frontiers in Physiology

ORIGINAL RESEARCH
published: 22 October 2021
doi: 10.3389/fphys.2021.725738

Effects of Different Levels of Variability and Pressure Support Ventilation on Lung Function in Patients With Mild–Moderate Acute Respiratory Distress Syndrome

Lorenzo Ball[1,2], Yuda Sutherasan[3], Martina Fiorito[1], Antonella Dall'Orto[1], Lorenzo Maiello[1], Maria Vargas[4], Chiara Robba[1,2], Iole Brunetti[2], Davide D'Antini[1,5], Pasquale Raimondo[1,5], Robert Huhle[6], Marcus J. Schultz[6,7,8†], Patricia R. M. Rocco[9†], Marcelo Gama de Abreu[10†] and Paolo Pelosi[1,2†]*

[1] Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy, [2] Anesthesia and Intensive Care, Ospedale Policlinico San Martino Istituto di Ricerca e Cura a Carattere Scientifico (IRCCS) for Oncology and Neurosciences, Genova, Italy, [3] Division of Pulmonary and Pulmonary Critical Care Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, [4] Department of Neurosciences, Reproductive and Odonthostomatological Sciences, University of Naples Federico II, Naples, Italy, [5] Department of Anaesthesia and Intensive Care, University of Foggia, Foggia, Italy, [6] Mahidol Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand, [7] Department of Intensive Care, Laboratory of Experimental Intensive Care and Anesthesiology (LEICA), Amsterdam University Medical Centers, Location Academic Medical Center (AMC), Amsterdam, Netherlands, [8] Nuffield Department of Medicine, Oxford University, Oxford, United Kingdom, [9] Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, [10] Pulmonary Engineering Group, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

OPEN ACCESS

Edited by:
Luigi Camporota, Guy's and St Thomas' NHS Foundation Trust, United Kingdom

Reviewed by:
Elena Spinelli, IRCCS Ca 'Granda Foundation Maggiore Policlinico Hospital, Italy
Lise Piquilloud, Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

***Correspondence:**
Lorenzo Ball
lorenzo.ball@unige.it

† These authors share senior authorship

Specialty section:
This article was submitted to Respiratory Physiology, a section of the journal Frontiers in Physiology

Received: *15 June 2021*
Accepted: *17 September 2021*
Published: *22 October 2021*

Citation:
Ball L, Sutherasan Y, Fiorito M, Dall'Orto A, Maiello L, Vargas M, Robba C, Brunetti I, D'Antini D, Raimondo P, Huhle R, Schultz MJ, Rocco PRM, Gama de Abreu M and Pelosi P (2021) Effects of Different Levels of Variability and Pressure Support Ventilation on Lung Function in Patients With Mild–Moderate Acute Respiratory Distress Syndrome. Front. Physiol. 12:725738. doi: 10.3389/fphys.2021.725738

Background: Variable pressure support ventilation (vPSV) is an assisted ventilation mode that varies the level of pressure support on a breath-by-breath basis to restore the physiological variability of breathing activity. We aimed to compare the effects of vPSV at different levels of variability and pressure support (ΔP_S) in patients with acute respiratory distress syndrome (ARDS).

Methods: This study was a crossover randomized clinical trial. We included patients with mild to moderate ARDS already ventilated in conventional pressure support ventilation (PSV). The study consisted of two blocks of interventions, and variability during vPSV was set as the coefficient of variation of the ΔP_S level. In the first block, the effects of three levels of variability were tested at constant ΔP_S: 0% ($PSV_{0\%}$, conventional PSV), 15% ($vPSV_{15\%}$), and 30% ($vPSV_{30\%}$). In the second block, two levels of variability (0% and variability set to achieve ±5 cmH_2O variability) were tested at two ΔP_S levels (baseline ΔP_S and ΔP_S reduced by 5 cmH_2O from baseline). The following four ventilation strategies were tested in the second block: PSV with baseline ΔP_S and 0% variability (PSV_{BL}) or ±5 cmH_2O variability ($vPSV_{BL}$), PSV with ΔP_S reduced by 5 cmH_2O and 0% variability (PSV_{-5}) or ±5 cmH_2O variability ($vPSV_{-5}$). Outcomes included gas exchange, respiratory mechanics, and patient-ventilator asynchronies.

Results: The study enrolled 20 patients. In the first block of interventions, oxygenation and respiratory mechanics parameters did not differ between $vPSV_{15\%}$ and $vPSV_{30\%}$

compared with $PSV_{0\%}$. The variability of tidal volume (V_T) was higher with $vPSV_{15\%}$ and $vPSV_{30\%}$ compared with $PSV_{0\%}$. The incidence of asynchronies and the variability of transpulmonary pressure (P_L) were higher with $vPSV_{30\%}$ compared with $PSV_{0\%}$. In the second block of interventions, different levels of pressure support with and without variability did not change oxygenation. The variability of V_T and P_L was higher with $vPSV_{-5}$ compared with PSV_{-5}, but not with $vPSV_{BL}$ compared with PSV_{BL}.

Conclusion: In patients with mild-moderate ARDS, the addition of variability did not improve oxygenation at different pressure support levels. Moreover, high variability levels were associated with worse patient-ventilator synchrony.

Clinical Trial Registration: www.clinicaltrials.gov, identifier: NCT01683669.

Keywords: variable pressure support ventilation, acute respiratory distress (ARDS), asynchronies, respiratory mechanic, assisted ventilation

INTRODUCTION

Pressure support ventilation (PSV) is an assisted ventilation mode commonly used in critically ill patients (Esteban et al., 2013). The maintenance of spontaneous respiratory activity in acute respiratory distress syndrome (ARDS) patients improves respiratory function and decreases the need for vasopressor and sedative drugs (Putensen et al., 2001). Assisted ventilation modes have been commonly used in the management of patients with ARDS, in particular those with mild to moderate hypoxemic respiratory failure (Bellani et al., 2016).

In the last years, researchers have proposed to vary the level of pressure support on a breath-by-breath basis to restore the physiological variability of breathing activity (Tobin et al., 1988). Variable pressure support ventilation (vPSV), compared with conventional PSV, improved oxygenation in the experimental models of ARDS (Gama de Abreu et al., 2008) and ventilator-patient synchrony in a small pilot study in critically ill patients with acute respiratory failure (Spieth et al., 2013). These effects could be mediated by an amelioration of the ventilation-perfusion matching (Huhle et al., 2016), as well as a recruitment effect due to the repetitive delivery of breaths with a higher tidal volume, which might also result in a reduction of lung inhomogeneity (Mauri et al., 2017). However, so far, the only clinical study published has used only one variability level at fixed pressure support (ΔP_S) (Spieth et al., 2013). Therefore, the effects of different levels of variability and the impact of variability at different ΔP_S levels remain unknown. Different levels of variability might modify differently the ventilation perfusion-matching and might affect differently gas exchange and respiratory mechanics.

The aim of this study was to evaluate the effects of vPSV, at different levels of variability and pressure support, on short-term lung function parameters in patients with mild to moderate ARDS. We tested the hypothesis that vPSV would improve gas exchange, respiratory mechanics, and patient-ventilator asynchrony. We also hypothesized that the degree of variability and the level of ΔP_S would influence the effects of vPSV.

Abbreviations: PSV, pressure support ventilation; ARDS, acute respiratory distress syndrome; vPSV, variable pressure support ventilation; ΔP_S, pressure support level; ICU, intensive care unit; PEEP, positive end-expiratory pressure; PBW, predicted body weight; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment score; RASS, richmond agitation-sedation scale; $PSV_{0\%}$, pressure support ventilation with no variability; $vPSV_{15\%}$, variable pressure support ventilation with 15% CV variability; $vPSV_{30\%}$, variable pressure support ventilation with 30% CV variability; V_T, tidal volume; PTP, esophageal pressure-time product; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure; PSV_{BL}, pressure support ventilation with no variability and baseline ΔP_S as per clinical indication; $vPSV_{BL}$, variable pressure support with variability set to achieve ± 5 cmH_2O and baseline ΔP_S as per clinical indication; PSV_{-5}, pressure support ventilation with no variability and ΔP_S reduced by 5 cmH_2O from the baseline value; $vPSV_{-5}$, variable pressure support ventilation with variability set to achieve ± 5 cmH_2O and ΔP_S reduced by 5 cmH_2O from the baseline value.

METHODS

Study Design

This was a prospective, crossover, randomized clinical trial conducted in a single university hospital intensive care unit (ICU).

Inclusion and Exclusion Criteria

Patients aged >18 years with mild to moderate ARDS (PaO_2/FIO_2 ratio between 100 and 300 mmHg with a positive end-expiratory pressure, PEEP $\geq$5 cmH_2O) already receiving PSV per clinical indication were screened for inclusion. Exclusion criteria were pregnancy, chronic obstructive pulmonary disease, presence of pneumothorax or chest tubes, and unavailability of research staff.

Interventions

According to the local clinical practice, conventional PSV was delivered by an Evita Infinity V500 ventilator (Dräger Medical AG, Lübeck, Germany) targeting a V_T of 6–8 ml/kg of predicted body weight, respiratory rate $\leq$25 min^{-1} with PEEP and FIO_2 titrated to achieve a peripheral oxygen saturation $\geq$92%. This ventilator can operate in vPSV mode setting the variability of the ΔP_S and delivers breaths with an approximately Gaussian distribution, truncated at 3 SDs from the mean ΔP_S. The parameter "variability" of this ventilator refers to the range of ΔP_S, e.g., 90% "variability" results in a 30% coefficient

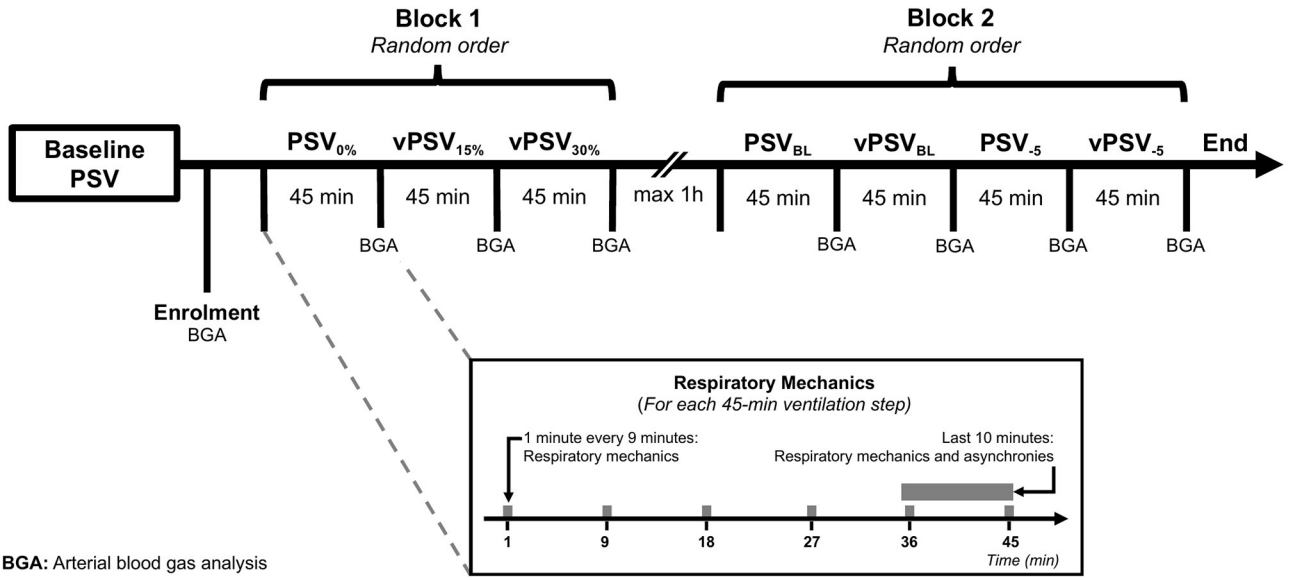

FIGURE 1 | Time course of interventions. Within each intervention block, different ventilation settings were delivered in random order. $PSV_{0\%}$, conventional PSV ventilation with no variability; $vPSV_{15\%}$, variable PSV with variability set to 15% CV; $vPSV_{30\%}$, variable PSV with variability set to 30% CV; PSV_{BL}, PSV with no variability and baseline ΔP_S as per clinical indication; $vPSV_{BL}$, variable pressure support with variability set to achieve ±5 cmH_2O and baseline ΔP_S as per clinical indication; PSV_{-5}, PSV with no variability and ΔP_S reduced by 5 cmH_2O from the baseline value; $vPSV_{-5}$, variable PSV with variability set to achieve ±5 cmH_2O and ΔP_S reduced by 5 cmH_2O from the baseline value; PSV, pressure support ventilation; CV, coefficient of variation.

of variation (CV). As illustrated in **Figure 1**, all patients underwent two blocks of interventions, receiving 45-min periods of ventilation with different settings. In the first block, the effects of three levels of variability were tested at constant ΔP_S to explore the effect of variability added to a fixed ΔP_S level, while in the second block, a variability of ±5 cmH_2O was added to ΔP_S set at either the baseline level or the baseline level minus 5 cmH_2O, to investigate the effects of variability at two ΔP_S levels. During the first block, the ΔP_S was set at a fixed value corresponding to the level chosen by the treating clinician before enrolment, and three different CV% levels were used: 0% ($PSV_{0\%}$), 15% ($vPSV_{15\%}$), and 30% ($vPSV_{30\%}$). During the second block, four ventilation settings were used: PSV with baseline ΔP_S (PSV_{BL}), baseline ΔP_S with variability set individually to ±5 cmH_2O ($vPSV_{BL}$), ΔP_S reduced by 5 cmH_2O compared with the baseline with either no variability (PSV_{-5}) or variability set to ±5 cmH_2O ($vPSV_{-5}$). The two blocks were performed sequentially, within 1 h from each other to allow for nursing assistance if required, and ventilation modes within each intervention block were assigned in random order with a Latin square design (as shown in **Figure 1**; **Supplementary Figures 1, 2**). The randomization sequence was generated with an online service, and a sealed envelope was opened at the moment of patient enrolment. Participants were blinded to the treatment assignment as were the operators involved in respiratory mechanics analysis.

Patient management procedures not related to mechanical ventilation, including sedation and fluid administration, were at the discretion of the treating clinician. When clinically feasible, we avoided changing FIO_2, PEEP, and ΔP_S during the study, and in case of desaturation below 92%, FIO_2 increase was prioritized over PEEP increase. After completion of the study protocol, ventilation was continued at the discretion of the treating physician.

Measurements

An esophageal balloon catheter (Compliance catheter, Microtek Medical B.V., Zutphen, The Netherlands) was inserted through the nose or mouth, filled with 1.5 ml, and correct positioning was verified with an occlusion maneuver (Akoumianaki et al., 2014). The flow was measured with a heated Fleisch-type pneumotachograph connected to a multi-channel transducer (ICU Lab, KleisTEK Engineering, Bari, Italy), while the tidal volume was measured as the integral of flow over time. Respiratory traces were recorded continuously throughout the study. An arterial blood gas analysis, heart rate, and invasive mean arterial pressure were recorded at baseline and the end of each ventilation step.

Pressure-time and flow-time curves were analyzed offline with a dedicated script written in MATLAB (MathWorks, MA, USA). The following parameters were computed breath by breath: V_T, PEEP, ΔP_S, mean airway pressure, inspiratory time to total time ratio (T_{insp}/T_{tot}), respiratory rate (RR), esophageal pressure swings (ΔP_{es}), and peak transpulmonary pressure (P_L). The respiratory muscle activity was quantified with the esophageal pressure-time product per min (PTP_{es}), calculated as follows (Mauri et al., 2016):

$$PTP_{es,min} = RR \cdot \int P_{mus}\, dt = RR \cdot \int (P_{cw,recoil} - P_{es})\, dt$$

where P_{mus} is the pressure generated by the respiratory muscles, and $P_{cw,recoil}$ is the chest wall recoil pressure, calculated assuming a fixed elastance of 5 cmH_2O/L. The asynchrony index was computed as the number of asynchronous events divided by the total number of ventilator cycles plus ineffective efforts during expiration multiplied by 100 (Blanch et al., 2015). Asynchronies were classified independently by two experienced operators (LB and MV), and discrepancies were resolved by consensus. The analysis of respiratory mechanics data was performed by three operators blinded to the ventilation settings (ADO, MF, and LM). Also, we measured the evolution of respiratory mechanics at min 1, 9, 18, 27, 36, and 45 from the start of each ventilation step. To allow sufficient time for patient adaptation, main analyses of respiratory mechanics and asynchronies were restricted to the last 10 min of each ventilation step.

Data Analysis and Sample Size Calculation

All variables are reported as medians [25th−75th percentile], if not otherwise specified. Measurements on multiple breaths were aggregated within-patients computing the median and the CV; then, between-patients medians [25th−75th percentile] were computed. Comparisons between continuous variables during the different ventilation steps were sought with Friedman's test and Dunn's *post-hoc* test. The primary endpoint was the partial pressure of arterial oxygen to FiO_2 ratio (PaO_2/FiO_2). From internal administrative data, we expected a baseline PaO_2/FiO_2 around 150 ± 50 mmHg. Using a Latin square crossover design, and assuming an intra-subject correlation of the PaO_2/FiO_2 between treatments with $\rho = 0.75$, we needed to enroll at least 16 patients to achieve 90% power (1-β) to detect a 20% relative increase in the PaO_2/FiO_2 ratio (Muller and Barton, 1989; Muller et al., 1992). To account for potential drop-off or missing respiratory mechanics data, we aimed to enroll 20 patients. Repeated measurement analysis of respiratory mechanics parameters at different timepoints within each ventilation block was performed using mixed-effects linear models using patients as random effects and timepoint, ventilation, and their interaction as fixed effects.

In one *post-hoc* analysis, associations were determined between the respiratory mechanics parameters of each breath and the ΔP_S received during the preceding breath in the $vPSV_{BL}$ and $vPSV_{-5}$ ventilation steps. For this purpose, mixed-effects linear models were used, using patients as random effects and the ΔP_S received during the preceding breath as the fixed effect.

All analyses were performed with R 3.2.3 (The R Foundation for Statistical Computing, www.r-project.org). Statistical significance was considered for two-tailed $p < 0.05$.

RESULTS

Twenty patients were enrolled and completed the study. Baseline characteristics are presented in **Table 1**. The FiO_2 and PEEP were kept constant during the study in all patients; one patient required ΔP_S reduction between ventilation block 1 and block 2 according to the treating clinician decision for reasons unrelated to the study procedures. **Tables 2, 3** show respiratory mechanics, hemodynamics, and arterial blood gas analysis in ventilation blocks 1 and 2, respectively. The distribution of key respiratory mechanics parameters in ventilation blocks 1 and 2 is illustrated in **Figures 2**, **3**, respectively. **Supplementary Figures 3–11** report details the evolution over time of the respiratory mechanics parameters in the different ventilation steps.

TABLE 1 | Baseline characteristics of patients.

Patient characteristics	
Number of patients	20
Age (years)	72 [59–79]
Female sex (N, %)	6/20 (30%)
Weight (kg)	80 [64–87]
Height (cm)	175 [165–180]
Body mass index (kg/m^2)	25.8 [22.7–29.5]
PBW (kg)	71 [58–75]
SAPS II	53 [38–60]
SOFA	7 [6–9]
RASS	−3 [−3 to −1]
Sedative drugs (N, %)	Propofol 5/20 (25%) Dexmedetomidine 3/20 (15%) Midazolam 4/20 (20%) None 8/20 (40%)
Analgesic drugs (N, %)	Fentanyl 8/20 (40%) Morphine 2/20 (10%) None 10/20 (50%)
Days of ventilation prior to inclusion	7 [5–9]
Primary reason for admission to the ICU	Acute respiratory failure: 10 (50%) Multiple trauma: 4 (20%) Brain hemorrhage: 3 (15%) Post-cardiac arrest: 3 (15%)
Risk factor for development of ARDS	Pneumonia: 11 (55%) Multiple fractures: 2 (10%) Sepsis: 4 (20%) Aspiration pneumonia: 3 (15%)
Blood gas analysis at enrolment PaO_2 (mmHg)	97 [79–120]
$PaCO_2$ (mmHg)	40 [36–46]
pHa	7.46 [7.44–7.51]
PaO_2/FIO_2 ratio (mmHg)	198 [154–250]
Ventilator settings at enrolment	
ΔP_S (cmH_2O)	15 [14–17]
PEEP (cmH_2O)	6 [5–8]
FIO_2 (%)	50 [43–58]
Tidal volume (mL/kg of PBW)	7.5 [7.0–8.5]
Respiratory rate (min^{-1})	15 [13–20]

PBW, predicted body weight; PEEP, positive end-expiratory pressure; ΔP_S, pressure support; SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment score; RASS, richmond agitation-sedation scale; ICU, intensive care unit.

Block 1: Physiological Effects of Different Variability Levels at Constant ΔP_S

The PaO_2/FiO_2 did not differ between ventilation steps in block 1 ($p = 0.62$, **Table 2**). Median respiratory mechanics variables, other gas exchange, and hemodynamic parameters did not

TABLE 2 | Gas exchange, hemodynamics, and respiratory mechanics in patients during pressure support ventilation at different levels of variability (Block 1).

	Ventilation modes			*p*-values		
	$PSV_{0\%}$	$vPSV_{15\%}$	$vPSV_{30\%}$	Overall	$vPSV_{15\%}$ vs. $PSV_{0\%}$	$vPSV_{30\%}$ vs. $PSV_{0\%}$
Ventilation settings						
$\Delta P_{S,set}$ (cmH_2O)	15.0 [13.0–16.0]	15.0 [13.0–16.0]	15.0 [13.0–16.0]	>0.99		
ΔP_S set variability (CV %)	0	15	30	<0.001		
Gas exchange						
PaO_2/FIO_2 (mmHg)	209 [157–242]	214 [160–256]	210 [179–252]	0.62		
PaO_2 (mmHg)	96 [79–118]	98 [85–116]	108 [82–123]	0.62		
$PaCO_2$ (mmHg)	44 [37–46]	43 [38–46]	43 [37–48]	0.95		
pH	7.45 [7.43–7.49]	7.49 [7.43–7.50]	7.47 [7.44–7.50]	0.64		
Hemodynamics						
Heart rate (min^{-1})	85 [72–92]	83 [75–90]	83 [73–91]	0.46		
Mean arterial pressure (mmHg)	78 [68–96]	79 [73–91]	82 [70–90]	0.37		
Respiratory mechanics						
$\Delta P_{S,measured}$ (cmH_2O)	14.6 [12.5–15.7]	14.6 [12.7–16.0]	14.7 [12.6–16.5]	0.39		
$PS_{measured}$ (CV, %)	1.2 [0.7–2.0]	15.6 [15.0–17.2][a]	29.7 [27.5–31.5][a]	<0.001	0.006	<0.001
Total PEEP (cmH_2O)	7.2 [6.1–8.5]	7.4 [6.2–8.6]	7.5 [6.2–8.4]	0.09		
Total PEEP (CV, %)	2.2 [1.1–3.1]	2.2 [1.2–3.8]	2.6 [1.7–3.3][a]	0.034	0.40	0.026
P_{mean} (cmH_2O)	11.6 [9.9–12.6]	12.1 [10.1–12.9]	11.6 [10.4–12.8]	0.16		
P_{mean} (CV, %)	3.7 [3.0–6.0]	8.1 [5.8–9.6][a]	13.2 [10.2–15.5][a]	<0.001	0.016	<0.001
Respiratory rate (min^{-1})	16.7 [13.7–21.4]	16.8 [13.9–21.4]	15.6 [13.8–19.7]	0.86		
Respiratory rate (CV, %)	11.6 [9.2–15.8]	12.5 [10.3–22.4]	17.9 [15.8–24.9][a]	0.002	0.17	<0.001
V_T (ml/kg of PBW)	8.1 [7.3–10.0]	8.8 [7.0–10.7]	8.9 [7.2–10.1]	0.95		
V_T (CV, %)	6.7 [4.5–9.1]	13.1 [10.7–14.4][a]	23.8 [17.8–28.1][a]	<0.001	0.006	<0.001
T_{insp}/T_{tot}	0.34 [0.29–0.41]	0.37 [0.32–0.41]	0.37 [0.30–0.43]	0.35		
T_{insp}/T_{tot} (CV, %)	11.1 [7.4–15.1]	10.9 [9.6–16.3]	14.6 [12.3–21.0]	0.08		
PTP_{es} (cmH_2O s min^{-1})	126 [102–226]	154 [103–194]	136 [121–208]	0.95		
PTP_{es} (CV, %)	26.8 [15.6–39.2]	30.1 [17.0–47.6]	36.2 [25.9–58.2][a]	0.029	0.71	0.026
ΔP_{es} (cmH_2O)	5.0 [2.1–7.6]	3.0 [1.3–7.4]	2.7 [1.6–5.4]	0.10		
ΔP_{es} (CV, %)	23.2 [18.0–34.2]	26.8 [19.7–40.9]	26.8 [24.3–47.5]	0.07		
P_L (cmH_2O)	18.0 [16.9–21.4]	17.8 [16.0–21.9]	17.4 [15.9–20.2]	0.27		
P_L (CV, %)	4.5 [2.7–11.7]	14.7 [13.2–15.9][a]	25.8 [21.4–27.3][a]	<0.001	0.025	<0.001
Asynchrony index (%)	1.6 [0.6–10.5]	2.2 [0.5–16.3]	5.1 [1.0–17.4][a]	0.031	0.21	0.019

Values are computed during the last 10 min of a 45-min ventilation period. Data are reported as inter-subject median [25th–75th percentile] of the intra-subject median values.
[a]Significantly different from $PSV_{0\%}$. $PSV_{0\%}$, pressure support ventilation with no variability; $vPSV_{15\%}$, variable pressure support ventilation with 15% CV variability; $vPSV_{30\%}$, variable pressure support ventilation with 30% CV variability.
CV, coefficient of variation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; ΔP_S, pressure support; V_T, tidal volume; PTP, esophageal pressure-time product; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure.

change between $vPSV_{15\%}$ and $vPSV_{30\%}$ compared with $PSV_{0\%}$ (**Table 2**). However, the variability of ΔP_S, $PEEP_{tot}$, P_{mean}, and V_T was higher with $PSV_{15\%}$ and $PSV_{30\%}$ compared with $PSV_{0\%}$ (**Table 2**). The RR and $PTP_{es,min}$ had higher variability only with $vPSV_{30\%}$ (**Table 2**). Moreover, asynchronies were more frequent with $vPSV_{30\%}$ compared with $PSV_{0\%}$ ($p = 0.019$, **Table 2**).

Block 2: Physiological Effects of Variability at Two Levels of ΔP_S

The PaO_2/FiO_2, as well as other gas exchange and hemodynamic parameters, did not differ between ventilation steps in block 2 (**Table 3**). Ventilation modes with ΔP_S reduced by 5 cmH_2O (PSV_{-5} and $vPSV_{-5}$) had lower P_{mean}, V_T, P_L, and higher RR (**Table 3**). Adding ±5 cmH_2O variability ($vPSV_{BL}$ and $vPSV_{-5}$ steps) increased the variability of ΔP_S and P_{mean} compared to PSV without variability at the corresponding ΔP_S level. Adding ±5 cmH_2O variability increased the variability of V_T and P_L only when using the baseline ΔP_S, but not when the ΔP_S was reduced by 5 cmH_2O. The incidence of asynchronies was not different between ventilation steps in block 2 (**Table 3**).

Tables 2, **3** report extensive details on respiratory mechanics, hemodynamics, and arterial blood gas analysis in ventilation blocks 1 and 2, respectively. The distribution of key respiratory mechanics parameters in ventilation blocks 1 and 2 is illustrated in **Figures 3**, **4**, respectively. **Supplemental Figures 3–11** report details the evolution over time of the respiratory mechanics parameters in the different ventilation steps.

TABLE 3 | Gas exchange, hemodynamics, and respiratory mechanics in patients during pressure support ventilation at different variability and pressure support level (Block 2).

	Ventilation modes				*p*-values			
	PSV_{BL}	$vPSV_{BL}$	PSV_{-5}	$vPSV_{-5}$	Overall	$vPSV_{BL}$ vs. PSV_{BL}	PSV_{-5} vs. PSV_{BL}	$vPSV_{-5}$ vs. PSV_{-5}
Ventilator Settings								
ΔP_S setting	Baseline		Baseline−5 cmH_2O					
$\Delta P_{S,set}$ (cmH_2O)	14.0 [12.0–16.0]	14.0 [12.0–16.0]	9.0 [7.0–11.0]	9.0 [7.0–11.0]	<0.001	0.99	<0.001	<0.001
Variability setting	None	± 5 cmH_2O	No variability	± 5 cmH_2O				
ΔP_S set variability (CV %)	0 [0–0]	11 [9–13]	0 [0–0]	15 [13–20]	<0.001	<0.001	0.99	<0.001
Gas exchange								
PaO_2/FIO_2 (mmHg)	213 [180–229]	194 [180–229]	215 [183–239]	197 [167–224]	0.61			
PaO_2 (mmHg)	95 [89–117]	99 [87–115]	99 [90–121]	98.8 [85–1112]	0.61			
$PaCO_2$ (mmHg)	42 [39–46]	43 [39–48]	44 [40–49]	44 [40–51]	0.18			
pH	7.47 [7.43–7.49]	7.48 [7.43–7.49]	7.47 [7.43–7.48]	7.47 [7.42–7.48]	0.21			
Hemodynamics								
Heart rate (min^{-1})	83 [77–93]	84 [77–92]	84 [77–92]	86 [76–92]	0.46			
Mean arterial pressure (mmHg)	88 [81–93]	82 [78–87]	80 [77–90]	86 [77–90]	0.37			
Respiratory mechanics								
$\Delta P_{S,measured}$ (cmH_2O)	13.2 [12.0–15.8]	13.6 [12.5–15.9]	8.4 [7.0–10.5][a]	8.5 [7.2–10.7]	<0.001	0.92	<0.001	0.67
$\Delta P_{Smeasured}$ (CV, %)	1.5 [0.9–4.8]	12.1 [11.1–14.3][a]	2.3 [1.7–6.6]	17.9 [15.2–18.6][b]	<0.001	0.001	0.99	<0.001
Total PEEP (cmH_2O)	7.6 [6.2–8.4]	7.5 [6.2–8.5]	7.7 [5.8–8.7][a]	7.7 [5.7–8.7]	0.001	0.99	0.009	0.92
Total PEEP (CV, %)	2.3 [1.4–4.9]	2.6 [1.8–8.0]	2.1 [1.6–4.3]	2.4 [1.4–5.9]	0.09			
P_{mean} (cmH_2O)	11.0 [9.7–12.6]	11.2 [9.7–13.1]	9.7 [8.4–11.9][a]	9.8 [8.4–11.8]	<0.001	0.67	<0.001	0.99
P_{mean} (CV, %)	5.4 [3.4–8.2]	8.1 [5.5–10.2][a]	2.5 [1.8–5.0]	6.0 [4.5–7.3][b]	<0.001	0.014	0.11	0.029
Respiratory rate (min^{-1})	14.7 [13.7–18.3]	17.6 [14.8–19.4]	22.9 [16.0–24.9][a]	20.1 [16.9–26.8]	0.022	0.96	0.041	0.95
Respiratory rate (CV, %)	18.8 [10.6–46.4]	32.0 [16.1–60.3]	13.1 [6.2–35.2]	14.6 [9.7–17.7]	0.003	0.43	0.43	0.99
V_T (ml/kg of PBW)	8.5 [7.2–9.4]	8.2 [7.0–9.1]	7.0 [5.9–7.6][a]	7.2 [6.0–7.7]	<0.001	0.92	<0.001	0.67
V_T (CV, %)	9.3 [5.1–15.7]	12.7 [11.1–15.3][a]	8.3 [4.2–13.6]	10.8 [9.4–14.6]	0.003	0.006	0.99	0.74
T_{insp}/T_{tot}	0.36 [0.30–0.37]	0.37 [0.30–0.39]	0.36 [0.32–0.39]	0.35 [0.32–0.38]	0.42			
T_{insp}/T_{tot} (CV, %)	9.3 [5.1–15.7]	12.7 [11.1–15.3][a]	8.3 [4.2–13.6]	10.8 [9.4–14.6]	0.058			
PTP_{es} (cmH_2O s min^{-1})	155.2 [118.4–262.8]	161.4 [87.1–248.3]	215.0 [128.1–357.9]	259.1 [151.1–422.8]	0.001	0.51	0.18	0.99
PTP_{es} (CV, %)	31.8 [20.6–52.3]	53.8 [23.9–71.1]	27.5 [16.0–40.5]	30.7 [18.5–44.7]	0.005	0.08	0.75	0.81
ΔP_{es} (cmH_2O)	4.4 [2.1–9.3]	5.3 [1.3–8.0]	5.6 [1.6–11.8]	10.4 [2.6–14.1]	<0.001	0.59	0.59	0.43
ΔP_{es} (CV, %)	32.7 [21.1–45.5]	40.9 [22.3–53.5]	22.8 [13.1–31.5]	20.6 [12.7–32.2]	<0.001	0.51	0.29	0.67
P_L (cmH_2O)	18.5 [15.9–23.2]	18.6 [16.1–23.4]	14.6 [11.5–20.8][a]	18.0 [14.0–21.6]	<0.001	0.99	<0.001	0.67
P_L (CV, %)	7.5 [3.8–12.6]	12.2 [11.1–17.0][a]	10.0 [4.2–13.1]	15.7 [12.4–17.3]	0.009	0.042	0.95	0.14
Asynchrony index (%)	1.5 [0.7–7.2]	2.4 [0.1–12.6]	0.9 [0.0–7.6]	1.3 [0–3.9]	0.21			

Values are computed during the last 10 min of a 45-min ventilation period. Data are reported as inter-subject median [25th−75th percentile] of the intra-subject median values.

[a] *Significant difference compared to PSV_{BL} ($p < 0.05$).*

[b] *Significant difference compared to PSV_{-5} ($p < 0.05$).*

PSV_{BL}, pressure support ventilation with no variability and baseline ΔP_S as per clinical indication; $vPSV_{BL}$, variable pressure support with variability set to achieve ±5 cmH_2O and baseline ΔP_S as per clinical indication; PSV_{-5}, pressure support ventilation with no variability and ΔP_S reduced by 5 cmH_2O from the baseline value; $vPSV_{-5}$, variable pressure support ventilation with variability set to achieve ±5 cmH_2O and ΔP_S reduced by 5 cmH_2O from the baseline value; CV, coefficient of variation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; ΔP_S, pressure support; V_T, tidal volume; PTP, esophageal pressure-time product; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure.

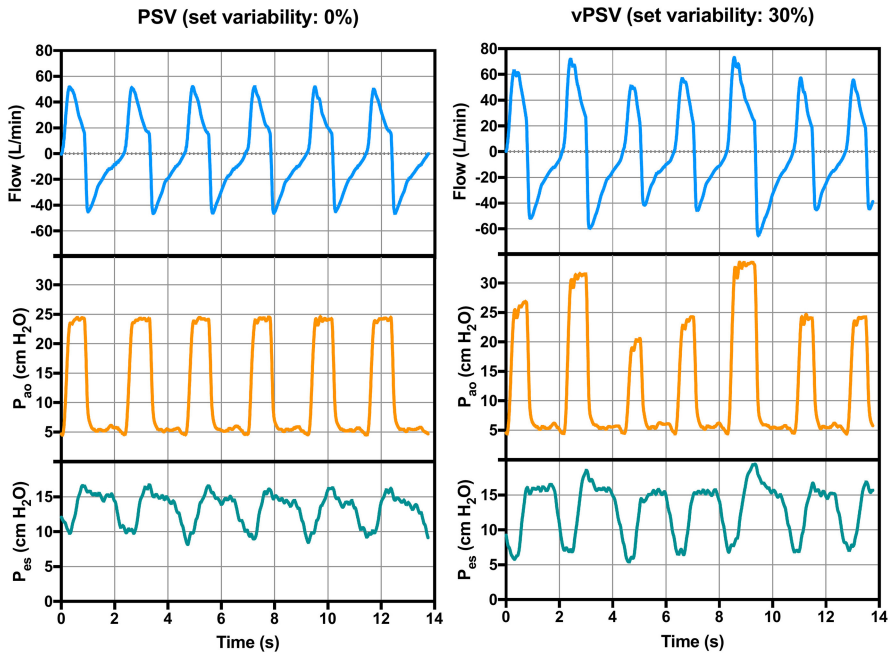

FIGURE 2 | Representative respiratory traces of a patient during conventional (left) and variable (right) pressure support ventilation. P_{ao}, pressure at the airway opening; P_{es}, esophageal pressure.

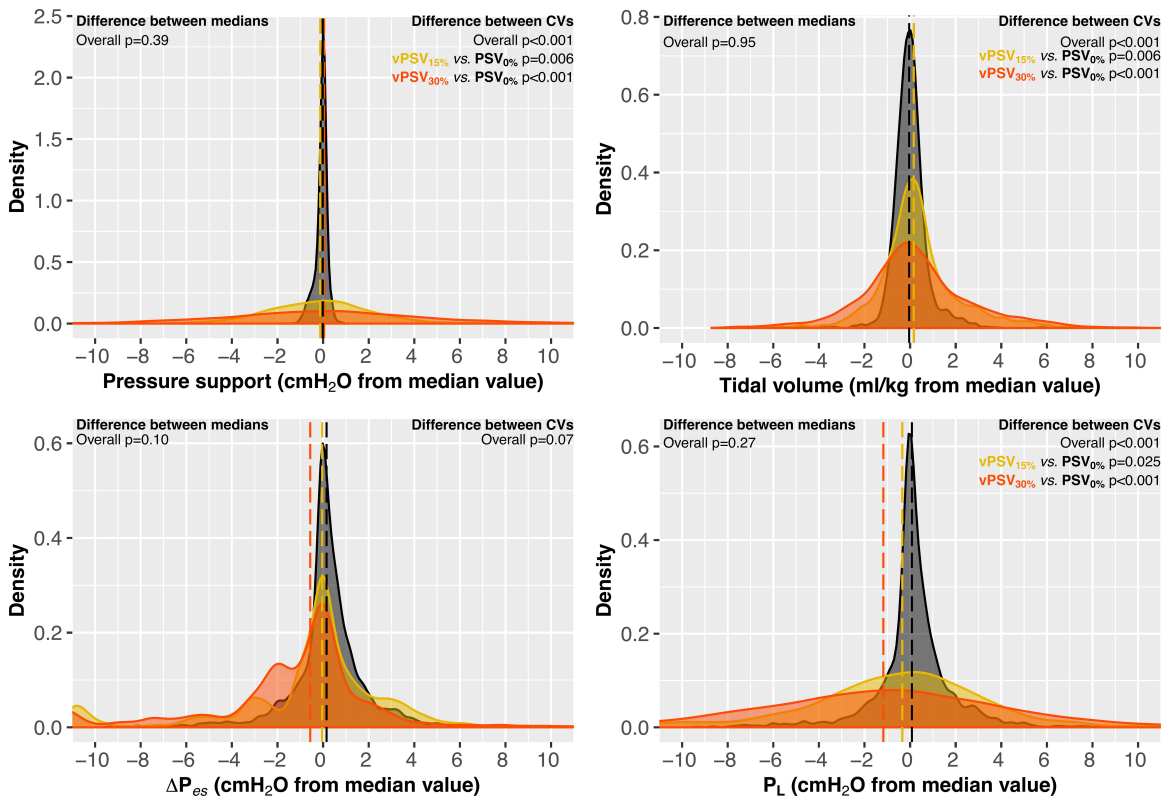

FIGURE 3 | Respiratory mechanics at different levels of variability (block 1). Variables are reported as the difference from the median value achieved during $PSV_{0\%}$ to allow between-patients visual comparisons. Dashed lines represent the medians of each ventilation step. $PSV_{0\%}$, conventional PSV ventilation with no variability; $vPSV_{15\%}$, variable PSV with variability set to 15% CV; $vPSV_{30\%}$, variable PSV with variability set to 30% CV; CV, coefficient of variation; ΔP_S, pressure support; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure.

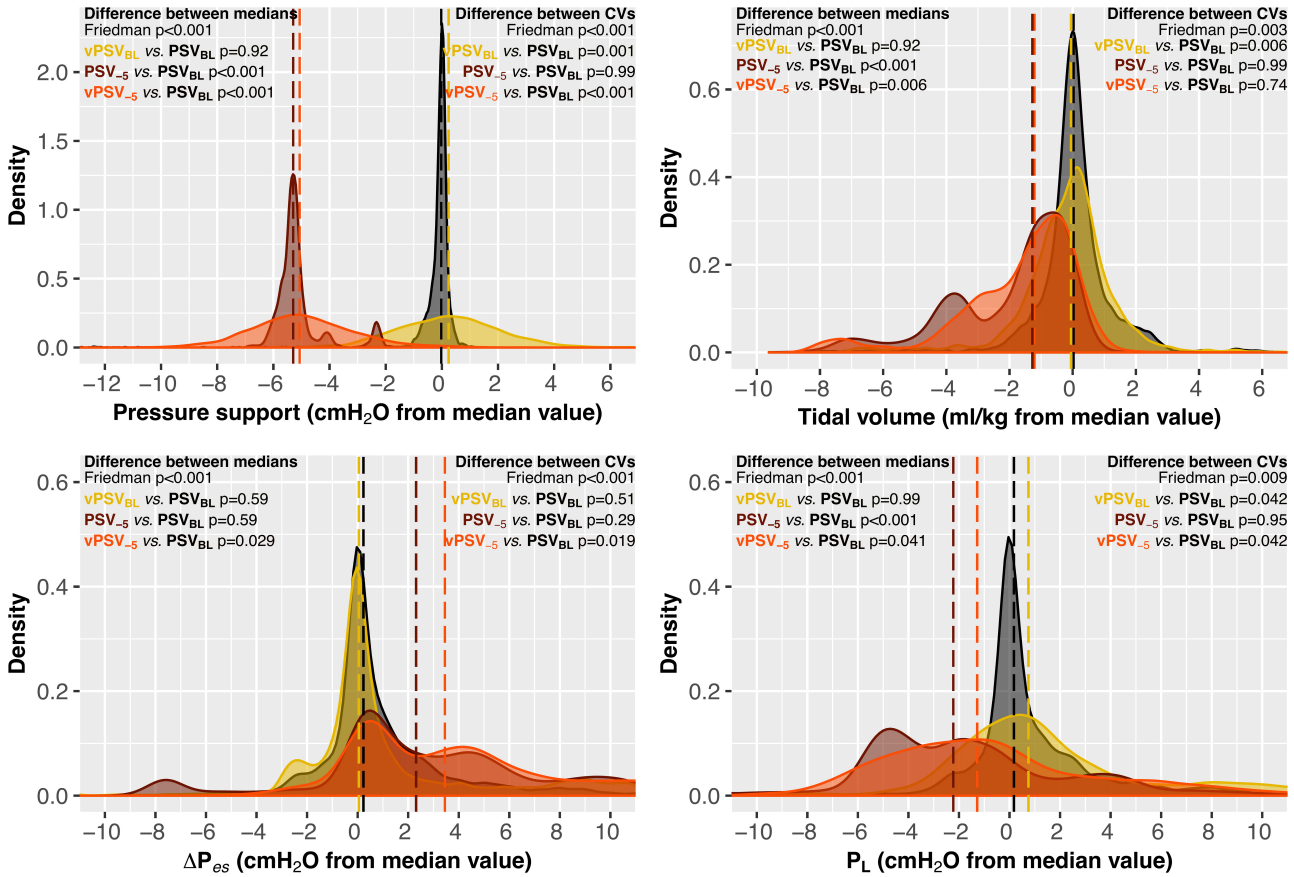

FIGURE 4 | Effects of variability on the distribution of respiratory mechanics parameters at different levels of pressure support (block 2). Variables are reported as the difference from the median value achieved during PSV_{BL} to allow between-patients visual comparisons. Dashed lines represent the medians of each ventilation step. PSV_{BL}, PSV with no variability and baseline ΔP_S as per clinical indication; $vPSV_{BL}$, variable pressure support with variability set to achieve ±5 cmH_2O and baseline ΔP_S as per clinical indication; PSV_{-5}, PSV with no variability and ΔP_S reduced by 5 cmH_2O from the baseline value; $vPSV_{-5}$, variable PSV with variability set to achieve ±5 cmH_2O and ΔP_S reduced by 5 cmH_2O from the baseline value; PSV, pressure support ventilation; CV, coefficient of variation; ΔP_S, pressure support; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure.

Post-hoc Analysis

Associations between respiratory mechanics parameters and the pressure level received in the preceding breath during $vPSV_{BL}$ and $vPSV_{-5}$ are reported in **Figure 5**. The ΔP_S received in the preceding breath was inversely associated with the magnitude of the inspiratory effort (ΔP_{es}) in the following breath, both during $vPSV_{BL}$ ($p = 0.003$) and $vPSV_{-5}$ ($p = 0.005$).

DISCUSSION

The main findings of this study are that in our mixed-ICU population of patients with mild to moderate ARDS: (1) vPSV with 15 or 30% variability did not influence gas exchange compared with conventional PSV; (2) at constant ΔP_S, vPSV increased the variability of V_T and P_L; (3) $vPSV_{30\%}$ increased the incidence of asynchronies; and (4) when the ΔP_S was reduced by 5 cmH_2O from the baseline value, adding variability did not increase the variability of V_T and P_L.

This is the first study comparing the short-term effects of vPSV at different levels of variability and ΔP_S in patients with ARDS. In previous studies, vPSV improved oxygenation in the experimental models of ARDS (Gama de Abreu et al., 2008; Spieth et al., 2011, 2012), but not in a cohort of hypoxemic critically ill patients (Spieth et al., 2013). However, that last study included mostly postoperative patients without a confirmed diagnosis of ARDS and investigated a single level of variability and pressure support. Opposite to what was found in preclinical studies in animals, vPSV had no effect on gas exchange, when the ΔP_S was set to the baseline value identified by the treating clinician and neither when it was reduced by 5 cmH_2O. This could be explained by several mechanisms; most importantly, the time investigated in each ventilation step was relatively short, and the fact that patients had an established diagnosis of ARDS mostly in their recovery phase and received mechanical ventilation for few days prior to the inclusion in this study. Under these conditions, patient lungs could have developed

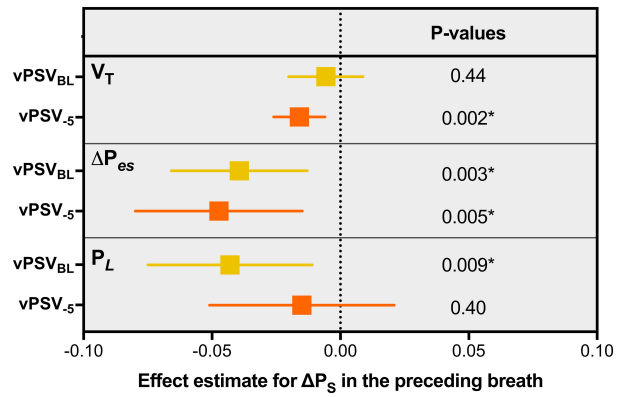

FIGURE 5 | Associations between respiratory mechanics parameters and the pressure level received in the preceding breath during variable PSV. Squares and confidence intervals refer to the effect estimate for ΔP_S in a mixed model comprising the ΔP_S received during the preceding breath as a fixed effect and the patient as a random effect with random intercept. The units of the estimates are expressed in the untransformed units of the variables, i.e., they represent the absolute change in V_T, ΔP_{es}, or P_L when the ΔP_S received during the preceding breath increases by 1 cmH_2O. $vPSV_{BL}$, variable PSV with variability set to achieve ±5 cmH_2O and baseline ΔP_S as per clinical indication; $vPSV_{-5}$, variable PSV ventilation with variability set to achieve ±5 cmH_2O and ΔP_S reduced by 5 cmH_2O from the baseline value; PBW, predicted body weight; PSV, pressure support ventilation; ΔP_S, pressure support; V_T, tidal volume; ΔP_{es}, esophageal pressure swings; P_L, peak transpulmonary pressure. *Significant association ($p < 0.05$).

consolidation, namely, the presence of lung regions scarcely responsive to recruitment (Cressoni et al., 2017). In this case, the breaths with higher ΔP_S received cyclically during variable pressure support might expose the patient to volutrauma in the aerated regions of the lung (Güldner et al., 2016; Pelosi et al., 2016) due to the reduced size of the lung aerated compartment. Another explanation for the possible lack of effect of variability on oxygenation might be that, different from what happens in PSV with a sigh, vPSV has no control over the time spent at higher pressure during tidal breathing. This might result in random breaths with higher P_S and short inspiratory time, both possibly insufficient to achieve recruitment. The tidal volume measured in this cohort was higher than the recommended targets, but this reflects the current clinical practice in patients with ARDS receiving assisted ventilation modes (Bellani et al., 2016; Writing Group for the PReVENT Investigators et al., 2018). During the second block of ventilations, the patients tolerated a ΔP_S reduction without worsening the gas exchange in the short term, at the price of a modest increase of the respiratory rate, suggesting that they were slightly over-assisted. This could have influenced patient-ventilator interaction (Kataoka et al., 2018) and the response to variability, as suggested by the finding that, during the second block of interventions, the variability of V_T was increased by vPSV compared with PSV only when the baseline ΔP_S was used. However, during ventilation steps with baseline ΔP_S, patients had a work of breathing estimated with the PTP_{es} of around 150 $cmH_2O \cdot s \cdot min^{-1}$, which is within the recommended range (Mauri et al., 2016). Interestingly, higher P_S resulted in a reduction in ΔP_{ES} in the following breath at both set ΔP_S levels, while the variability of V_T and P_L was increased by extrinsic variability only at higher ΔP_S. This seems to suggest that while a neural response to extrinsic variability is present independent of the level of assistance, its effects on the variability of V_T and P_L are influenced by the level of ΔP_S.

This study is underpowered to demonstrate the effects of vPSV on patient-centered outcomes like duration of ventilation. This is tested in another, yet ongoing clinical trial (Kiss et al., 2013). In the *post-hoc* analysis, the effects of vPSV on the response of patients in terms of inspiratory effort, transpulmonary pressure, and tidal volume developed in the following breath were studied. An inverse association between the ΔP_S received in the preceding breath and the inspiratory effort was observed. Different from other modified PSV modes such as the proportional assist ventilation (PAV) and the neurally adjusted ventilatory assist (NAVA), the variability of ΔP_S was random, i.e., is not related to the efforts of patients. This analysis suggests that there might be a complex interaction between the ventilator and a patient, in which the inspiratory effort and the adaptation of the patient to pressure support are influenced by the history of the previous breaths.

Limitations

This study has several limitations. The crossover design allowed the investigation of the effects of different levels of variability and ΔP_S in terms of gas exchange and respiratory mechanics in the short term but is intrinsically unable to investigate major clinical outcomes. The sample size is relatively low, no static measurements of respiratory mechanics were performed, and patients received heterogeneous sedation regimens that might have affected differently the respiratory drive. The population included in the study identifies a subgroup of critically ill patients meeting the criteria for mild to moderate ARDS who already received controlled or assisted mechanical ventilation for several days; however, the baseline patient characteristics were similar to those reported in a recent large observational study in patients with ARDS assisted non-invasively (Bellani et al., 2017). These patients with established respiratory failure, thus, possibly consolidated lung areas, might not benefit from the cyclic recruitment effect of vPSV, while patients with early ARDS might respond differently. However, the role of spontaneous breathing in the early management of ARDS is still unclear. This study could neither elucidate the mechanisms of the neural responses of the patients to variability nor the neuromuscular coupling of the respiratory muscles.

CONCLUSION

In our cohort of patients with mild to moderate ARDS, vPSV did not improve gas exchange at different levels of variability and pressure support. Compared with PSV, vPSV increased the variability of V_T, but not when low levels of variability were used in conjunction with lower pressure support. Moreover, vPSV did not exert a clinically relevant effect on the average inspiratory effort and work of breathing.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Local Ethical Review Board (Comitato Etico Aziendale Policlinico San Martino protocol no. 1052/12) and prospectively registered on clinicaltrials.gov (study identifier: NCT01683669). According to the local ethical requirements, the next of kin provided written informed assent, followed by delayed written consent from patients in case of recovery of consciousness.

AUTHOR CONTRIBUTIONS

LB takes responsibility for the integrity of data. LB, PP, MV, and MG designed the study. LB, YS, MF, AD'O, DD'A, PRa, and IB conducted the study. LB, LM, MF, RH, AD'O, and CR analyzed the data. LB, MS, PP, PRo, and MG wrote the manuscript. All authors read and approved the final version of the manuscript.

FUNDING

This study was performed with institutional funding only.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2021.725738/full#supplementary-material

REFERENCES

Akoumianaki, E., Maggiore, S. M., Valenza, F., Bellani, G., Jubran, A., Loring, S. H., et al. (2014). The application of esophageal pressure measurement in patients with respiratory failure. *Am. J. Respir. Crit. Care Med.* 189, 520–531. doi: 10.1164/rccm.201312-2193CI

Bellani, G., Laffey, J. G., Pham, T., Fan, E., Brochard, L., Esteban, A., et al. (2016). Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 315, 788–800. doi: 10.1001/jama.2016.0291

Bellani, G., Laffey, J. G., Pham, T., Madotto, F., Fan, E., Brochard, L., et al. (2017). Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am. J. Respir. Crit. Care Med.* 195, 67–77. doi: 10.1164/rccm.201606-1306OC

Blanch, L., Villagra, A., Sales, B., Montanya, J., Lucangelo, U., Luján, M., et al. (2015). Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med.* 41, 633–641. doi: 10.1007/s00134-015-3692-6

Cressoni, M., Chiumello, D., Algieri, I., Brioni, M., Chiurazzi, C., Colombo, A., et al. (2017). Opening pressures and atelectrauma in acute respiratory distress syndrome. *Intensive Care Med.* 43, 603–611. doi: 10.1007/s00134-017-4754-8

Esteban, A., Frutos-Vivar, F., Muriel, A., Ferguson, N. D., Peñuelas, O., Abraira, V., et al. (2013). Evolution of mortality over time in patients receiving mechanical ventilation. *Am. J. Respir. Crit. Care Med.* 188, 220–230. doi: 10.1164/rccm.201212-2169OC

Gama de Abreu, M., Spieth, P. M., Pelosi, P., Carvalho, A. R., Walter, C., Schreiber-Ferstl, A., et al. (2008). Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury. *Crit. Care Med.* 36, 818–827. doi: 10.1097/01.CCM.0000299736.55039.3A

Güldner, A., Braune, A., Ball, L., Silva, P. L., Samary, C., Insorsi, A., et al. (2016). Comparative effects of volutrauma and atelectrauma on lung inflammation in experimental acute respiratory distress syndrome. *Crit. Care Med.* doi: 10.1097/CCM.0000000000001721

Huhle, R., Pelosi, P., and de Abreu, M. G. (2016). Variable ventilation from bench to bedside. *Crit. Care Lond. Engl.* 20:62. doi: 10.1186/s13054-016-1216-6

Kataoka, J., Kuriyama, A., Norisue, Y., and Fujitani, S. (2018). Proportional modes versus pressure support ventilation: a systematic review and meta-analysis. *Ann. Intensive Care* 8:123. doi: 10.1186/s13613-018-0470-y

Kiss, T., Güldner, A., Bluth, T., Uhlig, C., Spieth, P. M., Markstaller, K., et al. (2013). Rationale and study design of ViPS - variable pressure support for weaning from mechanical ventilation: study protocol for an international multicenter randomized controlled open trial. *Trials* 14:363. doi: 10.1186/1745-6215-14-363

Mauri, T., Lazzeri, M., Bronco, A., Bellani, G., and Pesenti, A. (2017). Effects of variable pressure support ventilation on regional homogeneity and aeration. *Am. J. Respir. Crit. Care Med.* 195, e27–e28. doi: 10.1164/rccm.201609-1806IM

Mauri, T., Yoshida, T., Bellani, G., Goligher, E. C., Carteaux, G., Rittayamai, N., et al. (2016). Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. *Intensive Care Med.* 42, 1360–1373. doi: 10.1007/s00134-016-4400-x

Muller, K. E., and Barton, C. N. (1989). Approximate power for repeated-measures ANOVA lacking sphericity. *J. Am. Stat. Assoc.* 84, 549–555. doi: 10.1080/01621459.1989.10478802

Muller, K. E., Lavange, L. M., Ramey, S. L., and Ramey, C. T. (1992). Power calculations for general linear multivariate models including repeated measures applications. *J. Am. Stat. Assoc.* 87, 1209–1226. doi: 10.1080/01621459.1992.10476281

Pelosi, P., Ball, L., Abreu, M. G., de, and Rocco, P. R. M. (2016). General anesthesia closes the lungs: keep them resting. *Turk. J. Anesth. Reanim.* 44, 163–164. doi: 10.5152/TJAR.2016.002

Putensen, C., Zech, S., Wrigge, H., Zinserling, J., Stüber, F., Von Spiegel, T., et al. (2001). Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am. J. Respir. Crit. Care Med.* 164, 43–49. doi: 10.1164/ajrccm.164.1.2001078

Spieth, P. M., Carvalho, A. R., Güldner, A., Kasper, M., Schubert, R., Carvalho, N. C., et al. (2011). Pressure support improves oxygenation and lung protection compared to pressure-controlled ventilation and is further improved by random variation of pressure support. *Crit. Care Med.* 39, 746–755. doi: 10.1097/CCM.0b013e318206bda6

Spieth, P. M., Güldner, A., Beda, A., Carvalho, N., Nowack, T., Krause, A., et al. (2012). Comparative effects of proportional assist and variable pressure support ventilation on lung function and damage in experimental lung injury. *Crit. Care Med.* 40, 2654–2661. doi: 10.1097/CCM.0b013e3182592021

Spieth, P. M., Güldner, A., Huhle, R., Beda, A., Bluth, T., Schreiter, D., et al. (2013). Short-term effects of noisy pressure support ventilation in patients with acute hypoxemic respiratory failure. *Crit. Care Lond. Engl.* 17:R261. doi: 10.1186/cc13091

Tobin, M. J., Mador, M. J., Guenther, S. M., Lodato, R. F., and Sackner, M. A. (1988). Variability of resting respiratory drive and timing in healthy subjects. *J. Appl. Physiol. (1985)* 65, 309–317. doi: 10.1152/jappl.1988.65.1.309

Writing Group for the PReVENT Investigators, Simonis, F. D., Serpa Neto, A., Binnekade, J. M., Braber, A., Bruin, K. C. M., et al. (2018). Effect of a low vs intermediate tidal volume strategy on ventilator-free days in intensive care unit patients without ARDS: a randomized clinical trial. *JAMA* 320, 1872–1880. doi: 10.1001/jama.2018.14280

Conflict of Interest: MG was granted a patent on the variable pressure support ventilation mode of assisted ventilation (noisy PSV), which has been licensed to Dräger Medical AG (Lübeck, Germany).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.