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Moderately high frequency ventilation with a conventional ventilator allows reduction of tidal volume without increasing mean airway pressure

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Abstract

Background: The aim of this study was to explore if positive-pressure ventilation delivered by a conventional ICU ventilator at a moderately high frequency (HFPPV) allows a safe reduction of tidal volume (V_T) below 6 mL/kg in a porcine model of severe acute respiratory distress syndrome (ARDS) and at a lower mean airway pressure than high-frequency oscillatory ventilation (HFOV).

Methods: This is a prospective study. In eight pigs (median weight 34 [29,36] kg), ARDS was induced by pulmonary lavage and injurious ventilation. The animals were ventilated with a randomized sequence of respiratory rates: 30, 60, 90, 120, 150, followed by HFOV at 5 Hz. At each step, V_T was adjusted to allow partial pressure of arterial carbon dioxide ($PaCO_2$) to stabilize between 57 and 63 mmHg. Data are shown as median [P25th,P75th].

Results: After lung injury, the PaO_2/FiO_2 (P/F) ratio was 92 [63,118] mmHg, pulmonary shunt 26 [17,31]%, and static compliance 11 [8,14] mL/cmH$_2$O. Positive end-expiratory pressure (PEEP) was 14 [10,17] cmH$_2$O. At 30 breaths/min, V_T was higher than 6 (7.5 [6.8,10.2]) mL/kg, but at all higher frequencies, V_T could be reduced and $PaCO_2$ maintained, leading to reductions in plateau pressures and driving pressures. For frequencies of 60 to 150/min, V_T progressively fell from 5.2 [5.1,5.9] to 3.8 [3.7,4.2] mL/kg ($p < 0.001$). There were no detrimental effects in terms of lung mechanics, auto-PEEP generation, hemodynamics, or gas exchange. Mean airway pressure was maintained constant and was increased only during HFOV.

Conclusions: During protective mechanical ventilation, HFPPV delivered by a conventional ventilator in a severe ARDS swine model safely allows further tidal volume reductions. This strategy also allowed decreasing airway pressures while maintaining stable $PaCO_2$ levels.

Keywords: Mechanical ventilation; Acute lung injury; Critical care unit; Protective ventilation; Acute respiratory distress syndrome; High-frequency ventilation

Background

Acute respiratory distress syndrome (ARDS) is a common cause of mortality and morbidity in critically ill patients [1]. Although indispensable in the support of ARDS patients, artificial ventilation involves the application of mechanical forces to the lung parenchyma that can further induce injury [2], adding morbidity and mortality [3].

Reducing tidal volumes (V_Ts) below 6 mL/kg of ideal body weight could potentially decrease the cyclic stretch imposed on the lung [4,5]. Conversely, excessively low V_Ts have the potential to lead to clinically significant hypercapnia-related acidosis [6] with harmful side effects [7,8].

In this scenario, high-frequency oscillatory ventilation (HFOV) has been tested, because of its ability to provide adequate gas exchange even at very low tidal volumes [9-13]. This technique, however, may be cumbersome because it requires a dedicated ventilator and special training. Additionally, the V_T delivered can be susceptible to variations in airway resistance such as that which occurs with lung secretions [14]. Last but not least, it requires the use of high airway pressures, which may have deleterious effects, especially on the right ventricle [15]. Recently, two clinical studies in ARDS patients showed neutral [16] or disappointing [17] results in terms of mortality when HFOV was compared to a conventional mechanical ventilation strategy.

An alternative approach could be to apply moderately high frequency positive-pressure ventilation (HFPPV) using conventional mechanical ventilators. A similar strategy was explored in the 1980s [18,19], but with special ventilators and before the well-established recognition of the importance of lung-protective strategies. HFPPV consists of applying respiratory rates intermediate between those used conventionally ($\leq$ 35 breaths/min) and those used during HFOV (180 to 800 breaths/min). Potential advantages over HFOV would be the possibility to control the V_T delivered, the use of conventional mechanical ventilators obviating the need for specialized training, and maintenance of a low mean airway pressure. In this feasibility study, we tested in a swine model of ARDS whether such a strategy could result in V_T below 6 mL/kg while avoiding further increases in the partial pressure of arterial carbon dioxide ($PaCO_2$) and maintaining a reasonable mean airway pressure (P_{mean}).

Methods

This study was approved by the Institutional Animal Research Ethics Committees of Hospital Sírio Libanês and of Faculdade de Medicina da Universidade de São Paulo, both in São Paulo, Brazil, and was performed according to the National Institutes of Health (USA) guidelines for the use of experimental animals. The experiments were done in eight previously healthy Agroceres pigs.

Instrumentation

The animals were fasted overnight before the experiment with free access to water. They received an intramuscular injection of midazolam (0.3 mg/kg; Dormonid®, Roche, São Paulo, Brazil) and acepromazine (0.5 mg/kg; Acepran®, Andrômaco, São Paulo, Brazil). Through an auricular vein, anesthesia was induced with thionembutal (12 mg/kg; Tiopental®, Abbott, São Paulo, Brazil) and muscular relaxation with pancuronium bromide (0.1 mg/kg; Pavulon®, AKZO Nobel, São Paulo, Brazil). They were then submitted to tracheal intubation (cuffed 7.5-French cannula) and connected to the Servo-300 mechanical ventilator (Maquet, Rastatt, Germany) with the following parameters in a volume-controlled mode: tidal volume of 8 to 10 mL/kg, positive end-expiratory pressure (PEEP) of 5 cmH$_2$O, inspiratory fraction of oxygen (FiO$_2$) adjusted to keep arterial saturation between 94% and 96%, and respiratory rate (RR) necessary to keep PaCO$_2$ between 35 and 45 mmHg. Anesthesia was maintained during the study period with midazolam (0.3 mg/kg/h) and fentanyl citrate (5 μg/kg/h; Fentanyl®, Janssen-Cilag, São

Paulo, Brazil) and muscular relaxation with pancuronium bromide (0.2 mg/kg/h). The adequate depth of anesthesia during the surgical period was evaluated with maintenance of physiological variables (heart rate and arterial pressure) and absence of reflexes (corneal and hind limb flexion response), as well as unresponsiveness to stimuli during manipulation. Supplementary boluses of 3 to 5 μg/kg of fentanyl and 0.1 to 0.5 mg/kg of midazolam were administered as necessary. A continuous drip of 1,000 mL/h of Lactated Ringer's solution was infused until the end of the induction of pulmonary injury, and then a continuous infusion of 5 mL/kg/h of Lactated Ringer was maintained until the end of the study.

Monitoring with continuous electrocardiography, oxymetry, and blood pressures was done with a multiparametric monitor (Dixtal-Philips DX 2020, São Paulo, Brazil). The left femoral artery was cannulated for blood pressure monitoring and blood sampling. The right internal jugular vein was cannulated with a 9-French introducer sheath (Arrow, Reading, PA, USA) through which a pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) was introduced for monitoring of the mean pulmonary artery pressure (PAPm), cardiac output, central venous pressure (CVP), and mixed venous blood gases (SvO_2). A central venous catheter was introduced in the left internal jugular vein. A surgical cystostomy was done to quantify the urine output. The animal was connected to the $NICO_2$ device (Novametrix Medical Systems, Wallingford, CT, USA) for airway end-tidal pressure of carbon dioxide ($EtCO_2$), tidal volume, airway pressures, and airway flow monitoring.

The regional ventilation was monitored with electrical impedance tomography (EIT; Dixtal-Philips, São Paulo, Brazil) [20,21]. The lungs were split in sternal and vertebral regions of the same height. The amount of ventilation to the regions studied was reported according to the ventilator settings used. Arterial blood gas analyses were done with the ABL 800 device (Radiometer, Copenhagen, Denmark). After the surgical period, the animals were allowed to rest for 60 min prior to the baseline data acquisition.

Measurements

In all the steps of the study, the following data were collected:

1. Hemodynamic: heart rate, cardiac output, CVP, mean systemic arterial blood pressure (ABPm), PAPm, pulmonary artery occlusion pressure (PAOP), SvO_2, and norepinephrine use and dosage
2. Respiratory: arterial partial pressure of oxygen (PaO_2), $PaCO_2$, $EtCO_2$, V_T, airway peak pressure (P_{peak}), airway plateau pressure ($P_{plateau}$) through expiratory valve occlusion after 2 s of inspiratory pause, intrinsic positive end-expiratory pressure (PEEPi) through expiratory valve occlusion after 4 s of expiratory pause, extrinsic positive end-expiratory pressure (PEEPe), mean airway pressure (P_{mean}), inspiratory flow, inspiratory time (T_{insp}), and ventilatory distribution EIT data
3. Metabolic: pH, lactate, temperature, and fluid balance

Calculated variables

To obtain the calculated variables, we used the following formulas:

- Cardiac index (CI) = Cardiac output/Weight
- Systemic vascular resistance index = (ABPm − CVP) × 80/CI

- Pulmonary vascular resistance index = (PAPm − PAOP) × 80/CI
- Blood oxygen content (C × O_2) = P × O_2 × 0.0031 + 1.36 × Hb × S × O_2
- Minute ventilation = V_T × RR
- PEEPtotal = PEEPi + PEEPe
- Alveolar oxygen partial pressure (P_AO_2) = 643 × FiO_2/100 − ($PaCO_2$/0.8)
- Alveolar-arterial oxygen [(A-a)O_2] gradient = P_AO_2 − PaO_2
- Pulmonary capillary oxygen content (CcO_2) = PAO_2 × 0.0031 + 1.36 × Hb
- Pulmonary shunt = (CcO_2 − CaO_2) × 100/(CcO_2 − CvO_2)
- Static compliance (C_{static}) = V_T/($P_{plateau}$ − PEEPtotal)
- Dynamic compliance (C_{dyn}) = V_T/(P_{peak} − PEEPtotal)
- Resistance (P_{peak} − $P_{plateau}$)/Inspiratory flow

ARDS induction

After the baseline data collection, ARDS was induced with repeated whole-lung lavage using 1 L of isotonic saline (37°C) until the PaO_2 was below 100 mmHg for at least 10 min. Lung injurious ventilation was then started with the animal ventilated in pressure control mode with PEEP = 3 cmH_2O, FiO_2 = 1, inspiratory/expiratory time ratio (I/E) = 1:1, P_{peak} = 42 cmH_2O, and a RR of 20 to 30 breaths/min [22]. Arterial blood gases were obtained every 15 min, and the PEEP could be increased up to 19 cmH_2O targeting a PaO_2 level between 55 and 80 mmHg, whereas the inspiratory pressure was limited at 48 cmH_2O. The injurious ventilation was maintained until one of the following parameters was reached:

- An interval of 240 min of injurious ventilation
- A PAPm > 50 mmHg
- A C_{static} < 10 mL/cmH_2O (with a PEEP = 10 cmH_2O and V_T = 6 mL/kg)
- A PEEP persistently ≥ 15 cmH_2O for at least two consecutive arterial blood sample analyses
- An ABPm < 70 mmHg in spite of the use of norepinephrine in a dosage higher than 0.5 μg/kg/min

After lung injury induction, the stabilization step started. The animal was ventilated according to the recommendations of the interventional group in the "ARMA" study [5] in a volume-controlled mode, with V_T = 6 mL/kg, RR = 35 breaths/min (the maximal respiratory rate allowed by the protocol - because of hypercapnia and acidosis), initial PEEP = 10 cmH_2O (mean value used in the ARMA study), and FiO_2 = 1.

An arterial blood sample was obtained every 10 min. Subsequently, PEEP and FiO_2 were titrated according to the ARMA study PEEP table (aiming at a PaO_2 = 55 to 80 mmHg) [5]. V_T and RR were kept constant during the stabilization step with no attempt to correct the $PaCO_2$ level.

Experimental protocol

After reaching a $PaCO_2$ equilibrium (variation < 5% in three consecutive arterial blood samples), we considered that the stabilization phase was finished. The same PEEP level titrated at this time was used in the following steps of the study.

Four sequences of five different RRs were randomly tested, and these sequences were chosen to alternate higher and lower respiratory frequencies (Figure 1). The five RRs (ventilatory modes) randomized were as follows: RR = 30, 60, 90, 120, 150 breaths/min. At each sequence, V_T was adjusted to reach a $PaCO_2$ target of 57 to 63 mmHg.
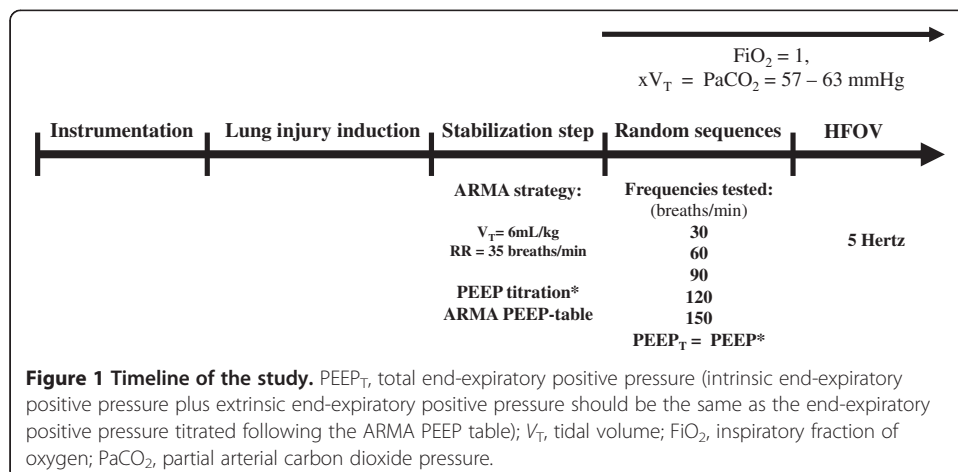
The randomization was done using sealed envelopes containing the proportion of 1:1:1:1 of the following RR sequences:

- Sequence 1 (60, 150, 90, 120, 30)
- Sequence 2 (90, 30, 120, 60, 150)
- Sequence 3 (120, 150, 90, 30, 60)
- Sequence 4 (150, 90, 30, 120, 60)

During this part of the protocol, the animals were ventilated using volume control ventilation, with $FiO_2 = 1$ and square inspiratory flow = 1 L/s. At each step, PEEPi was measured every 10 min, and PEEPe was corrected in order to keep the PEEPtotal equal to the PEEP obtained during the equilibrium step using the ARMA PEEP table.

After completion of these randomized sequences, the animals were submitted to HFOV (Figure 1) at 5 Hz (SensorMedics 3100B, Yorba Linda, CA, USA) with a P_{mean} set at 30 cmH$_2$O, I/E = 1:2, bias flow = 30 L/min, and the initial pressure amplitude = 80 cmH$_2$O [9]. Unlike the other five RRs, of which the sequence was randomized, HFOV was always performed last, because of its higher P_{mean}, which could induce lung recruitment.

An arterial blood sample was obtained each 10 min throughout the remainder of the study. After V_T changes or after pressure amplitude changes during HFOV, we waited until there were three consecutive measurements with the $PaCO_2$ levels stable between 57 and 63 mmHg. Data were then collected, and the next step of the sequence was started. Between consecutive steps, a 40-s disconnection from the ventilator was done in order to avoid the carryover of the time-dependent alveolar recruitment. At the end of the experiments, the anesthesia was deepened with propofol overdose, and the animals were euthanized with a bolus of 10 mL of potassium chloride 19.1%.

Figure 1 Timeline of the study. PEEP$_T$, total end-expiratory positive pressure (intrinsic end-expiratory positive pressure plus extrinsic end-expiratory positive pressure should be the same as the end-expiratory positive pressure titrated following the ARMA PEEP table); V_T, tidal volume; FiO$_2$, inspiratory fraction of oxygen; PaCO$_2$, partial arterial carbon dioxide pressure.

Statistical analysis

The Shapiro-Wilk goodness-of-fit model showed a non-parametrical distribution for most variables; therefore, data are reported as median [P25th,P75th]. Wilcoxon's signed rank test was used to test variables before and after lung injury induction and to compare the upper and lower regional ventilation with the EIT. In order to avoid type I error, a modified Bonferroni's correction was used to account for the multiple comparisons between upper and lower regions of ventilation. Therefore, the p value considered significant was 0.007 when comparing upper and lower regions during the various frequencies studied and 0.012 when comparing the effects of inspiratory pauses and the alveolar recruitment with a RR of 60 breaths/min. The analysis of variance for repeated measures on ranks (Friedman's test) was used for analyses during the ventilatory modes tested. The *post hoc* analyses were done using Student-Newman-Keuls' test. A $p < 0.05$ was considered significant. The analyses and graphs were done with the SigmaPlot 12.0 statistical package software (Systat Software, Inc. San Jose, CA, USA).

Results

Eight pigs weighing 34 [29,39] kg were used. ARDS was induced using 10 [7,16] L of normal saline followed by injurious mechanical ventilation for 210 [40,225] min. The respiratory variables at baseline and after the induction of lung injury are shown in Table 1.

The FIO_2 during the stabilization step was 0.7 [0.5,0.9]. The time to $PaCO_2$ equilibrium was similar in the different phases of the experiment and equal to 50 [40,75] min. The most important respiratory data with different RRs are shown in Figure 2 and Table 2. During the stabilization step, $PaCO_2$ was 81 [78,92] mmHg. In all other experimental phases, the $PaCO_2$ was kept in the planned range of 57 to 63 mmHg (Figure 2A). V_T could be progressively reduced with increasing RRs (Figure 2B), as did regional ventilation (Figure 3). The ventilation to the dependent parts of the lung reduced to a greater extent leading to an increase in the sternal/vertebral ratio of regional ventilation (Figure 4). Additionally, low values of plateau and driving pressures were maintained at all RRs (Figure 2C,D, respectively). The HFOV led to the highest oxygenation, the lowest V_T, and the most homogeneous distribution of ventilation (Table 2, Figures 2B and 4, respectively).
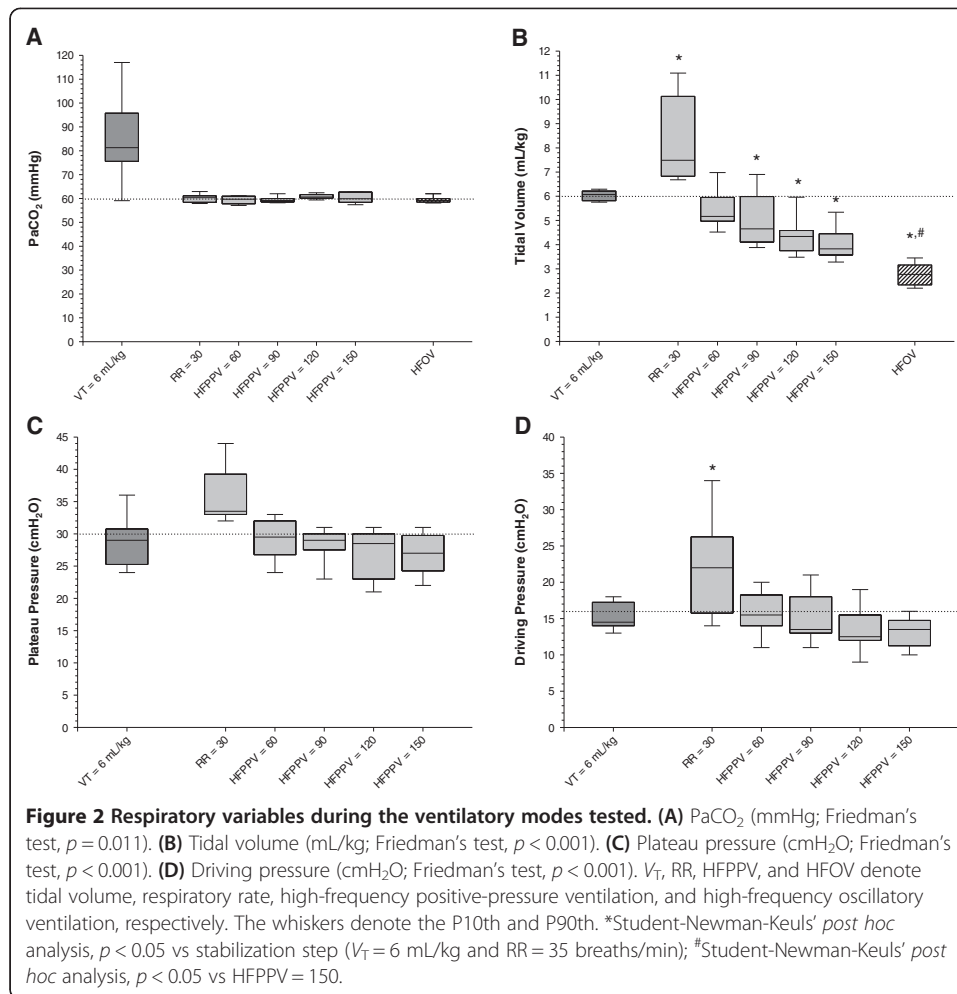
Only one animal needed norepinephrine during HFPPV, and the dose varied between 2.4 μg/kg/min (HFPPV = 60) and 3.2 μg/kg/min (HFOV). The hemodynamic and metabolic data with different RRs are shown in Table 3. Of note, the stabilization step with

Table 1 Respiratory variables at baseline and after the induction of lung injury

Variable	Baseline	After lung injury
P/F ratio (mmHg)	427 [368,473]	97 [67,130]*
Shunt (%)	13 [12,15]	23 [16,32]*
Tidal volume (sternal)	4.8 [3.7,5.9]	4 [4.5,3.5]
Tidal volume (ventral)	4.2 [3.0,5.4]	2.5 [2,3]
C_{static} (mL/cmH$_2$O)	27 [15,30]	12 [9,14]
Resistance (cmH$_2$O/L/s)	8 [7,10]	18 [14,26]*

Values are presented as median [P25th,P75th] C_{static} and P/F denote static compliance and the ratio of arterial oxygen concentration to the fraction of inspired oxygen, respectively. *$p < 0.05$ vs baseline, Wilcoxon's signed rank test.

Figure 2 Respiratory variables during the ventilatory modes tested. (A) $PaCO_2$ (mmHg; Friedman's test, $p = 0.011$). **(B)** Tidal volume (mL/kg; Friedman's test, $p < 0.001$). **(C)** Plateau pressure (cmH_2O; Friedman's test, $p < 0.001$). **(D)** Driving pressure (cmH_2O; Friedman's test, $p < 0.001$). V_T, RR, HFPPV, and HFOV denote tidal volume, respiratory rate, high-frequency positive-pressure ventilation, and high-frequency oscillatory ventilation, respectively. The whiskers denote the P10th and P90th. *Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs stabilization step ($V_T = 6$ mL/kg and RR = 35 breaths/min); #Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs HFPPV = 150.

$V_T = 6$ mL/kg and RR = 35 breaths/min was associated with higher pulmonary artery pressures and lower pH.

Discussion

Our main finding was that, during protective mechanical ventilation of a severe ARDS swine model, the use of HFPPV with a conventional ventilator allows further reductions in V_T and $PaCO_2$, leading to reductions in driving pressures and plateau pressures without increasing mean airway pressure. We did not identify any significant detrimental effect of the high RRs applied, even after careful assessment of hemodynamics, respiratory system mechanics, and gas exchange.

The possibility of further reducing the ventilator-associated lung injury is of utmost importance, with possible implications in terms of reducing death and multiple organ failure in ARDS patients [23]. Ventilation with low V_Ts (6 mL/kg) is still the standard support for those patients [5], although lower V_Ts might produce additional protection [6,24]. Of note, one third of ARDS patients under protective ventilation still have lung hyperdistension, which is associated with increases in systemic inflammatory markers [25]. This subset of patients, usually more severely injured, could possibly benefit from further V_T reductions [24].
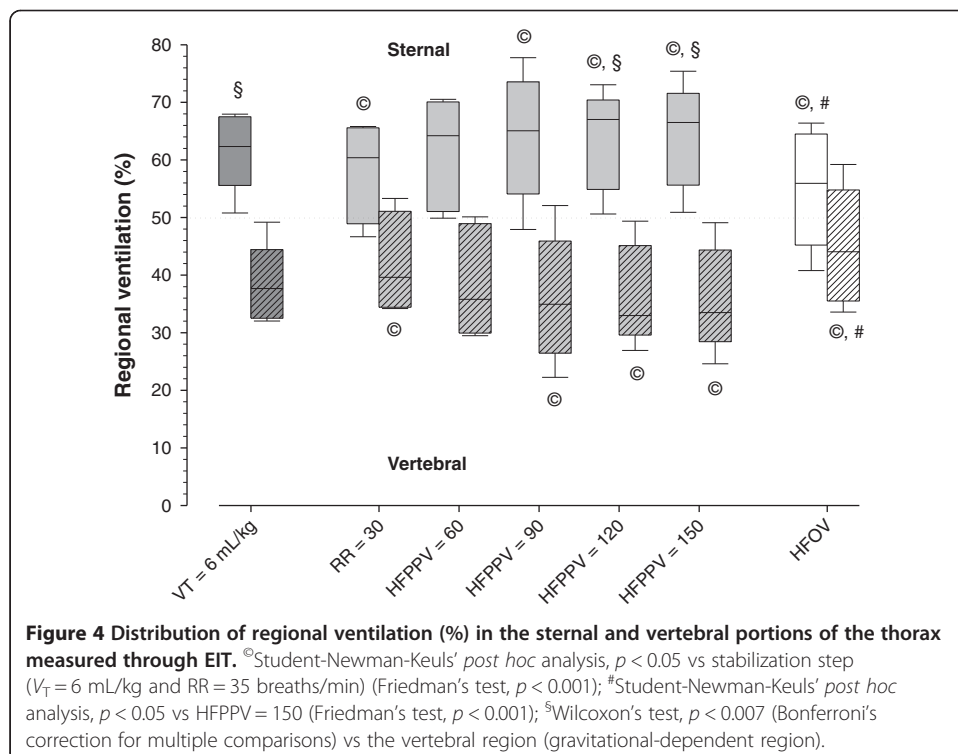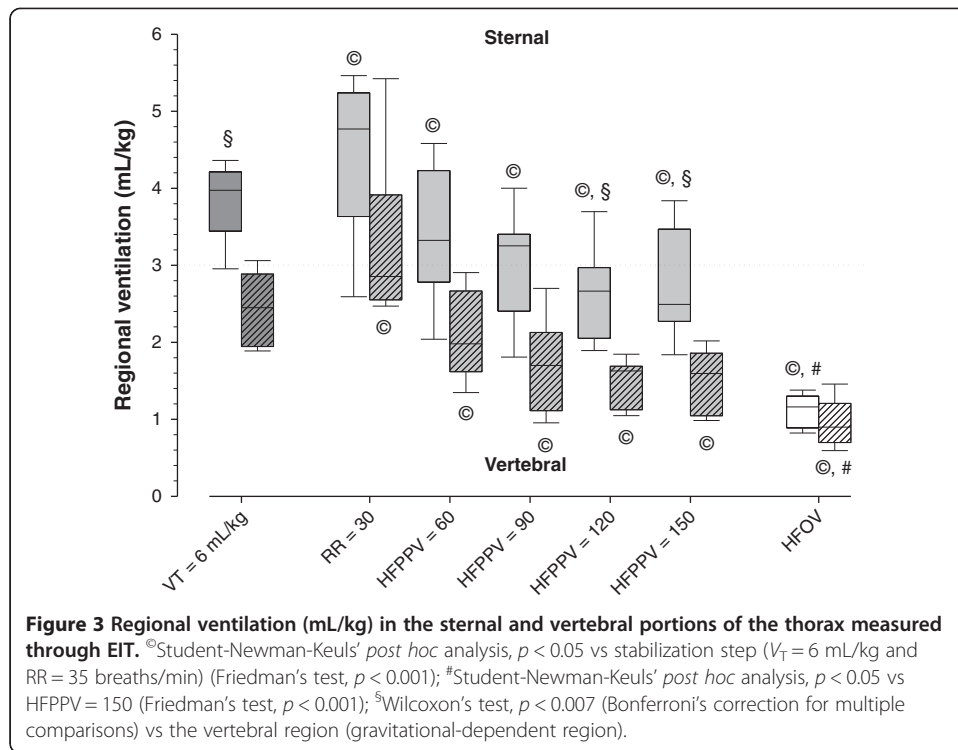
Table 2 Respiratory variables through the ventilatory modes tested

Variable	$V_T =$ 6 mL/kg	RR = 30	HFPPV = 60	HFPPV = 90	HFPPV = 120	HFPPV = 150	HFOV	p value[a]
P/F ratio (mmHg)	95 [87,105]	151 [117,181][b]	141 [102,189][b]	132 [95,169][b]	111 [86,162][b]	112 [90,171][b]	193 [146,216][b,c]	P = 0.003
Gradient (A-a)O_2	480 [465,493]	396 [383,452][b]	427 [378,468][b]	427 [394,466]	455 [406,481]	458 [394,478]	365 [350,420][b,c]	P = 0.014
Minute ventilation (L/min)	6.9 [6.6,8.8]	8.7 [7.4,10.0]	11.1 [11.0,11.5][b]	15.6 [14.0,17.5][b]	18.6 [13.0,19.2][b]	20.2 [19.5,21.3][b]	27 [23.5,28.4][b,c]	P < 0.001
Shunt (%)	43 [41,45]	29 [26,34][b]	34 [30,40]	31 [28,44]	34 [31,45]	38 [30,43]	27 [25,32][b,c]	P = 0.003
EtCO$_2$ (mmHg)	58 [52,60]	43 [32,47][b]	41 [37,49][b]	40 [30,45][b]	40 [31,48][b]	34 [28,36][b]	27 [23,30][b,c]	P < 0.001
C_{static} (mL/cmH$_2$O)	12 [10,14]	12 [9,14]	10 [9,13]	10 [9,12][b]	10 [7,11][b]	9 [8,11][b]	-	P = 0.001
C_{dyn} (mL/cmH$_2$O)	8 [7,9]	9 [6,10]	7 [6,9]	7 [6,8]	6 [5,7][b]	6 [5,7][b]	-	P < 0.001
Resistance (cmH$_2$O/L/s)	8 [8,10]	10 [9,12][b]	9 [8,9][b]	9 [8,9][b]	8 [8,11][b]	9 [8,13][b]	17 [13,20][b,c]	P < 0.001
PEEP total (cmH$_2$O)	14 [11,17]	14 [10,17]	14 [10,17]	13 [10,16]	13 [10,17]	13 [10,17]	-	P = 0.744
PEEP intrinsic (cmH$_2$O)	0	0	0	0 [0,1]	0 [0,1]	2 [1,3][b]	-	P < 0.001
PEEP extrinsic (cmH$_2$O)	14 [11,16]	14 [11,16]	13 [10,17]	13 [10,16]	13 [10,16]	12 [9,14]	-	P < 0.001
Peak pressure (cmH$_2$O)	45 [44,48]	54 [47,58][b]	44 [42,47]	44 [41,45]	41 [38,44]	41 [38,43]	59 [51,79][b,c]	P < 0.001
P_{mean} (cmH$_2$O)	17 [15,20]	18 [16,22][b]	18 [15,22][b]	20 [18,23][b]	20 [18,24][b]	20 [17,23][b]	29 [28,30][b,c]	P < 0.001
Inspiratory flow (L/s)	1	1	1	1	1	1	-	P = 1.000
T_{insp}/T_{tot} (%)	15 [14,17]	19 [14,22]	24 [20,28][b]	34 [30,37][b]	38 [33,44][b]	42 [37,49][b]	56 [50,67][b,c]	P < 0.001

Values are presented as median [P25th,P75th]. [a]The p value was obtained through Friedman's test; [b]Student-Newman-Keuls' *post hoc* analysis, p < 0.05 vs V_T = stabilization step (V_T = 6 mL/kg and RR = 35 breaths/min); [c]Student-Newman-Keuls' *post hoc* analysis, p < 0.05 vs HFPPV = 150.

Increasing the RR at constant alveolar ventilation, we obtained a progressive decrease in V_Ts reaching levels below 4 mL/kg. This finding challenges the paradigm - promulgated by the design of many clinical trials that RRs should be kept equal to or less than 35 breaths per minute [5,26-28]. In our model of severe ARDS, the standard of care [5] settings of V_Ts at 6 mL/kg and a maximum RR of 35 breaths/min led to a median PaCO$_2$ value of 81 mmHg with a median pH of 7.13. Targeting a PaCO$_2$ of 60 mmHg, we were able to reduce V_Ts by 36% with a RR of 150 breaths per minute. Other authors have shown, in an experimental model of ARDS, that higher RRs allow for a reduction in V_T when associated with a strategy to lower the dead space (aspiration of dead space) [29,30]. Similarly, a recent study in patients with ARDS showed that protective V_T around 4 mL/kg can be achieved with modest increments in RR, provided that care is taken to minimize the circuit dead space [31]. These studies combined increases in RR with other measures to decrease the dead space. Our findings on the isolated effect of RR on the reduction of tidal volume help understand the independent effect of manipulating the RR.

Figure 3 Regional ventilation (mL/kg) in the sternal and vertebral portions of the thorax measured through EIT. [©]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs stabilization step ($V_T = 6$ mL/kg and RR = 35 breaths/min) (Friedman's test, $p < 0.001$); [#]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs HFPPV = 150 (Friedman's test, $p < 0.001$); [§]Wilcoxon's test, $p < 0.007$ (Bonferroni's correction for multiple comparisons) vs the vertebral region (gravitational-dependent region).

Figure 4 Distribution of regional ventilation (%) in the sternal and vertebral portions of the thorax measured through EIT. [©]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs stabilization step ($V_T = 6$ mL/kg and RR = 35 breaths/min) (Friedman's test, $p < 0.001$); [#]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs HFPPV = 150 (Friedman's test, $p < 0.001$); [§]Wilcoxon's test, $p < 0.007$ (Bonferroni's correction for multiple comparisons) vs the vertebral region (gravitational-dependent region).

Table 3 Hemodynamic and metabolic variables during the ventilatory modes studied

Variable	$V_T =$ 6 mL/kg	RR = 30	HFPPV = 60	HFPPV = 90	HFPPV = 120	HFPPV = 150	HFOV	p value[a]
Hemodynamic								
Heart rate (bpm)	144 [125,165]	165 [124,182]	173 [144,181]	169 [130,189]	164 [128,196]	173 [142,196]	145 [122,155]	P = 0.210
Cardiac index (mL/kg/min)	138 [128,153]	126 [121,145]	145 [120,169]	127 [115,158]	141 [118,166]	132 [116,168]	126 [101,142]	P = 0.363
SV (mL)	28 [26,42]	27 [24,41]	27 [26,35]	26 [23,44]	27 [26,34]	30 [26,35]	31 [22,44]	P = 0.916
ABPm (mmHg)	90 [75,107]	86 [75,112]	84 [72,97]	91 [77,100]	83 [70,112]	78 [69,105]	82 [72,98]	P = 0.320
PAPm (mmHg)	43 [38,52]	34 [31,37][b]	34 [28,36][b]	36 [33,37][b]	33 [30,47][b]	38 [30,43][b]	31 [30,40][b]	P = 0.018
CVP (mmHg)	9 [9,12]	8 [7,12]	8 [6,10]	9 [6,10]	8 [7,10]	9 [7,10]	11 [10,12][c]	P = 0.017
PAOP (mmHg)	12 [11,15]	12 [11,15]	12 [9,14]	12 [10,14]	12 [10,15]	12 [10,15]	14 [12,17]	P = 0.042
SvO_2 (mmHg)	54 [47,70]	70 [49,79]	68 [48,71]	63 [48,66]	64 [43,74]	65 [55,73]	65 [50,75]	P = 0.140
SVRI (dynes.s^{-1} (cm^5)$^{-1}$.kg^{-1})	51.8 [41.8,56.4]	47.1 [39.8,65.6]	47.0 [35.0,50.9]	52.7 [36.7,61.4]	41.7 [33.4,63.6]	42.4 [28.8,66.5]	50.4 [31.6,55.8]	P = 0.558
PVRI (dynes.s^{-1}. (cm^5)$^{-1}$.kg^{-1})	22.3 [17.5,25.7]	15.7 [13.0,16.8]	15.6 [10.9,17.7]	16.7 [13.9,17.7]	14.2 [12.4,20.8]	16.8 [12.0,20.7]	13.6 [10.9,18.2]	P = 0.133
Metabolic								
Lactate (mEq/L)	1.7 [1.1,2.1]	1.3 [0.8,1.7]	1.6 [0.8,2.0]	1.7 [1.1,2.0]	1.4 [1.0,1.9]	1.6 [0.9,2.3]	1.5 [1.1,1.8]	P = 0.762
pH	7.13 [7.08,7.2]	7.25 [7.24,7.33][b]	7.25 [7.24,7.35][b]	7.26 [7.23,7.33][b]	7.27 [7.2,7.3][b]	7.26 [7.21,7.34][b]	7.25 [7.2,7.32][b]	P = 0.002
Temperature (°C)	38.6 [37.3,39.2]	39.7 [38.0,39.8][b]	39.4 [37.6,39.6][b]	39.2 [38.1,39.6][b]	38.8 [37.6,39.6][b]	39.0 [37.8,39.5][b]	39.2 [38.1,39.8][b]	P = 0.007
Fluid balance (mL)	−50 [−242,−5]	170 [101,278]	40 [−22,102]	100 [67,110]	60 [5,108]	40 [−58,88]	30 [−21,50]	P = 0.044

Values are presented as median [P25th,P75th]. [a]The p value was obtained through Friedman's test; [b]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs V_T = stabilization step (V_T = 6 mL/kg and RR = 35 breaths/min); [c]Student-Newman-Keuls' *post hoc* analysis, $p < 0.05$ vs HFPPV = 150.

The increases in RR were not associated with significant changes in gas exchange. We did notice a not significant but progressive fall in the median PaO_2/FiO_2 (P/F) ratio with increases in RR above 30 breaths per minute amounting to a fall of 26% at a RR of 150 breaths per minute (Table 2). Concurrently, the T_{insp}/T_{tot} ratio increased from 19% to 42% when RR increased from 30 to 150 (Table 2), due to the fixed inspiratory flow rate and the need for higher minute ventilation at high RR. These increases in the T_{insp}/T_{tot} ratio would favor a change in the P/F ratio in the opposite direction of the trend we found. These observations emphasize that with our relatively small sample size, we might have been underpowered to detect some differences such as the P/F ratio variation. If such trend proved significant in a larger study, it is possible that the lower tidal volumes at higher RR have favored the development of absorption atelectasis, although we cannot exclude that hemodynamic factors may played a role.

HFOV, a more classical strategy than HFPPV to provide adequate gas exchange at very low V_Ts [32,33], has been recently shown to provide no benefit or even cause harm to patients with ARDS [16,17]. Our results showed that HFOV = 5 Hz could stabilize the $PaCO_2$ with V_Ts 26% lower than HFPPV = 150, however, with a RR twice as high

and a P_{mean} 30% higher [15]. This is illustrative of the disproportionate increases in RR to maintain alveolar ventilation at progressively lower V_{T}s, especially when close to the dead space, and the need to increase P_{mean}, which may have deleterious hemodynamic effects. The consequence of this ventilation inefficiency might be an increased dissipation of energy in the lungs, potentially leading to more lung injury even at reduced stress and strain per breath. Therefore, reducing V_{T} without increasing mean airway pressure might be of special interest. In that sense, HFPPV might offer a better compromise between V_{T} and RR than HFOV.

Ventilation decreased more in the gravitation-dependent regions, a finding suggestive of reabsorption atelectasis, air trapping, or incomplete filling of those regions due to airway narrowing. Even after taking this 'functional baby lung' into account, the net result was likely a lesser degree of tidal lung stretch as suggested by the decrease in driving pressures and plateau pressures. Additionally, despite a preferential reduction in dependent ventilation (Figure 4), HFPPV could result in lower regional V_{T} in non-dependent regions (Figure 3).

Limitations

Our study has several limitations. First, the arbitrary choice of the target CO_2 level during HFPPV can be criticized. The CO_2 value can be a confounding factor of the ventilatory settings during ARDS ventilation, with some studies showing a protective [34,35] and others a potentially deleterious role [36,37]. We chose a narrow range of 57 to 63 mmHg to avoid such potential confounding effect and to avoid significant acidosis (pH < 7.15), a goal we achieved in all experimental conditions. Likely, the main findings of the study would maintain had a normocapnia target been applied. Second, our study design, with sequential changes in the ventilator settings, was susceptible to carryover phenomena. We tried to avoid that effect through the randomization of sequences, the disconnection from the ventilator between the steps, and through a prolonged wait to the $PaCO_2$ equilibrium. Third, the performance of conventional ventilators declines at very high RRs and low V_{T}s, especially if low-compliance tubing is not employed [38]. Fourth, we did not rule out that histological damage to the lungs might have happened at those very high RRs. Fifth, HFOV was the last step of the study due to logistic issues and at this time the animals had significant positive fluid balances. This could be one explanation why HFOV was not associated with hemodynamic alterations, even with the use of higher P_{mean}. Finally, we cannot directly extrapolate these experimental findings to patients, who have longer time constants than pigs and might not tolerate RRs as high. Interestingly, those with the most severe lung injury tolerate better very high RR, because of their low time constants. Even so, in our experience, it is difficult to apply RR > 60 breaths per minute to patients without leading to intrinsic PEEP.

Conclusions

In an animal model of severe ARDS, as compared to the standard protective ventilation, high-frequency positive-pressure ventilation delivered by a conventional ventilator allowed further reductions in tidal volume and in inspiratory pressures. As such, HFPPV could be a well-suited alternative in the treatment of severe ARDS with very low lung compliance, although its impact on lung inflammation still awaits evaluation.

Abbreviations

ABPm: mean systemic arterial blood pressure; ARDS: acute respiratory distress syndrome; CcO_2: pulmonary capillary oxygen content; C_{dyn}: dynamic compliance; CI: cardiac index; C_{static}: static compliance; CVP: central venous pressure; CxO_2: blood oxygen content; EIT: electrical impedance tomography; $EtCO_2$: airway end-tidal pressure of carbon dioxide; FiO_2: inspiratory fraction of oxygen; HFOV: high-frequency oscillatory ventilation; HFPPV: high-frequency positive-pressure ventilation; I/E: inspiratory/expiratory time ratio; $PaCO_2$: partial arterial carbon dioxide pressure; PaO_2: partial pressure of arterial oxygen; PAOP: pulmonary artery occlusion pressure; PAPm: mean pulmonary artery pressure; PEEP: positive end-expiratory pressure; PEEPe: extrinsic positive end-expiratory pressure; PEEPi: intrinsic end-expiratory pressure; P_{mean}: mean airway pressure; P_{peak}: airway peak pressure; $P_{plateau}$: airway plateau pressure; RR: respiratory rate; SvO_2: mixed venous blood gases; T_{insp}: inspiratory time; V_T: tidal volumes.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RLC designed the study, participated in the research protocols, analyzed and interpreted the data, and drafted the manuscript. MP designed the study, participated in the research protocols, helped interpret the data, and drafted the manuscript. ELVC helped design the study, participated in the research protocols, analyzed and interpreted the data, and helped draft the manuscript design. SG participated in the research protocols and analyzed the data. LB participated in the discussion, helped interpret the data, and drafted the manuscript. MBPA designed the study, analyzed and interpreted the data, and reviewed the manuscript. LCPA designed and conceived the study, participated in the research protocols, and reviewed the manuscript. All authors read and approved the final manuscript.

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