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Selecting the best ventilator hyperinflation technique based on physiologic markers: A randomized controlled crossover study

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ABSTRACT

Background: Ventilator hyperinflation (VHI) is effective in improving respiratory mechanics, secretion removal, and gas exchange in mechanically ventilated subjects; however, there are no recommendations for the best ventilator settings to perform the technique.
Objective: To compare six modes of VHI, concerning physiological markers of efficacy and safety criteria to support the selection of optimal settings.
Methods: Thirty mechanically ventilated patients underwent six modes of VHI in a randomized order. The delivered volume, expiratory flow bias criteria, overdistension, patient–ventilator asynchronies and hemodynamic variables were assessed during the interventions.
Results: Volume-controlled ventilation with inspiratory flow of 20 lpm (VC-CMV20) and pressure support ventilation (PSV) achieved the best effectiveness scores ($P < 0.05$). The target peak pressure of 40 cmH_2O was associated with a high incidence of overdistension. PSV showed a lower incidence of patient–ventilator asynchronies.
Conclusions: The modes VC-CMV20 and PSV are the most effective for VHI. Alveolar overdistension and patient–ventilator asynchronies must be considered when applying VHI.

Introduction

Mechanically ventilated subjects are at risk of airway mucus retention due to the presence of an endotracheal tube, muscle weakness, drugs, inadequate humidification of respiratory gases, body position, relative immobility of the patient, and underlying diseases affecting pulmonary function.[1,2] As secretion retention leads to undesirable adverse effects, a number of airway clearance techniques have been applied with the aim of improving the respiratory function.[3] Among these techniques, manual hyperinflation (MHI) and ventilator hyperinflation (VHI) have proven beneficial in respiratory mechanics, secretion removal, and gas exchange in mechanically ventilated subjects.[4,5] MHI requires the disconnection of the patient from the ventilator resulting in a loss of PEEP and is often performed with no direct measurement of variables such as airway pressure, tidal volume, flow and inspired oxygen fraction. Therefore, VHI has been postulated as a safer method to provide therapeutic hyperinflation in mechanically ventilated patients.[6–9]

Although many studies were performed using different modes and ventilatory parameters to deliver VHI,[7–10] there are no recommendations on the best settings to apply the technique. Based on the premise that the airflow has the potential to influence mucus movement, previous studies have identified expiratory flow bias thresholds which are associated with a higher mucus displacement towards the glottis. The following three main expiratory flow bias criteria were obtained in "in vitro" studies using a mucus simulant: a peak inspiratory flow rate (PIFR) less than 90% of the peak expiratory flow rate (PEFR),[11,12] a PEFR of at least 40 l/min,[13] and a PEFR to PIFR difference of at least 17 l/min.[13] However, different expiratory flow bias thresholds were identified in a study using an animal model, namely, PEFR/PIFR > 4.3 and PEFR-PIFR > 33 lpm.[14] In 2015, Thomas used the

Abbreviations: VHI, ventilator hyperinflation; MHI, manual hyperinflation; PEEP, positive end-expiratory pressure; PIFR, peak inspiratory flow rate; PEFR, peak expiratory flow rate; VC-CMV20, volume control continuous mandatory ventilation with inspiratory flow = 20 lpm; VC-CMV50, volume control continuous mandatory ventilation with inspiratory flow = 50 lpm; PC-CMV1, pressure control continuous mandatory ventilation with inspiratory time = 1 s.; PC-CMV3, pressure control continuous mandatory ventilation with inspiratory time = 3 s.; PSV10, pressure support ventilation with cycling off = 10% of peak inspiratory flow; PSV25, pressure support ventilation with cycling off = 25% of peak inspiratory flow; RASS, Richmond Agitation Sedation Scale; MAP, mean arterial pressure; MPAW, mean airway pressure; HR, heart rate; Cst, static compliance of the respiratory system; Rrs, total resistance of the respiratory system

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"in vitro" expiratory flow bias thresholds to compare the effectiveness of different VHI modes.[15] After 232 trials using a bench-top lung model circuit, the volume-controlled continuous mandatory ventilation (VC-CMV) was more successful than pressure support ventilation (PSV) and pressure-controlled continuous mandatory ventilation (PC-CMV) for ventilator hyperinflation. Since "in vitro" models provide a simplified representation of the respiratory system, these results point in a certain direction, but more studies are needed to confirm if they are applicable in clinical settings. Moreover, the total volume delivered and the distribution of ventilation are also important physiological parameters to be considered when performing any lung hyperinflation technique.[4–6] Considering these physiological principles, both MHI and VHI are performed using high tidal volumes and long inspiratory times, which, in turn, may cause patient-ventilator asynchrony, alveolar hyperdistention, hypoventilation or hyperventilation and hemodynamic adverse effects. Therefore, the aim of this study was to compare six modes of VHI, concerning physiological markers of effectiveness and safety criteria to support the selection of optimal VHI settings for mechanically ventilated subjects.

Methods

Study design and participants

In a randomized, controlled, crossover trial, all mechanically ventilated subjects admitted to the ICU at the Bonsucesso Federal Hospital, Rio de Janeiro, RJ, Brazil, between February 2017 and September 2017 were considered for inclusion. Aiming to avoid differences in baseline between interventions, patients with mucus hypersecretion (defined as the need for suctioning < 2-h intervals) and atelectasis were not included in the study. Other exclusion criteria were the following: Richmond Agitation Sedation Scale (RASS) score > 0 (because agitated patients could cause artifacts in respiratory signals), absence of respiratory drive (subjects in controlled ventilation), severe bronchospasm, positive end-expiratory pressure > 10 cmH_2O, PaO_2-FiO_2 relationship < 150 (patients with possible indication for recruitment maneuvers, not VHI), mean arterial pressure < 60 mmHg, inotrope requirement equivalent to > 15 ml/h total of adrenaline and noradrenaline (dilution 3 mg/50 ml), and/or intracranial pressure > 20 mmHg.[10] The project was approved by the institution's ethics committee and written informed consent was obtained from the subjects' next of kin before the study began.

Because we found no studies comparing different modes of VHI, we based the sample size calculation on the study of Savian et al.,[7] which reported the results of a flow bias criterion when comparing MH and VHI. Therefore, a total of 14 participants would provide sufficient power (80%) at the 5% level, to detect a difference of 20% in PIFR/PEFR, assuming an SD of 22% and allowing for a 15% drop-out rate.

The order of interventions was determined using block randomization. The sequence of interventions was generated by a computerized randomization system, and the allocation was concealed from the enrolling investigators. The study coordinator prepared sealed opaque envelopes containing a preassigned treatment order, which were opened sequentially by the physiotherapist on the day of intervention. According to the random order, the participants received 6 modes of VHI. All participants received the interventions on the same day, with a washout interval of at least 15 min between them. The washout was considered completed if the hemodynamic (MAP and HR) and respiratory mechanics variables (static compliance – Cst and total resistance - Rrs of the respiratory system) differed less than 10% from the baseline values. During the washout interval, the subjects were kept in their baseline ventilatory mode.

Interventions

All study subjects were ventilated with an iX5 ClearView™ ventilator (Carefusion/Intermed, SP, Brazil). The subjects were positioned in a 30° semifowler supine position, and tracheal suctioning was performed before the onset of the experimental protocol. After a stabilization period, baseline variables were recorded in the current ventilatory mode. Then, the following six VHI modalities were applied: volume control continuous mandatory ventilation (VC-CMV) with inspiratory flow = 20 lpm (VC-CMV20), VC-CMV with inspiratory flow = 50 lpm (VC-CMV50), pressure control continuous mandatory ventilation (PC-CMV) with inspiratory time = 1 s (PC-CMV1), PC-CMV with inspiratory time = 3 s (PC-CMV3), pressure support ventilation (PSV) with cycling off = 10% of peak inspiratory flow (PSV10), and PSV with cycling off = 25% of peak inspiratory flow (PSV25). In VC-CMV20 and VC-CMV50, the tidal volume was increased in steps of 200 ml until the peak airway pressure of 40 cmH_2O was achieved.[15] In PC-CMV1, PC-CMV3, PSV10 and PSV25, the pressure support or pressure control was increased until the peak pressure of 40 cmH_2O was reached.[8,11] Rise time was set at 70% for all VHI modalities. PEEP and FiO2 were not modified and in case of need for suctioning, the protocol was interrupted, and a new washout period ensued as described previously. Each VHI modality lasted 15 min.

Outcome measurements

In this study, respiratory mechanics (including flow, volume and pressure signals) and hemodynamic variables were used as physiological markers of VHI effectiveness and adverse effects. The VHI effectiveness considered two criteria: 1. expiratory flow-bias profile; and 2. the degree of lung expansion (delivered volume above the ideal tidal volume). The flow bias criteria were separated into "from in vitro studies" (PIFR/PEFR ≤ 0.9, PEFR > 40 l/min, and PEFR-PIFR > 17 lpm)[11–13] and "from animal study" (PEFR/PIFR > 4.3 and PEFR-PIFR > 33 lpm)[14] to distinguish the origin of each parameter. Lung expansion was considered satisfactory when the volume during VHI was >150% of the ideal tidal volume[15] (calculated for 8 ml/kg considering the ideal body weight).

Respiratory mechanics were measured using the end-inspiratory occlusion method.[16] The primary variables of tidal volume, inspiratory flow, plateau and peak pressures were collected from the ventilator display and used to calculate Cst and Rrs.[16]

Safety and adverse effects considered hemodynamics (heart rate and mean arterial pressure) and minute ventilation variations as well as the occurrence of patient-ventilator asynchronies and lung hyperdistention. Patient-ventilator asynchronies were considered present if observed in at least 30% of the respiratory cycles during a 2-min period of real-time observation. Two experienced therapists, with more than ten years of experience and specialized in critical care examined the respiratory signals from the ventilator display and, by consensus, identified the trigger, flow and phase patterns.[17,18] Plateau pressure was measured during each VHI modality, and values >30cmH_2O were considered as alveolar hyperdistension.[16,19]

For all outcome measures, the variables were recorded at baseline and the 10th minute of every intervention using the information from the ventilator display. The accuracy of the iX5 ClearView™ sensors were within the accepted range for clinical and research purposes. Moreover, we followed the recommended calibration procedures before every trial. The representative value for every outcome measure was calculated as the mean of at least 3 reliable readings.

Data analysis

First, the data were tabulated and reviewed on a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA). To assess the

distribution of variables and extreme values, box plots for visual checks and the Shapiro-Wilk test were performed. This preliminary exploratory analysis showed that there were neither outliers nor missing data in this study.

Flow-bias parameters, lung expansion, patient-ventilator asynchronies, and hyperdistention were considered dichotomic according to the thresholds described above. The number of subjects who met flow-bias and lung expansion criteria in the 6 VHI modalities was computed. The overall effectiveness of every VHI mode was defined as the proportion of subjects achieving all flow-bias and lung expansion criteria. Differences among the six VHI modalities were assessed using the Cochran-Q test, followed by the McNemar test for multiple comparisons.

The continuous variables were represented as the means (SD), and the values were compared using the Repeated Measures Analysis of Variance. Tukey's test was used for multiple comparisons, and the significance level was set at 0.05. The criterion of Cohen was used to interpret the effect size, where a value of 0.2 is considered a small effect, a value of 0.5 is considered a moderate effect, and a value of 0.8 is considered a large effect.[20] The data were analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

From the initial 42 subjects assessed for the study, 12 patients did not meet the inclusion criteria (5 hypersecretive, 4 without ventilatory drive, 2 in use of high doses of vasoactive drugs and one presenting with intracranial pressure > 20 mmHg). The flow chart of the study is shown in Fig. 1, and data from the 30 participants are shown in Table 1. No clinically relevant adverse events were observed during the experimental protocol, and all subjects completed the measurements. Subjects presented with a wide range of respiratory mechanics profiles, with static compliance ranging from 23 to 81.8 ml/cmH_2O and respiratory system resistance ranging from 9.5 to 19.9 cmH_2O/l/s. The median values of Cst and Rrs were 48.6 ml/cmH_2O and 12.4 cmH_2O/l/s, respectively. Comparison between the total scores among VHI modes showed that VC-CMV20 and PSV modes were the most effective (Tables 2 and 3).

When compared to baseline, the mean arterial pressure was reduced in VC-CMV20 and VC-CMV50 ($P < 0.05$), with an effect size of 0.62 and 0.51, respectively. The modes PC-CMV3 and PSV10 showed the highest values of alveolar pressure, with 93% of the cases above 30 cmH_2O. The modes with more patient-ventilator asynchronies were VC-CMV20 and PC-CMV3, while in PC-CMV1 and PSV modes there were few cases. In all VHI modes, the ventilatory pattern changed; however, the minute ventilation was reduced only during PC-CMV3 (effect size = 0.65). The adverse effects and safety results are shown in Table 4.

Discussion

Our results showed that when considering expiratory flow bias and volume delivered criteria, all VHI modes showed good performance, with VC-CMV and PSV being the most effective modes. In a recent bench study by Thomas (2015),[15] the results showed the following: VHI using VC-CMV20 achieved the best flow bias scores, PC-CMV reached these mucus-flow criteria better when using an inspiratory time of 3 s, and PSV demonstrated a good performance only for the PEF > 40 lpm criterion. Although using a bench model, some of these results are similar to ours, except for those related to the PSV mode, since we found a satisfactory success rate with both PSV10 and PSV25. The fact that our trials were performed in-vivo rather than using a unicompartmental bench model, and different ventilator characteristics and settings (e.g., rise time) between studies might have determined these differences. Thus, as rise time directly influences PIFR, it is important to adjust this parameter taking into

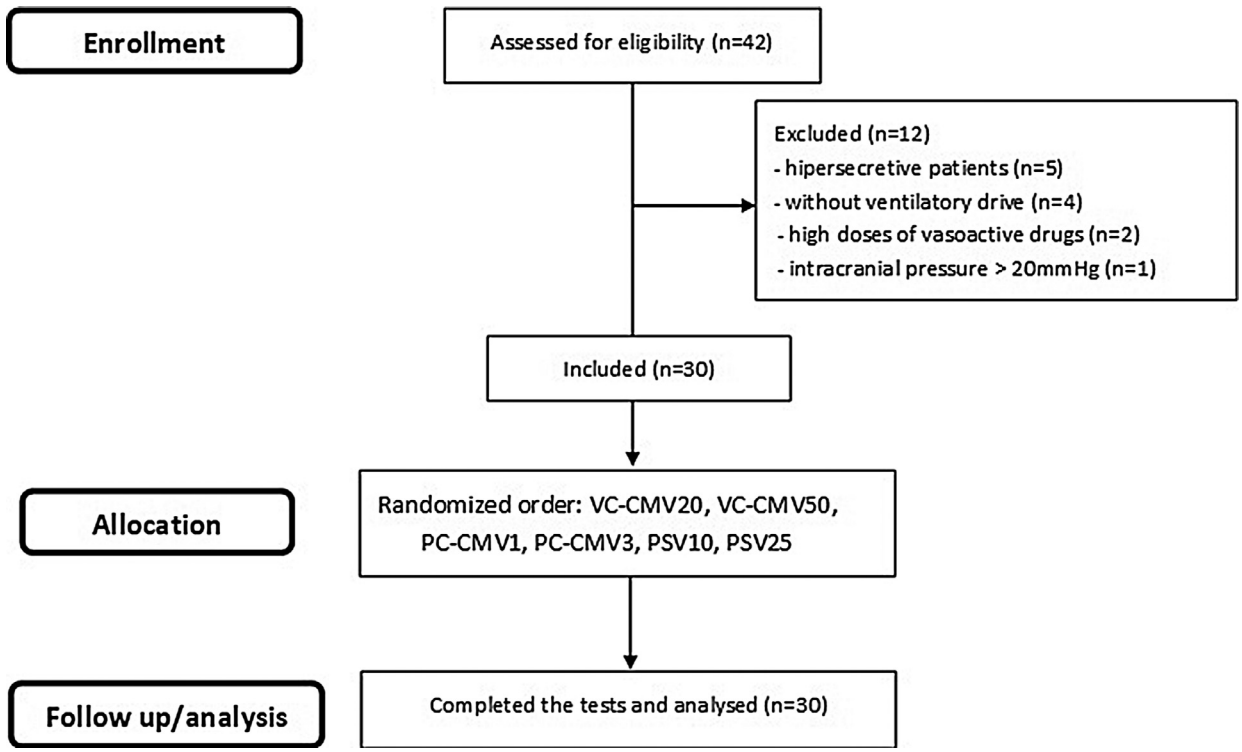

Fig. 1. Flow of the patients throughout the study. VC-CMV20: volume control continuous mandatory ventilation (VC-CMV) with inspiratory flow = 20 lpm, VC-CMV50: VC-CMV with inspiratory flow = 50 lpm, PC-CMV1: pressure control continuous mandatory ventilation (PC-CMV) with inspiratory time = 1 s., PC-CMV3: PC-CMV with inspiratory time = 3 s., PSV10: pressure support ventilation (PSV) with cycling off = 10% of peak inspiratory flow, PSV25: PSV with cycling off = 25% of peak inspiratory flow.

Table 1
Clinical and demographic characteristics.

Characteristic	*N* = 30
Age (*yr*), mean (SD)	61.5 (19.8)
Gender, n males (%)	12 (40)
APACHE II, mean (SD)	24.6 (7.2)
Predicted body mass, mean (SD)	57.2 (7.8)
PaO_2/FiO_2, mean (SD)	377 (104)
Cst,rs, mean (SD)	46.3 (16.7)
Rrs, mean (SD)	13.1 (2.6)
Diagnosis, n (%)	
Pneumonia	4 (13)
Cardiovascular disease	6 (20)
Neurosurgery	2 (7)
Kidney failure	2 (7)
Neoplasm	6 (20)
Sepsis	2 (7)
Others	7 (23)
RASS, score, median [IQ]	−2 [−3 to −2]
GCS, score, median [IQ]	6,5 [5.75 to 8.25]
Ventilatory mode, n (%)	
VC-CMV	2 (7)
PC-CMV	10 (33)
PSV	18 (60)
Predicted tidal volume (6 mL/kg), mean (SD)	343 (47)
Predicted tidal volume (8 mL/kg), mean (SD)	457 (62)
PEEP, cmH_2O, median (IQ)	8 (1)
FiO2, mean (SD)	32.8 (9.1)
Duration of ventilation, d, mean (SD)	9.3 (9.4)

Cst,rs: static compliance of respiratory system; Rrs: total resistance of respiratory system; RASS: Richmond agitation-sedation score; GCS: Glasgow Coma Score; VC-CMV: volume controlled continuous mandatory ventilation; PC-CMV: pressure controlled continuous mandatory ventilation; PEEP: positive end expiratory pressure; FiO2: fraction of inspired oxygen.

consideration the flow bias criteria and subjects' ventilatory requirements. For instance, prolonged rise times are associated with lower PIFR, which favors expiratory flow bias criteria but may not meet the subjects inspiratory flow demand, resulting in flow asynchrony and discomfort.

Interestingly, when analyzing the flow bias results using thresholds "from animal study", PEFR/PIFR > 4.3 was achieved only in VC-CMV20. PEFR-PIFR > 33 lpm was observed in all VHI modes, with VC-CMV20 presenting the best scores, followed by PSV modes. Even if we consider the difference between PEFR and PIFR as the most representative of mucus displacement (as postulated by Volpe et al.),[14] VC-CMV20 and PSV modes are the most effective. It is noticeable that the thresholds obtained from both "animal study" and "in vitro studies" may not represent the expiratory flow bias needed to displace mucus in humans under mechanical ventilation. Nevertheless, these values were obtained in conditions that aimed to represent the human condition; therefore, they are commonly used to study the effectiveness of airway clearance techniques.

As for the lung expansion criteria, although no studies compared the effects of different insufflation volumes during manual or ventilator hyperinflation, a value of at least 50% above the ideal tidal volume has been advocated.[5,23] Using this threshold, many authors found improvement in secretion removal, gas exchange, and respiratory mechanics.[6,9,24,25] In our study, with a target pressure of 40 cmH_2O, all VHI modes presented with a satisfactory pulmonary expansion performance, with PSV being the best.

Although the hyperinflation techniques are not associated with relevant adverse effects,[4,5] we did not find a negligible incidence of patient-ventilator asynchronies, reduction in minute ventilation and mean arterial pressure, and alveolar hyperdistention in our study. These results point to the fact that the theoretical assumptions for VHI effectiveness, i.e., long inspiratory time and high tidal volume, are associated with hemodynamic and ventilatory hazards. The hyperinflation cycles might result in increased mean airway pressure (MPAW) leading to hemodynamic repercussions, specially in subjects who are under controlled modes. Assisted modes, as used in this study, tend to attenuate the MPAW increase, because the respiratory centers determine a reduction in respiratory rate, increasing the interval between the high-pressure cycles.[8] Nevertheless, our results showed that in VC-CMV modes, there was a clinically relevant decrease in MAP, while in PC-CMV3, the MPAW was high without any adverse hemodynamic effect. These results suggest that both MPAW and MAP should be monitored during VHI in more susceptible subjects, such as those with hypovolemia and/or use of higher doses of vasopressors. The reduced respiratory rate observed during the VHI maneuvers might be attributed to a compensatory mechanism to maintain CO_2 homeostasis. Although we didn't record the end-tidal CO_2 pressure, the similarity between baseline and VHI minute ventilation observed during the protocol supports this hypothesis.

The target peak pressure of 40 cmH_2O used in this study is in accordance with the current recommendations for hyperinflation techniques.[4–11,15,23,24] The peak pressure represents a sum of resistive, elastic and viscoelastic pressures at end-inspiration.[16] Therefore, even with this high peak pressure value, it is not possible to predict the ocurrence of alveolar hyperdistension in the different modes of

Table 2
Number of patients who met every considered physiological criteria for ventilator hyperinflation efficacy considering the thresholds from "in vitro" and "animal" studies (*n* = 30).

	Baseline	VC-CMV20	VC-CMV50	PC-CMV1	PC-CMV3	PSV10	PSV25
Secretion removal (Flow Bias)							
1 - From "in vitro studies"							
PIF/PEFR ≤ 0.9	9	30	30	24	25	28	30
PEFR-PIFR > 17 lpm	3	30	24	22	21	28	28
PEFR > 40 lpm	22	30	30	30	30	30	30
2 - From "animal study"							
PEFR/PIFR > 4.3	0	18	0	0	0	0	0
PEFR-PIFR > 33 lpm	0	30	11	9	6	14	16
Lung expansion (Inspiratory volume)							
>150% (8 ml/kg IBW)	2	26	26	26	26	30	28
All flow bias 1 + lung expansion criteria met	0	26	20	18	14	28	26
All flow bias 2 + lung expansion criteria met	0	16	0	0	0	0	0

From "in vitro studies": thresholds obtained from studies using bench models, outside a biological context.[11–13] From "animal study": thresholds obtained from an experimental animal study.[14] PIFR: peak inspiratory flow rate, PEFR: peak expiratory flow rate. VC-CMV20: volume control continuous mandatory ventilation (VC-CMV) with inspiratory flow = 20 lpm, VC-CMV50: VC-CMV with inspiratory flow = 50 lpm, PC-CMV1: pressure control continuous mandatory ventilation (PC-CMV) with inspiratory time = 1 s., PC-CMV3: PC-CMV with inspiratory time = 3 s., PSV10: pressure support ventilation (PSV) with cycling off = 10% of peak inspiratory flow, PSV25: PSV with cycling off = 25% of peak inspiratory flow. Tidal volume > 150% corresponds to the proportion of delivered volume above the ideal body weight (IBW) tidal volume (considering 8 ml/kg and IBW). All flow bias 1: all flow bias criteria from "in vitro studies", All flow bias 2: all flow bias criteria from "animal study".

Table 3
Pairwise comparison between the proportion of patients achieving all effectiveness criteria at baseline and in six modes of ventilator hyperinflation.

	Baseline	VC-CMV20	VC-CMV50	PC-CMV1	PC-CMV3	PSV10
VC-CMV20	<**0.001**	–	–	–	–	–
VC-CMV50	<**0.001**	**0.031**	–	–	–	–
PC-CMV1	<**0.001**	**0.008**	0.688	–	–	–
PC-CMV3	<**0.001**	**0.004**	0.238	0.454	–	–
PSV10	<**0.001**	0.688	**0.008**	**0.002**	**0.001**	–
PSV25	<**0.001**	1.000	0.109	**0.008**	**0.012**	0.688

VC-CMV20: volume control continuous mandatory ventilation (VC-CMV) with inspiratory flow = 20 lpm, VC-CMV50: VC-CMV with inspiratory flow = 50 lpm, PC-CMV1: pressure control continuous mandatory ventilation (PC-CMV) with inspiratory time = 1 s, PC-CMV3: PC-CMV with inspiratory time = 3 s, PSV10: pressure support ventilation (PSV) with cycling off = 10% of peak inspiratory flow, PSV25: PSV with cycling off = 25% of peak inspiratory flow.

VHI and respiratory mechanics profiles. In this way, it is likely that the greater differences between peak and plateau pressures observed in some subjects were associated with VHI using a high inspiratory flow rate, short inspiratory time, and/or in patients with augmented airways resistance.

The modes VC-CMV20, PC-CMV3, and PSV10 presented with the highest prevalence of alveolar overdistention. It is well known that the ventilation with higher alveolar pressures and tidal volumes are associated with increased mortality in subjects with acute respiratory distress syndrome (ARDS). Increasing evidence suggests that the "biotrauma hypothesis" can also be applied to non-ARDS subjects and that avoiding alveolar overdistention reduces their rate of pulmonary complications and improves the outcomes.[21,22] Although VHI uses high volumes (sometimes above 20 ml/kg) and distension pressures, it is applied for short periods of time. Since we don't know to which extent these maneuvers can promote or aggravate the lung injury associated with mechanical ventilation, the adoption of inflation volumes resulting in alveolar pressures lower than 30 cmH_2O might be recommended. This idea calls into question the principle of inflating the lungs until the peak pressure of 40 cmH_2O, which is considered the highest pulmonary expansion within a safe pressure limit for the application of VHI techniques.[6–10] Thus, aiming to estimate if lower peak pressures during VC-CMV20 are enough to provide expansion volumes above the recommended threshold (at least 150% of the ideal tidal volume), we introduced the subjects' Cst and Rrs into the "equation of motion of the respiratory system" (the equation that relates distension pressure, flow, volume and respiratory mechanics characteristics of a subject during mechanical or spontaneous ventilation).[16] In this model, considering a peak pressure of 35 cmH_2O only for three subjects (10%), the resulting insufflation volumes were below 150%. These subjects had low Cst (25, 26 and 30 ml/cmH_2O, respectively). When the calculations were performed for a peak pressure of 30 cmH_2O, 17 subjects (67%) achieved the criterion. This result strongly suggests that for many patients (especially those with less impaired respiratory mechanics), a peak pressure of 35 cmH_2O might be used without compromising the VHI effectiveness and with less undesirable effects. In this way, VC-CMV20 with peak pressure of 40 cmH_2O could be reserved for subjects with very impaired respiratory mechanics (in which higher inflation pressures are needed to deliver a volume above 150% of the ideal tidal volume) and/or the need for a more aggressive expansion maneuver, such as in those presenting with atelectasis. As these results are an estimation using a unicompartmental linear model, future studies should address if lower peak pressures during VHI can provide proper delivered volumes in a sample of mechanically ventilated patients.

In our study, although the peak pressures were the same for all VHI modes, PC-CMV3 and PSV provided higher inspiratory volumes. These results are in accordance with the use of decelerated flow in mechanically ventilated patients aiming to improve the ventilation distribution and accommodate a higher volume with lower inspiratory pressures.[26,27] This recommendation may be extended for hyperinflation techniques with the goal to promote adequate pulmonary hyperinflation within a safer pressure limit.

The total scores of the PSV modes are practically the same as that for VC-CMV20 (Table 2), with the advantage of PSV being a pressure-limited spontaneous mode with a low incidence of patient-ventilator asynchronies. Because of its preset low inspiratory flow (20 lpm), VC-CMV20 was associated with a high incidence of flow and phase asynchrony. Therefore, since previous studies showed that both VHI modes, VC-VMC and PSV improved secretion removal and respiratory mechanics,[6,8] VC-CMV20 may be indicated for subjects in controlled modes, while PSV10 or PSV25 may be recommended for subjects with preserved respiratory drive. As suggested for VC-CMV20, peak pressures lower than 40 cmH_2O may also be used in PSV modes aiming to prevent overdistension and adverse hemodynamic effects. Future studies are needed to demonstrate if flow bias criteria,

Table 4
Parameters related to the safety of ventilator hyperinflation in different ventilatory modes.

	Baseline	VC-CMV20	VC-CMV50	PC-CMV1	PC-CMV3	PSV10	PSV25
Hemodinamics							
MAP, mmHg, mean (SD)	92.9 (13.1)	**84.2 (14.9)***	**85.6 (15.2)***	86.2 (14.6)	87.3 (17.3)	89.5 (15.1)	85.8 (20.4)
HR, bpm, mean (SD)	91.7 (19.8)	89.7 (19.3)	88.9 (18.8)	90.6 (18.2)	92.0 (19.7)	90.9 (20.4)	90.9 (18.5)
Pressures (cmH_2O)							
MPAW, mean (SD)	11.0 (1.6)	**13.1 (2.0)***	10.7 (1.6)	11.3 (2.2)	**15.3 (4.3)***	12.3 (2.3)	11.7 (1.8)
Ppl, mean (SD)	18.8 (3.9)	**30.6 (3.7)***	26.9 (3.4)	**29.1 (3.9)***	**35.7 (2.6)***	**34.5 (2.2)***	**32.9 (2.4)***
Ppl > 30 (n)	0	16	2	10	28	28	26
Patient-ventilator asynchrony (*n*)							
Trigger	–	0	1	0	0	0	0
Phase (Tn > Tv)	–	0	0	1	0	0	0
Phase (Tv > Tn)	–	6	2	0	18	6	3
Flow	–	20	10	0	0	0	0
Ventilation							
RR, bpm, mean (SD)	17.9 (5.2)	**7.0 (2.8)***	**8.4 (3.3)***	**8.1 (3.0)***	**6.0 (2.2)***	**8.4 (3.9)***	**7.6 (3.3)***
Vt, ml, mean (SD)	490 (91)	**1186 (437)***	**996 (355)***	**966 (244)***	**1291 (478)***	**1223 (464)***	**1219 (447)***
VE, L, mean (SD)	8.7 (2.9)	7.5 (2.1)	7.5 (2.1)	7.4 (2.3)	**7.1 (1.9)**	9.2 (3.2)	8.3 (2.5)

MAP: mean arterial pressure, HR: heart rate, MPAW: mean airway pressure, Ppl: plateau pressure, Tn: neural time, Tv: ventilator time, RR: respiratory rate, Vt: tidal volume, VE: minute ventilation. *Significantly different from baseline ($P < 0.05$). VC-CMV20: volume control continuous mandatory ventilation (VC-CMV) with inspiratory flow = 20 lpm, VC-CMV50: VC-CMV with inspiratory flow = 50 lpm, PC-CMV1: pressure control continuous mandatory ventilation (PC-CMV) with inspiratory time = 1 s., PC-CMV3: PC-CMV with inspiratory time = 3 s, PSV10: pressure support ventilation (PSV) with cycling off = 10% of peak inspiratory flow, PSV25: PSV with cycling off = 25% of peak inspiratory flow.

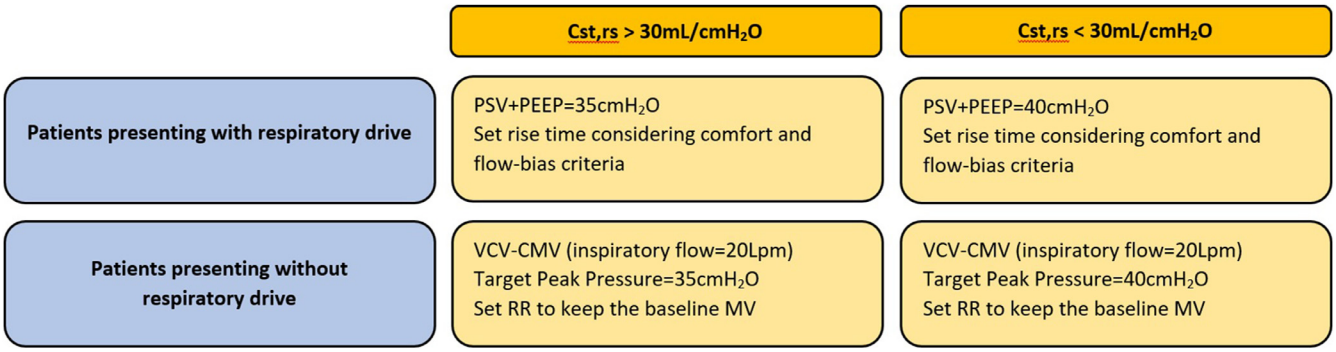

Fig. 2. Proposed framework for ventilator hyperinflation application based on the results of this study and the current knowledge about mechanical ventilation. In this study, considering flow bias and expansion volume criteria, the best performance for ventilator hyperinflation (VHI) was observed for pressure support ventilation (PSV) and volume-controlled ventilation with inspiratory flow = 20 lpm (VCV-CMV20). Since VCV-CMV20 was associated with high incidence of flow and phase asynchronies, PSV is preferable for patients with preserved respiratory drive. As rise time influences the patient-ventilator interaction and flow bias, it has to be properly set in this mode. By using the equation of motion of respiratory system and the patients' respiratory mechanics, it was estimated that a target peak pressure of 35 cmH_2O is enough to provide a delivered volume above 150% of the ideal tidal volume when applying VHI for patients with static compliance > 30 cmH_2O. Therefore, aiming at reducing the hemodynamic repercussions and alveolar overdistension the target peak pressure of 40 cmH_2O is recommended only for patients with very impaired respiratory mechanics. During the VHI with PSV the patients controlled their own RR, resulting in an unaltered minute ventilation. Conversely, when applying VHI in patients without respiratory drive, RR should be reduced to keep the baseline minute ventilation (MV), otherwise there will be hyperventilation and significant increase of mean airway pressure, with augmented risk of hemodynamic repercussions.

adequate expansion volume, and clinically relevant outcomes are achieved in these modes even with a peak pressure of 35 cmH_2O or lower. Nevertheless, regardless of the VHI mode used, a general recommendation for clinical practice is that physiotherapists use these efficacy and safety criteria to individualize the technique.

As twelve subjects did not meet the inclusion criteria, it may raise questions on the generalizability of our findings. Among these nonincluded subjects, three had contra-indications for VHI (intracranial pressure > 20 mmHg and high doses of vasopressors), five were hypersecretive, and four had no respiratory drive. Although many patients in a real scenario present with hypersecretion, it is unlikely that this condition would determine a result different from ours since we included patients with different Rrs profiles. Regarding the respiratory drive, its interference in respiratory signals is more pronounced in spontaneous ventilation modes, such as PSV. As the use of PSV is contra-indicated for patients without respiratory drive, we consider that the results of our study may be applied in both conditions, i.e., patients with and without respiratory drive.

The fact that the subjects were not hypersecretive might be considered a limitation of this study. However, the presence of secretions in the airways would preclude the homogeneity of the pre-interventions condition and, thus, the comparison between VHI modes. Different from measuring short-term clinical outcomes, such as the amount of secretion removed in every VHI mode, the rationale of this study was to add new clinically relevant information on the physiological mechanisms involved with effectiveness and adverse effects in patients presenting with a wide range of respiratory mechanics profiles. We believe that our results bring some important insights for the application of the VHI modalities more safely and effectively. However, as we used physiological markers of effectiveness rather than clinical outcomes, new well-designed trials comparing secretion removal, gas-exchange and respiratory mechanics in different VHI modes are needed to confirm our results. Aiming at helping the selection of the best ventilatory mode and parameters when applying VHI, we propose a framework based on the results of this paper and the current knowledge about mechanical ventilation (Fig. 2).

In conclusion, considering the expiratory flow bias thresholds and the inspiratory volume delivered, the VHI modes VC-CMV20, PSV10, and PSV25 were the most effective modes. As VHI techniques are associated with patient-ventilator asynchronies, PSV modes are indicated for subjects in assisted mechanical ventilation, while VC-CMV20 is indicated for subjects in controlled ventilation. Lower peak pressures may be used during VHI aiming at reducing the incidence of alveolar overdistension and hemodynamic repercussions, as long as the volume delivered achieves at least 150% of the ideal tidal volume.

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