

Effects of Different Levels of Pressure Support on Intra-Individual Breath-to-Breath Variability

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BACKGROUND: Evidence exists that during pressure support ventilation (PSV), the addition of an extrinsic (ie, ventilator-generated) breath-to-breath variability (BBV) of breathing pattern improves respiratory function. If BBV is beneficial per se, choosing the PS level that maximizes it could be considered a valid strategy for conventional PSV. In this study, we evaluated the effect of different PS levels on intrinsic BBV in acutely ill, mechanically ventilated subjects to determine whether a significant relationship exists between PS level and BBV magnitude. **METHODS:** Fourteen invasively mechanically ventilated subjects were prospectively studied. PS was adjusted at 20 cm H₂O and sequentially reduced to 15, 10, and 5 cm H₂O. Arterial blood gas analysis and pressure at 0.1 s after the onset of inspiration ($P_{0.1}$) were measured at each PS level. Airway and esophageal pressure and air flow were continuously recorded. Peak inspiratory flow, tidal volume (V_T), breathing frequency, and pressure-time product (PTP) were calculated on a breath-by-breath basis. The breathing pattern variability was assessed by the coefficient of variation of the time series of V_T , peak inspiratory flow, and breathing frequency from ~60 consecutive breath cycles at each PS level. A general linear model for repeated measures was applied, with PS as an independent factor. A significance level of .05 was considered. **RESULTS:** Despite a large inter-individual difference in all measured variables ($P < .001$), the coefficient of variation was as low as 30%, and no significant differences in the coefficient of variation of peak inspiratory flow, breathing frequency, and V_T between PS levels were observed ($P > .15$). Additionally, a significant increase in $P_{0.1}$, PTP, and breathing frequency ($P < .01$) and a reduction in V_T ($P < .001$) were observed with PS reduction. **CONCLUSIONS:** Despite a significant increase in spontaneous activity with PS reduction, BBV was not influenced by the PS level and was as low as 30% for all evaluated parameters. *Key words:* pressure support ventilation; breath-to-breath variability; patient-ventilator interaction; coefficient of variation. [Respir Care 2014;59(12):1888–1894. © 2014 Daedalus Enterprises]

Introduction

During controlled artificial ventilation, the breathing pattern is usually monotonous with constant minute ventila-

tion, tidal volume (V_T), and breathing frequency.¹ The intrinsic (ie, patient-generated) breath-to-breath variability (BBV) of breathing pattern, controlled by multiple feedback loops as well as neural and chemical factors, is fre-

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quently suppressed by sedation and muscle paralysis in critically ill patients.²

The addition of an extrinsic (ie, ventilator-generated) BBV of breathing pattern during controlled mechanical ventilation has been shown to be beneficial in experimental lung injury as well as during anesthesia,¹ improving gas exchange, respiratory system elastance, and intrapulmonary shunt.³ In a recent experimental study, pressure support ventilation (PSV) with extrinsic BBV in PS (so-called noisy PSV) also improved pulmonary function while reducing inflammation and structural damage.⁴ Notably, several authors reported that the use of conventional PSV (with fixed PS) is associated with a relevant intrinsic BBV.⁵ Hence, if BBV is beneficial per se as suggested by studies using extrinsic variability, maximizing the intrinsic variability could be considered a target for conventional PSV to be achieved by choosing the PS level that results in the greatest BBV intrinsically generated by the subject.

In this context, in this study, we performed a preliminary assessment of the effect of different PS levels on intrinsic BBV in acutely ill, mechanically ventilated patients. Our hypothesis is that BBV is not affected by changes in PS, independent of its levels in acutely ill, mechanically ventilated patients.

Methods

Study Population

We conducted a prospective interventional study in the ICU of the National Institute of Infectious Disease at the Oswaldo Cruz Foundation in Rio de Janeiro, Brazil, from March to October 2011. The institutional review board approved the protocol, and written informed consent was obtained from all patients or their legal representatives before study inclusion.

Patients admitted to the ICU for respiratory failure and requiring invasive mechanical ventilation were screened for the protocol when switched to a spontaneous PS mode of ventilation and achieving sedation levels corresponding to a Richmond Agitation-Sedation Scale score of between -2 and $+2$. Inclusion criteria were > 18 y of age, hemodynamic stability defined by mean arterial pressure of > 65 mm Hg, and norepinephrine dose of < 0.1 $\mu\text{g}/\text{kg}/\text{min}$. Mild sedation was allowed with morphine, midazo-

QUICK LOOK

Current knowledge

Pressure support ventilation (PSV) provides a constant level of pressure with each patient-triggered breath. During PSV, the intrinsic variability in tidal volume (V_T) is reduced with changes in minute ventilation accomplished through a change in breathing frequency.

What this paper contributes to our knowledge

During PSV, a decrease in the pressure setting from 20 to 5 cm H_2O in 5-cm H_2O increments increased subject breathing frequency but did not impact breath-to-breath V_T variability. The coefficient of variation of V_T was $< 30\%$ in 90% of subjects.

lam, and/or dexmedetomidine, and this, as well as PEEP and F_{IO_2} , was set by the attending physician. These parameters were not changed throughout the protocol. Subjects were mechanically ventilated (PB840, Covidien, Mansfield, Massachusetts) using the PSV mode with a flow trigger of 2.5 L/min, rise time of 90%, and cycling criteria on 25% of peak inspiratory flow.

Study Protocol

After recording baseline ventilation, PS was adjusted at 20 cm H_2O and sequentially reduced to 15, 10, and 5 cm H_2O , with 10-min intervals⁶ between changes (Fig. 1). In case of poor tolerance of the protocol, we defined as interruption criteria: (1) decrease in oxygen saturation of $< 90\%$, (2) respiratory distress with tachypnea over 35 breaths/min, and (3) psychomotor agitation and need for increasing sedation.

Data Acquisition

Airway pressure was measured proximal to the artificial airway, and esophageal pressure was measured with an esophageal balloon catheter (SmartCath, Bicare Monitoring Systems, Irvine, California) positioned at the distal part of the esophagus using gas pressure transducers (163PC01D48, Honeywell, Richmond, Virginia). The position of the balloon was verified before the beginning of measurement by the occlusion maneuver during 3–4 consecutive spontaneous breaths.⁷ Air flow was measured with a pneumotachometer (Hamilton Medical, Reno, Nevada) positioned right after the Y-piece of the circuit and connected to a differential pressure transducer (176PC07HD2, Honeywell).

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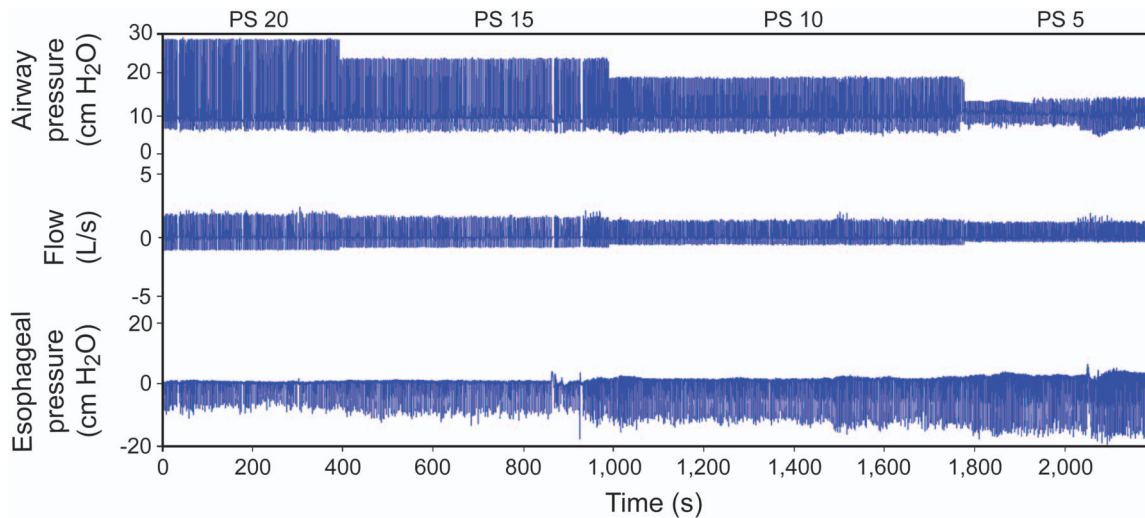


Fig. 1. Study protocol. Tracings from subject 13 showing continuous 2,180-s recordings of airway pressure, flow, and esophageal pressure during decremental pressure support (PS).

Airway pressure, esophageal pressure, air flow, mean arterial pressure, and electrocardiograms were continuously acquired with a sampling frequency of 1,000 Hz using custom-built data acquisition software and an analog-digital converter (NI 6008, National Instruments, Austin, Texas).

Before each change in PS, arterial blood was sampled for gas analysis (Stat Profile pHox Plus L, Nova Biomedical, Waltham, Massachusetts) via a catheter previously inserted in the radial or femoral artery for mean arterial pressure monitoring.

Data Processing

Volume was calculated by the numerical integration of flow. Peak inspiratory flow, V_T , and breathing frequency were calculated for each respiratory cycle. The onset of inspiration and expiration was detected automatically as the points at which the flow signal crossed the zero value. Breathing frequency was calculated as the inverse of the interval between the onset of 2 consecutive inspirations. Airway pressure changes at 0.1 s from the onset of inspiration ($P_{0.1}$) were measured at the end of each step. The esophageal pressure-time product (PTP) was calculated during inspiration, taking the first value at the beginning of the respiratory cycle as the offset.^{8,9} Additionally, PTP was also corrected by breathing frequency for comparison with previous studies.¹⁰

The breathing pattern variability was assessed by the coefficient of variation (SD/mean) of the time series of V_T , peak inspiratory flow, and breathing frequency for at least 3 min at the end of each PS level.¹¹ Artifacts induced by cough, swallowing, and physical agitation of the subjects were excluded from our analysis. In case of artifacts, the

record of the step could be prolonged. To measure ineffective triggers, a purpose-built routine (written in Matlab, Matworks, Natick, Massachusetts) was used to automatically identify the decrease in esophageal pressure without the occurrence of an effective inspiration on a breath-by-breath basis. A visual inspection was also performed after the automatic procedure.

Statistical Analysis

Statistical analysis was performed with Prism 4.0a (GraphPad Software, La Jolla, California) and Deducer 1.7–9 (Java GUI for R, <http://www.deducer.org/manual.html>, Accessed July 10, 2014). The normality of the data (Shapiro-Wilk test) and the homogeneity of variances (Levene median test) were tested. If a null hypothesis failed to be rejected, a logarithmic transformation was applied, and after the null hypothesis was rejected, the test was repeated. All data are expressed as mean \pm SD. The effects of PS levels and intra-individual variability in all measured parameters were assessed with a general linear model (with subjects and PS levels as factors). The significance level was set at .05.

Results

Fourteen subjects were included; the main indications for mechanical ventilation were acute hypoxemic respiratory failure in 12 subjects and reduced level of consciousness in 2 subjects. Primary diagnoses, mechanical ventilation times before the study, PS levels before the study, P_{aO_2}/F_{IO_2} indices at baseline, vasopressor use, PEEP, and Richmond Agitation-Sedation Scale scores of all subjects are shown in Table 1. Nine subjects were sedated during

Table 1. Clinical Characteristics of Subjects

Subject	Age (y)	SAPS II	SOFA Score	Vasopressors	P _{aO₂} /F _{IO₂}	Mechanical Ventilation Time (d)	Baseline PS (cm H ₂ O)	PEEP (cm H ₂ O)	Diagnosis	RASS Score
1	32	45	6	No	392	6	7	5	Tuberculosis	0
2	30	21	9	No	383	2	9	5	Urinary sepsis	-1
3	34	21	7	Yes	267	10	14	10	Pulmonary embolism	-1
4	26	33	2	No	560	2	7	5	Tuberculosis	0
5	39	66	9	No	498	5	10	5	Meningitis	-2
6	33	36	2	Yes	502	6	20	5	Lung abscess	-2
7	25	34	6	Yes	440	2	10	6	Tuberculosis	-2
8	42	48	8	Yes	271	3	16	8	CAP	-2
9	52	26	5	No	177	23	17	10	CAP	-2
10	67	36	5	Yes	416	6	15	6	Urinary sepsis	+1
11	45	63	12	Yes	200	10	15	5	CAP	-2
12	43	50	5	No	350	8	13	5	CAP	+2
13	41	45	7	Yes	355	7	10	5	CAP	-1
14	43	44	8	Yes	142	5	5	8	Tuberculosis	-1
Mean ± SD	39 ± 11	40 ± 13	6.5 ± 2.7		353 ± 128	6.7 ± 5.3	12 ± 4.3	6.3 ± 1.8		

SAPS II = Simplified Acute Physiology Score II
 SOFA = Sequential Organ Failure Assessment
 PS = pressure support
 RASS = Richmond Agitation-Sedation Scale
 CAP = community-acquired pneumonia

the study, and the maximum doses used were: morphine, 0.05 mg/kg/h; midazolam, 0.15 mg/kg/h; and dexmedetomidine, 0.5 µg/kg/h.

Effect of PS Level on Respiratory Variables, PTP, and P_{0.1}

During the sequential reduction of the PS level, V_T progressively decreased from 0.65 ± 0.20 to 0.45 ± 0.11 L, and there was a significant increase in breathing frequency from 18 ± 7 to 24 ± 8 breaths/min (P < .001) (Fig. 2). No significant differences were observed in minute ventilation (average value of 10.4 ± 2.1 L/min, P = .29). A significant increase in work of breathing was also observed since PTP increased from 150 ± 220 to 390 ± 540 cm H₂O × s/min (P < .01), and P_{0.1} increased from 2 ± 2 to 6.5 ± 3.7 cm H₂O (P < .001). No ineffective trigger was detected in any of the subjects.

Effect of PS Level on Breathing Pattern Variability

PS reduction did not significantly affect the coefficient of variation of the time series of V_T, peak inspiratory flow, breathing frequency, and inspiratory time (P > .15) (Fig. 3). The coefficient of variation of V_T was < 30% in 52 of the 56 measurements performed.

A considerable heterogeneity among subjects was found in the coefficient of variation of the parameters considered. For V_T, the coefficient of variation ranged from 2%

(almost absent) to 37% (similar to that of spontaneously breathing, healthy subjects). For breathing frequency and peak inspiratory flow, the coefficient of variation varied from 6 to 43% and from 3 to 37% between subjects, respectively.

Effect of PS Level on Gas Exchange, Heart Rate, and Mean Arterial Pressure

No significant effects of PS level on mean arterial pressure, heart rate, P_{aO₂}, and P_{aCO₂} were found as shown in Table 2. The mean coefficient of variation of heart rate and that of mean arterial pressure were 9 ± 17% and 3.1 ± 1.6%, respectively, and did not change with PS reduction.

Discussion

The main findings of this study are as follows. (1) In this group of acutely ill, mechanically ventilated subjects, despite the low level of sedation, changes in PS did not result in significant changes in BBV even though they caused significant adaptations in terms of subject effort measured by PTP and P_{0.1}. (2) The coefficient of variation of the time series of peak inspiratory flow, breathing frequency, and V_T was generally lower than that reported in the literature during spontaneous breathing but was comparable to that in patients with slight-to-moderate hypoxia and in patients with acute respiratory failure under PSV. (3) Significant inter-individual variability exists in all re-

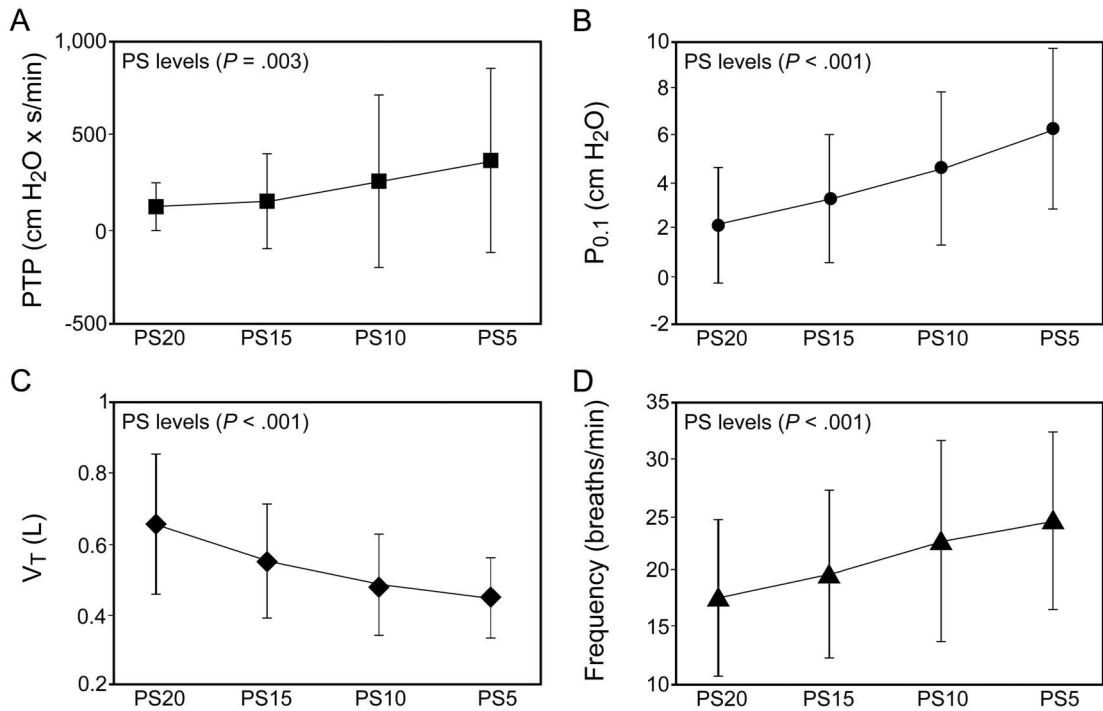


Fig. 2. Values of pressure-time product (PTP) (A), respiratory drive ($P_{0.1}$) (B), tidal volume (V_T) (C), and breathing frequency (D) at different levels of pressure support (PS). Data are shown as mean \pm SD.

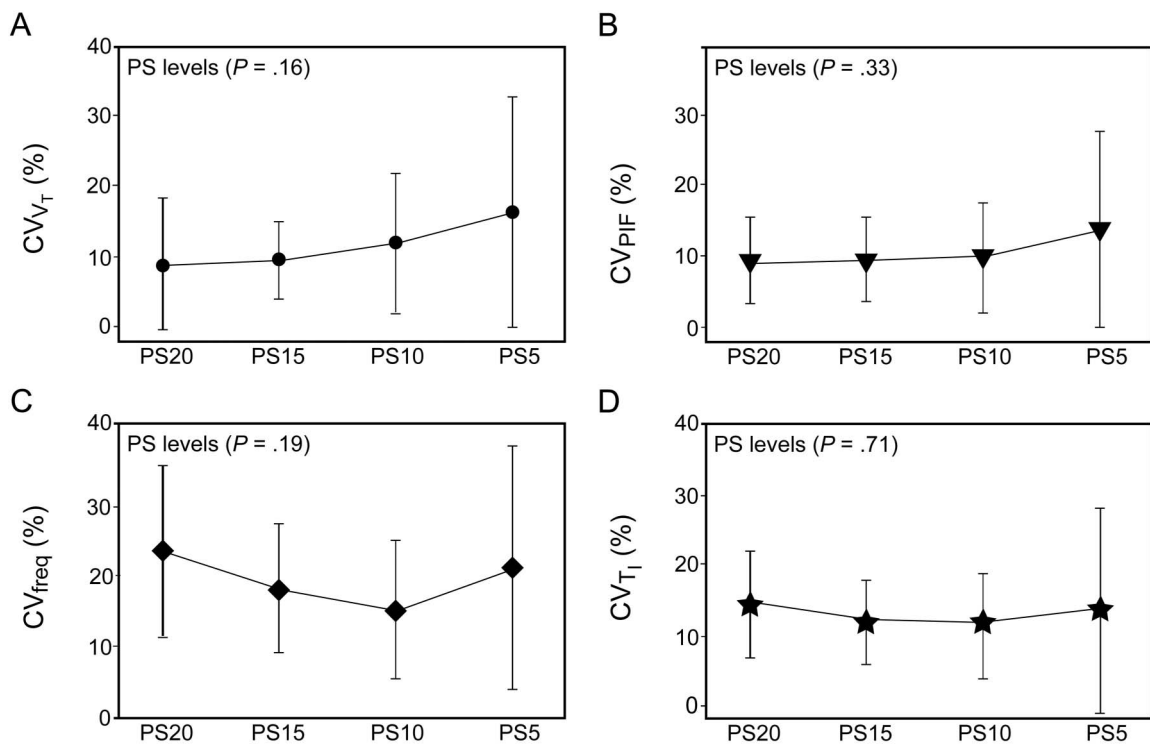


Fig. 3. Values of the coefficient of variation (SD/mean) of tidal volume (CV_{V_T}) (A), peak inspiratory flow (CV_{PIF}) (B), breathing frequency (CV_{freq} ; breaths/min) (C), and inspiratory time (CV_{T_i}) (D) at different levels of pressure support (PS). Data are presented as mean \pm SD.

Table 2. Analysis of Arterial Blood Gases and Hemodynamic Variables

	Pressure Support				PS Effect
	20 cm H ₂ O	15 cm H ₂ O	10 cm H ₂ O	5 cm H ₂ O	
pH	7.49 ± 0.03	7.48 ± 0.03	7.49 ± 0.05	7.49 ± 0.06	.15
P _{aCO₂}	40.8 ± 9	42.5 ± 9.1	43.4 ± 10.5	42.4 ± 10.5	.27
P _{aO₂}	131 ± 50	119.5 ± 44.7	120 ± 36.9	119.7 ± 34.3	.44
Heart rate, beats/min	91 ± 18	87.7 ± 19.7	88 ± 20.3	89.6 ± 19.3	.14
Mean arterial pressure, mm Hg	97.6 ± 14	101.3 ± 14	102.2 ± 12	103.6 ± 11	.06

spiratory parameters, especially those related to BBV, suggesting that other factors seem to influence BBV beyond differences in ventilation. (4) To assure a certain level of BBV during PSV in a group of patients, the use of ventilator-generated variability seems necessary.

During assisted ventilation in critically ill patients, intrinsic BBV can be reduced depending on several factors, such as the mode of assisted ventilation, the level of sedation, and the severity of the underlying disease itself.

In the present study, we assessed the possible relationship between the mean level of PS and the amount of BBV. A progressive reduction in PS resulted in considerable respiratory adaptations. In fact, PTP and P_{0.1} increased significantly, suggesting a progressively larger work load. However, BBV did not change significantly. Actually, if we assume that a reduction in the PS level increases respiratory work load, one would expect a reduction in the intrinsic BBV as a result of increased resistive or elastic loads, as reported previously in spontaneously breathing patients.^{12,13} Most likely, intrinsic mechanisms, such as respiratory drive or even the level of sedation, play a complex role in patient-ventilator interaction that might be more important than PS for the generation of BBV.^{14,15}

The intra-individual breath-to-breath fluctuations in ventilatory variables, such as V_T, peak inspiratory flow, and breathing frequency, are well recognized and can be cyclically observed.¹⁶ Healthy subjects breathing spontaneously show a coefficient of variation of V_T between 26%¹⁷ and 33%,¹⁸ which is reduced during lung disease.¹⁹ The coefficient of variation of V_T during PSV in deeply sedated animals or patients with acute lung injury has been reported to be as low as 10%^{18,20} and up to 30% at a fixed PS level. In agreement with our results, a recent study reported the same level of intrinsic BBV, with a coefficient of variation of V_T of 13.7 ± 9.1% (mean ± SD), in critically ill patients ventilated with the PS mode. Interestingly, even intra-individual BBV in the present study was similar to that reported by Spieth et al.²¹

Increased variability in V_T in critically ill patients has been associated with successful weaning from mechanical ventilation,^{18,22} and the coefficient of variation of V_T has been proposed as a predictor for extubation outcome.¹⁸ In this context, our results suggest that such a prediction is

not influenced by the PS level and that very low PS levels can be avoided for this assessment, reducing the occurrence of fatigue and distress in the patient.

The results suggest that fine-tuning the PS is an effective strategy to obtain a level of BBV associated with potential improvements in gas exchange, lung mechanics, and lung pro-inflammatory mediators, as suggested in a previous study.⁴ From this point of view, the use of ventilator-generated variability seems indispensable. However, the interaction between intrinsically and extrinsically generated BBV is still unknown, and it is possible to speculate that some patients would maintain basically the same breathing pattern irrespective of the presence of BBV, undermining the expected benefits of this ventilation strategy. This possibility deserves further investigation to fully exploit extrinsic BBV in a broad clinical population.

Limitations

No randomization of the sequence of PS levels was applied in our protocol, which was planned to reduce the ventilatory support progressively. Hence, a sequence effect cannot be excluded, but it seems more likely that this could have induced, rather than suppressed, a dependence of respiratory variability on PS by inducing changes in variability secondary to loading or fatigue. Moreover, the severity of illness of our subjects may have influenced the BBV, as described by other authors.

It is also possible that increased subject effort related to PS reduction promoted some level of anxiety, which is known to affect BBV considerably,¹⁶ possibly masking a relationship between BBV and PS levels. Although we maintained sedation control in our subjects at Richmond Agitation-Sedation Scale scores of between -2 and +2, we cannot exclude that these drugs may still have some effect on BBV.

Conclusions

BBV during PSV was not influenced by the level of pressure assistance offered to the subject despite significant changes in V_T, breathing frequency, and PTP. The possible beneficial effects of an extrinsic BBV and its

interaction with the intrinsic breath pattern variability in patients during PSV remain to be determined.

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