hours (86.8%) free of missing data. Respiratory rate was positively associated with DC in all modes. Ventilator Ti was negatively associated with DC in all modes. Peak flow was negatively related to DC in PCV and VCV. PEEP was negatively related to DC in PCV and VCVDF and positively related in VCV. P_{peak} was positively associated with DC in PCV, but negatively associated in VCV. VT was positively associated with DC in PCV and VCVDF, but negatively associated in VCV. Levels of significance are reported in Table 2. **Supplemental Figure 5** (Supplemental Digital Content 10, http://links.lww.com/CCM/D717) shows boxplots for each physiologic variable and ventilatory mode included in the model.

Clusters of DC were identified and characterized (supplemental data 2, Supplemental Digital Content 5, http://links.lww.com/CCM/D712). When clusters were defined as greater than or equal to 10% DC breaths within a 3-minute period, a 59.7% of the total number of patients exhibited clusters, with a median of six cluster events per patient, a power of 41 DC breaths per cluster, median duration of 15.5 minutes, and an area under the curve of 20.3. See supplemental data 2 (Supplemental Digital Content 5, http://links.lww.com/CCM/D712) for DC clusters characteristics with other definition.

DISCUSSION

To our knowledge, this is the first study presenting a rigorous quantification of DC as result of continuous monitoring of patients during volume- and pressure-targeted time-cycled modes throughout the complete MV period. DC was infrequent, but occurred in all patients. Its distribution and clustering over time varied widely among patients (Supplemental

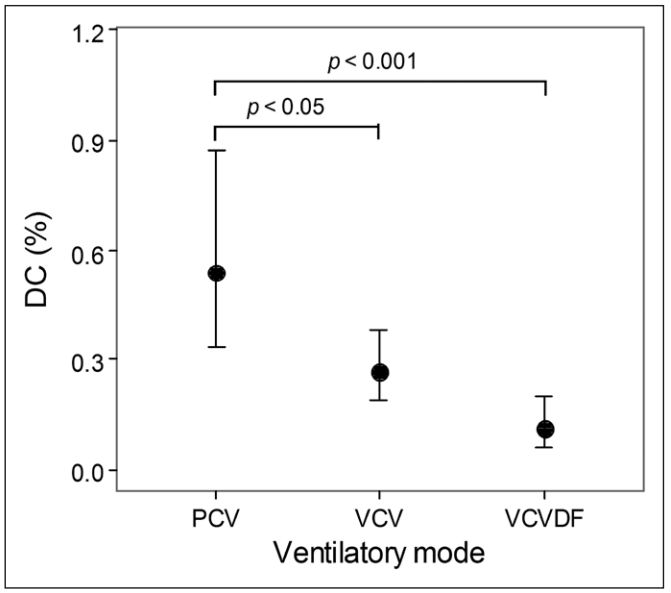

Figure 2. Mean percentages of double-cycle (DC) breaths estimated with the generalized linear mixed-effects model by ventilatory modes. A higher percentage of DC breaths/hr was found in pressure control-continuous mandatory ventilation (PCV) than in volume control-continuous mandatory ventilation with constant flow (VCV) or volume control-continuous mandatory ventilation with decelerated flow (VCVDF). Data are represented as mean (95% CI). Statistical significance among means in each mode is indicated in the figure.

Fig. 4, Supplemental Digital Content 8, http://links.lww.com/CCM/D715; and supplemental data 2, Supplemental Digital Content 5, http://links.lww.com/CCM/D712), underlining the importance of continuous real-time analysis of asynchrony events, which normally go undetected.

The delivered volume accumulated during DC was very high, sometimes even doubling the VT of normal breaths in volume-targeted modes (Fig. 3; Supplemental Fig. 2, Supplemental Digital Content 4, http://links.lww.com/CCM/D711) as reported by others (4, 8). This might result in overinflation, which can lead to ventilator-induced lung injury. Low VT, recommended for lung-protective ventilation (18), results in more frequent DC (8) and flow asynchrony (2, 6). In our study, DC was more frequent in PCV than in VCV and VCVDF although the overall volume delivered during DC in PCV was lower than in VCV or VCVDF. However, this does not mean that PCV is more lung protective. In pressure-preset or pressure-targeted modes, the negative pleural pressure during vigorous spontaneous diaphragmatic contractions is added to the peak alveolar pressure, potentially establishing harmful transpulmonary pressure swings (19–21). This phenomenon also occurs in double-cycled breaths in VCV, where P_{peak} of the second breath is markedly elevated (Supplemental Table 2, Supplemental Digital Content 9, http://links.lww.com/CCM/D716). Yoshida et al (22, 23) recently showed that vigorous spontaneous inspiratory efforts promote tidal recruitment associated with pendelluft (lung volume redistribution) and consequent regional lung overdistension.

In low VT ventilation, especially in healthy lungs, DC could be due to natural sighs; whether this situation is harmful will depend on the generated transpulmonary pressure and frequency of DC. Recent evidence suggests that VT should also be limited in patients without acute respiratory distress syndrome (ARDS) (24); therefore, clinicians might believe that they are delivering 6–8 mL/kg VT, but the patient is actually receiving greater than 10 mL/kg VT, a setting that might affect outcome even in non-ARDS patients. We also found that clusters of DC were often present. Vaporidi et al (25) found that clusters of ineffective efforts were often present in patients receiving MV, and unlike overall incidence, clusters were associated with prolonged MV and increased mortality. Therefore, Vaporidi et al (25) and study of ours show the variability of asynchrony events during MV and suggest that clusters of DC could increase the mechanical power (a measure that integrates different ventilator-related causes of lung injury) transferred from the ventilator to lungs (7).

The statistical model determined that numerous physiologic factors, selected for clinical suspicion, were associated with DC. This model is robust since it took into account interpatient variability, and that there were different ventilatory modes and covariates, allowing us to investigate their simultaneous effects on DC. In this context, each variable is influenced by the other variables, making interpretation more complex, and each coefficient represents the additive effect on the response of its corresponding variable while holding all other variables fixed (26). Patient's inspiratory demands may vary throughout MV without the critical care team being aware of it. This may explain DC occurring throughout the MV period and underlines the need to tailor ventilator settings to the patient's needs at all times.

Longer Ti and higher inspiratory peak flow were associated with less DC in all modes, probably suggesting better matching among neural Ti, ventilator Ti, and inspiratory demand. Likewise, we found more asynchronies at higher ventilator respiratory rates, attributable to shorter ventilator Tis. Setting a shorter Ti to improve patient comfort can produce mismatch between neural time and ventilator time and thus increase the probability of DC. However, Pohlman et al (8) found that respiratory rate did not affect DC. Duty cycles are crucial in generating double-cycled breaths. Thus, increasing respiratory rates at similar duty cycles decreases Ti, which may favor DC, whereas promoting longer Tis at higher rates may decrease DC. In fact, clinical strategies against DC are switching from VCV to pressure-support ventilation or increasing Ti or peak airflow (5, 27) to prolong ventilator assist during diaphragm activation (28) and decrease flow asynchrony (29). However, this approach might result in undesirably high volumes. Furthermore, when assistance is relatively high and mechanical inflation extends well into neural expiration, other asynchronies (e.g., ineffective efforts) may develop (5, 30, 31).

Unlike Thille et al (10) who observed more DC at higher PEEP or Robinson et al (32) who found PEEP had no effect on DC, we found that higher PEEP was associated with less DC in PCV and VCVDF. At higher PEEP levels, a decrease in the inspiratory effort can occur at higher lung volumes, explaining the decrease in the incidence of DC. Consistent with

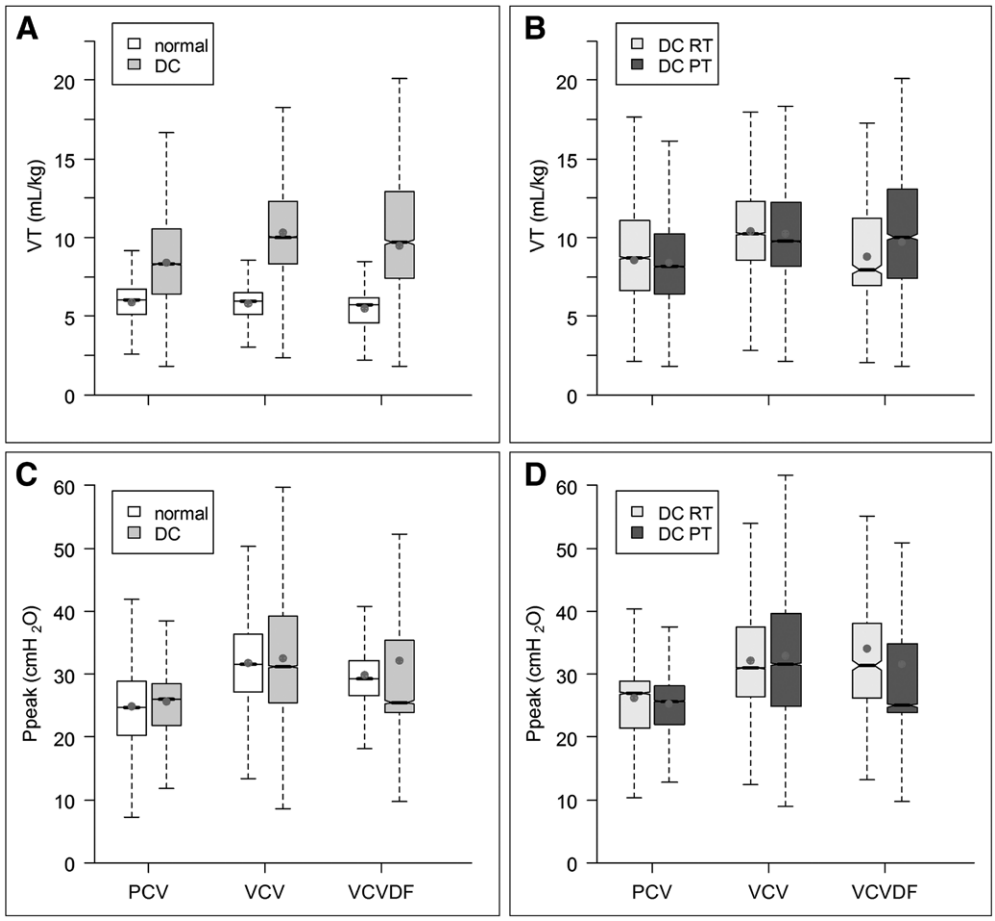

Figure 3. Descriptive notched *boxplots* for tidal volume (VT) (*top*) and peak pressure (P_{peak}) (*bottom*) in each ventilatory mode. **A** and **C**, Breaths without double cycling (DC; *white*) versus DC breaths (*gray*). **B** and **D**: Reverse-triggered (RT) (*light gray*) versus patient-triggered (PT) (*dark gray*) DC breaths. *Dots* represent means, and *box plots* indicate medians and 25th–75th percentiles. Note that outliers have been omitted for visualization purposes. PCV = pressure control-continuous mandatory ventilation, VCV = volume control-continuous mandatory ventilation with constant flow, VCVDF = volume control-continuous mandatory ventilation with decelerated flow.

Pohlman et al (8), we found low VT favors DC in VCV. In PCV, the positive association between VT and DC may be related to ventilator settings other than VT. Finally, the fact that low P_{peak} in VCV favored DC may reflect the presence of unmet ventilatory demand and flow asynchrony. The opposite occurs in PCV, where more DC occurred at high levels of P_{peak}. Since patients in all modes were ventilated at low VT, the fast decay in airflow during PCV may reflect unmet inspiratory demand and flow asynchrony.

Therefore, several physiologic factors, none of which are mutually exclusive, may account for DC. At the bedside careful adjustment of ventilator settings specific for each patient's diagnosis and neurorespiratory physiology; specific measures that can be useful for managing DC include increasing ventilator Ti, use of pressure-support ventilation or proportional assist modes, and considering paralyzing/sedating agents if VT is markedly elevated (1, 2, 4, 8).

TABLE 2. Mean Effects[a] for the Factors Influencing Double Cycling: Multivariate Analysis for Variables Clinically Suspected to Impact the Development of Double Cycling

Factors	Ventilatory Modes		
	Pressure Control-Continuous Mandatory Ventilation	Volume Control-Continuous Mandatory Ventilation With Constant Flow	Volume Control-Continuous Mandatory Ventilation With Decelerated Flow
Inspiratory time	−2.32 (−2.94 to −1.69)[b]	−0.58 (−1.11 to −0.05)[c]	−2.71 (−4.29 to −1.13)[b]
Peak flow	−0.10 (−0.11 to −0.08)[b]	−0.01 (−0.03 to −0.00)[c]	−0.01 (−0.04 to 0.03)
Peak airway pressure	0.08 (0.06–0.10)[b]	−0.06 (−0.08 to −0.05)[b]	−0.01 (−0.05 to 0.03)
Positive end-expiratory pressure	−0.05 (−0.10 to −0.00)[d]	0.03 (−0.01 to 0.07)	−0.25 (−0.34 to −0.16)[b]
Respiratory rate	0.08 (0.04–0.11)[b]	0.03 (0.02–0.05)[b]	0.07 (0.01–0.12)[c]
Tidal volume	0.01 (0.01–0.01)[b]	−0.00 (−0.01 to −0.00)[b]	0.01 (0.01–0.02)[b]

[a]Mean effects are in the logarithmic scale and expressed as mean (95% CI). The negative sign indicates an inverse association between the factor and double cycling (dependent variable).

Statistically significant associations between the explanatory variable and the response are indicated as follows:

[b]$p < 0.001$; [c]$p < 0.05$.

Patient-ventilator interaction induces continuous cross-talk among respiratory muscles, lung, and brain (33, 34). Our work is the first examining separately reverse-triggered and patient-triggered DC breaths during the whole period of MV. We found that one third of DC breaths originated from respiratory muscle contractions triggered by the ventilator or reverse-triggered breaths. Such a high proportion of DC originated by reverse triggering has never been reported. Reverse-triggered efforts may generate higher plateau pressure in VCV and large VT in VCV and PCV; although DC is reduced by deep sedation, potentially deleterious VTs may still be delivered (35). This phenomenon was reported several years ago (36, 37) and was recently described as entrainment; it usually occurs in heavily sedated patients, mostly with ARDS, and often goes unnoticed (11, 38–40). However, the incidence of reverse triggering in the general population of ICU patients was unknown. In our series, the proportions of DC and type of breath initiation (patient or reverse triggered) were not different in the five ARDS patients compared with the other patients studied (**Supplemental Table 3**, Supplemental Digital Content 11, http://links.lww.com/CCM/D718). In addition, the number of hours patients in each mode were under pharmacologic-controlled ventilation was not available, and the differences in the frequency of DC between PCV and VCV may be a result of when and the amount of time each approach was used in given patients. Just considering the percentage of the breaths that were reversed triggered in VCV (37.8%) versus those in PCV (21.9%) and VCVDF (19.3%), one would assume that patients spent a greater percentage of the time were under controlled ventilation during VCV.

Our study focused on the incidence and physiologic mechanisms associated with DC. However, some reverse-triggered breaths may have resulted in ineffective triggering of the ventilator, so DC did not occur (12), thus underestimating the real incidence of reverse triggering. Prospective studies are needed to investigate respiratory entrainment in different forms of respiratory failure, at different levels of consciousness, and under different sedation and pain control regimens.

Our study has some limitations. The algorithm-based approach might underestimate the frequency of DC compared with gold-standard approaches based on monitoring esophageal pressure or electrical activity of the diaphragm. The study analyzed the frequency, physiologic implications, and factors favoring DC; however, the design was based on breath analysis, regardless of the heterogeneity of the patients' clinical characteristics (e.g., severity of illness, reason for intubation, and others). We did not measure plateau airway pressures (unreliable in the context of active patient inspiration); thus, our assumptions on the effects of high transpulmonary swings inducing lung injury might not be accurate. We used only three types of ventilators for this study, and we cannot assume that other ventilators would produce similar patient-ventilator interactions using the same modes. Similarly, we analyzed breaths only in VCV, PCV, and VCVDF modes, so we cannot infer the incidence of DC in other modes such as adaptive pressure control modes or in the frequently used pressure-support mode. Reverse triggering was assessed only in DC breaths, precluding conclusions about the overall incidence of reverse triggering during MV. Finally, the design of our study does not allow us to assess the effect of different sedation levels on DC or the effects of DC on long-term cognitive dysfunction in critical care survivors (41).

In conclusion, DC is much less frequent than physicians might think, even when VT is set low and DC might appear in clusters. The total volume of the two stacked breaths can double the set VT in VCV and VCVDF. Since various interdependent physiologic factors related to patients' clinical conditions and ventilator settings can cause DC, it is crucial to tailor gas delivery to patients' neuroventilatory demand. When DC is present, reverse triggering occurs more frequently than previously thought. One third of double-cycled breaths were ventilator-triggered diaphragmatic contractions, and this phenomenon seems common in all ICU patients receiving MV.

REFERENCES

1. Branson RD, Blakeman TC, Robinson BR: Asynchrony and dyspnea. *Respir Care* 2013; 58:973–989
2. Gilstrap D, MacIntyre N: Patient-ventilator interactions. Implications for clinical management. *Am J Respir Crit Care Med* 2013; 188:1058–1068
3. Sassoon CSh: Triggering of the ventilator in patient-ventilator interactions. *Respir Care* 2011; 56:39–51
4. Beitler JR, Sands SA, Loring SH, et al: Quantifying unintended exposure to high tidal volumes from breath stacking dyssynchrony in ARDS: The BREATHE criteria. *Intensive Care Med* 2016; 42:1427–1436
5. Chanques G, Kress JP, Pohlman A, et al: Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. *Crit Care Med* 2013; 41:2177–2187
6. Figueroa-Casas JB, Montoya R: Effect of tidal volume size and its delivery mode on patient-ventilator dyssynchrony. *Ann Am Thorac Soc* 2016; 13:2207–2214
7. Gattinoni L, Tonetti T, Cressoni M, et al: Ventilator-related causes of lung injury: The mechanical power. *Intensive Care Med* 2016; 42:1567–1575
8. Pohlman MC, McCallister KE, Schweickert WD, et al: Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. *Crit Care Med* 2008; 36:3019–3023
9. Blanch L, Villagra A, Sales B, et al: Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015; 41:633–641
10. Thille AW, Rodriguez P, Cabello B, et al: Patient-ventilator asynchrony during assisted mechanical ventilation. *Intensive Care Med* 2006; 32:1515–1522
11. Akoumianaki E, Lyazidi A, Rey N, et al: Mechanical ventilation-induced reverse-triggered breaths: A frequently unrecognized form of neuromechanical coupling. *Chest* 2013; 143:927–938
12. Murias G, de Haro C, Blanch L: Does this ventilated patient have asynchronies? Recognizing reverse triggering and entrainment at the bedside. *Intensive Care Med* 2016; 42:1058–1061
13. Murias G, Montanyà J, Chacón E, et al: Automatic detection of ventilatory modes during invasive mechanical ventilation. *Crit Care* 2016; 20:258
14. Blanch L, Sales B, Montanya J, et al: Validation of the Better Care® system to detect ineffective efforts during expiration in mechanically ventilated patients: A pilot study. *Intensive Care Med* 2012; 38:772–780
15. Colombo D, Cammarota G, Alemani M, et al: Efficacy of ventilator waveforms observation in detecting patient-ventilator asynchrony. *Crit Care Med* 2011; 39:2452–2457
16. de Wit M, Pedram S, Best AM, et al: Observational study of patient-ventilator asynchrony and relationship to sedation level. *J Crit Care* 2009; 24:74–80
17. Bates D, Maechler M, Bolker B, et al: Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; 67:1–48

18. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group: Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800
19. Akoumianaki E, Maggiore SM, Valenza F, et al; PLUG Working Group (Acute Respiratory Failure Section of the European Society of Intensive Care Medicine): The application of esophageal pressure measurement in patients with respiratory failure. *Am J Respir Crit Care Med* 2014; 189:520–531
20. Mauri T, Yoshida T, Bellani G, et al; PLeUral Pressure Working Group (PLUG–Acute Respiratory Failure Section of the European Society of Intensive Care Medicine): Esophageal and transpulmonary pressure in the clinical setting: Meaning, usefulness and perspectives. *Intensive Care Med* 2016; 42:1360–1373
21. Richard JC, Lyazidi A, Akoumianaki E, et al: Potentially harmful effects of inspiratory synchronization during pressure preset ventilation. *Intensive Care Med* 2013; 39:2003–2010
22. Yoshida T, Fujino Y, Amato MB, et al: Fifty years of research in ARDS. Spontaneous breathing during mechanical ventilation. Risks, mechanisms, and management. *Am J Respir Crit Care Med* 2017; 195:985–992
23. Yoshida T, Roldan R, Beraldo MA, et al: Spontaneous effort during mechanical ventilation: Maximal injury with less positive end-expiratory pressure. *Crit Care Med* 2016; 44:e678–e688
24. Neto AS, Simonis FD, Barbas CS, et al; PROtective Ventilation Network Investigators: Lung-protective ventilation with low tidal volumes and the occurrence of pulmonary complications in patients without acute respiratory distress syndrome: A systematic review and individual patient data analysis. *Crit Care Med* 2015; 43:2155–2163
25. Vaporidi K, Babalis D, Chytas A, et al: Clusters of ineffective efforts during mechanical ventilation: Impact on outcome. *Intensive Care Med* 2017; 43:184–191
26. James G, Witten D, Hastie T, et al: An Introduction to Statistical Learning with Applications in R. New York, NY, Springer, 2013
27. Thille AW, Roche-Campo F, Brochard L: Ten reasons to be more attentive to patients when setting the ventilator. *Intensive Care Med* 2016; 42:572–575
28. Beck J, Gottfried SB, Navalesi P, et al: Electrical activity of the diaphragm during pressure support ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 2001; 164:419–424
29. Murias G, Lucangelo U, Blanch L: Patient-ventilator asynchrony. *Curr Opin Crit Care* 2016; 22:53–59
30. Georgopoulos D, Prinianakis G, Kondili E: Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006; 32:34–47
31. Tobin M, Jubran A, Laghi F, (Eds): Fighting the Ventilator. Third Edition. New York, McGraw-Hill Medical, 2013
32. Robinson BR, Blakeman TC, Toth P, et al: Patient-ventilator asynchrony in a traumatically injured population. *Respir Care* 2013; 58:1847–1855
33. Blanch L, Quintel M: Lung-brain cross talk in the critically ill. *Intensive Care Med* 2017; 43:557–559
34. Quilez ME, Rodríguez-González R, Turon M, et al: Moderate Peep after tracheal lipopolysaccharide instillation prevents inflammation and modifies the pattern of brain neuronal activation. *Shock* 2015; 44:601–608
35. Sottile PD, Albers D, Higgins C, et al: The association between ventilator dyssynchrony, delivered tidal volume, and sedation using a novel automated ventilator dyssynchrony detection algorithm. *Crit Care Med* 2018; 46:e151–e157
36. Flick GR, Bellamy PE, Simmons DH: Diaphragmatic contraction during assisted mechanical ventilation. *Chest* 1989; 96:130–135
37. Kallet RH, Campbell AR, Dicker RA, et al: Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: A comparison between volume and pressure-regulated breathing modes. *Respir Care* 2005; 50:1623–1631
38. Delisle S, Charbonney E, Albert M, et al: Patient-ventilator asynchrony due to reverse triggering occurring in brain-dead patients: Clinical implications and physiological meaning. *Am J Respir Crit Care Med* 2016; 194:1166–1168
39. Simon PM, Habel AM, Daubenspeck JA, et al: Vagal feedback in the entrainment of respiration to mechanical ventilation in sleeping humans. *J Appl Physiol (1985)* 2000; 89:760–769
40. Simon PM, Zurob AS, Wies WM, et al: Entrainment of respiration in humans by periodic lung inflations. Effect of state and CO(2). *Am J Respir Crit Care Med* 1999; 160:950–960
41. Fernandez-Gonzalo S, Turon M, De Haro C, et al: Do sedation and analgesia contribute to long-term cognitive dysfunction in critical care survivors? *Med Intensiva* 2018; 42:114–128

APPENDIX 1. Asynchronies in the ICU (ASYNICU) Group

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