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ORIGINAL ARTICLE

Models of PaO₂ response to the continuous distending pressure maneuver during high frequency oscillatory ventilation in healthy and ARDS lung model pigs

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ABSTRACT

Purpose/Aim: High-frequency oscillatory ventilation (HFOV) is a method of ventilation that theoretically achieves the goals of lung protective ventilation in acute respiratory distress syndrome (ARDS) patients. It is characterized by a rapid delivery of small tidal volumes at high frequencies oscillating around a continuous distending pressure (CDP). Optimization of CDP is not an easy task and it is titrated empirically in the clinical practice. The aim of this study is to investigate whether the level of CDP consistently affects the shape of the partial pressure of oxygen (PaO₂) response to stepwise changes in CDP during HFOV of healthy and ARDS-induced pigs. **Materials and Methods:** We performed two stepwise maneuvers of CDP in 14 pigs: one before and one after the lung lavage, inducing ARDS. For each CDP step performed, we fitted a segment of PaO₂ curve with a one-term power model. **Results:** PaO₂ course follows shapes modeled by root, linear, quadratic, and cubic functions for values of PaO₂ ≤ 110 mmHg and PaO₂ ≤ 200 mmHg, before and after the lung lavage, respectively. PaO₂ course follows a shape modeled exclusively by a root function for values of PaO₂ > 110 mmHg and PaO₂ > 200 mmHg, before and after the lung lavage, respectively. It is not possible to describe a relationship between the shape of the PaO₂ course and the values of CDP. **Conclusions:** The PaO₂ curve may give information about the level of recruitment of alveoli, but cannot be used for optimization of CDP level during HFOV in healthy and ARDS lung model pigs.

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KEYWORDS

ARDS; continuous distending pressure; HFOV; lung lavage; oxygenation; power model

Introduction

Acute respiratory distress syndrome (ARDS) is an acute severe lung disease commonly encountered in intensive care units. It is triggered by injury to the alveolar-capillary membrane from any of a variety of causes, resulting in fluid accumulation and acute respiratory failure. ARDS results in severe hypoxemia, which is refractory to oxygen treatment and requires assisted ventilation.^[1]

The Berlin definition describes the severity of the condition using the ratio of the partial pressure of oxygen (PaO₂ measured in mmHg) to the inspiratory oxygen fraction (F_IO₂; where room air is 0.21 and pure oxygen is 1.0). The grading of ARDS is defined as follows: mild ARDS for 300 mmHg > PaO₂/F_IO₂ > 200 mmHg; moderate ARDS for 200 mmHg > PaO₂/F_IO₂ > 100 mmHg, and severe ARDS for PaO₂/F_IO₂ ≤ 100 mmHg.^[1, 2]

Mechanical ventilation is a major component of the treatment of ARDS as it keeps the patient alive and

ensures gas exchange despite the fact that it may lead to further lung injury and may contribute to the systemic inflammatory response in patients with ARDS.^[3, 4] High-frequency oscillatory ventilation (HFOV), characterized by the rapid delivery of small tidal volumes (1 to 3 mL/kg) at frequencies of 3 to 15 Hz, is a method of ventilation that theoretically achieves all of the goals of lung protective ventilation.^[5] HFOV oscillates the lung around a continuous distending pressure (CDP, i.e. the mean airway pressure during HFOV) that is higher than that usually applied during conventional ventilation. Although the oscillations may cause significant pressure swings in the endotracheal tube, the pressure fluctuations are significantly attenuated at the alveolar level.^[6, 7] Application of a constant CDP during HFOV allows maintenance of alveolar recruitment while avoiding low end-expiratory pressure and high peak pressures. The small tidal volumes limit the alveolar overdistension.^[4, 8] HFOV improved oxygenation in severe respiratory failure when conventional ventilation has been ineffective with an overall survival

similar to patients receiving ECMO (Extra-corporeal Membrane Oxygenation).^[9, 10] HFOV, being less invasive and requiring fewer resources than extracorporeal techniques, has the potential to be applied in more intensive care units, but should not be considered a substitute for ECMO.^[11]

Experimental data are converging towards beneficial effects of HFOV over conventional mechanical ventilation strategies in situations where pure lung collapse and major alveolar instabilities coexist and threat to cause a ventilator-induced lung injury.^[12–15] HFOV may be beneficial mostly as a rescue therapy in oxygenation failure^[16] with substantial improvements in oxygenation^[17] and possibly a more effective CO₂ elimination.^[18]

In clinical practice, the CDP is one of the most important parameters of HFOV. An increase in CDP often causes rapid improvement in oxygenation; however, higher CDP levels compromise hemodynamics. As a standard, a CDP level is increased in a stepwise manner while PaO₂ is improving but not severe signs of hemodynamic compromise are observed.^[19] During our former HFOV experiments with continuous measurement of PaO₂, we noticed that the response of PaO₂ to a sudden change in CDP varied significantly not only in amplitude but also in its shape. This is demonstrated in Figure 1 both for a healthy pig and an animal model of ARDS.

We hypothesize that this shape of the PaO₂ response to the sudden change in CDP depends on the actual CDP level. Furthermore, we expect that the shape of the response might be related to a certain CDP level, above which a higher CDP level starts to have a significant adverse effect on hemodynamics and starts to compromise the systemic circulation.

The aim of this study is to investigate whether the level of CDP consistently affects the shape of the PaO₂ response to stepwise changes in CDP during HFOV of healthy and ARDS induced pigs.

Materials and methods

Animal preparation and protocol

The study was approved by the Institutional Animal Care and Use Committee of the First Faculty of Medicine, Charles University in Prague, on March 27, 2013. The study was performed in an accredited animal

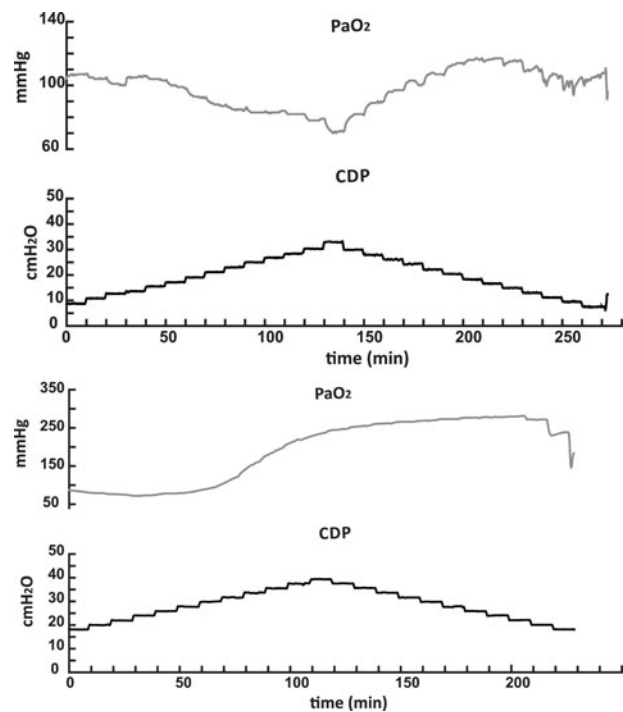


Figure 1. Representative course of PaO₂ in arterial blood (grey line) during CDP steps. The top panel shows PaO₂ course before the lung lavage and the bottom panel shows PaO₂ course after the lung lavage during the ascending and descending CDP steps (black line).

laboratory in accordance with Act No. 246/1992 Coll., on the protection of animals against cruelty.

Fourteen crossbred Landrace female pigs (*Sus scrofa domestica*) with an average body weight of 48 kg were used in this study. The animals were premedicated with azaperone (2 mg/kg IM).

Anesthesia was performed with ketamine hydrochloride (20 mg/kg IM) and atropine sulphate (0.02 mg/kg IM) followed by initial boluses of propofol (2 mg/kg IV) and morphine (0.1 mg/kg IV).

Animals were placed in supine position on a heated pad; body temperature was kept in the normal range (38–39°C).

The animals were intubated with a cuffed endotracheal tube (I.D. 7.5 mm) and connected to a conventional ventilator (CV) Hamilton G5 (Hamilton Medical, Bonaduz, Switzerland). Anesthesia was maintained by continuous infusion of propofol (8 to 10 mg/kg/h IV) combined with morphine (0.1 mg/kg/h IV) and heparin (40 U/kg/h IV). Myorelaxant pipecuronium bromide (4 mg boluses every 45 min) was administered during artificial lung ventilation to suppress spontaneous breathing. Initial rapid infusion of 1,000 mL of normal saline was given intravenously, followed by a

continuous IV drip of 250 mL/h to reach and maintain central venous pressure of 6 to 7 mmHg. Vein and arterial cannulation for central venous pressure, arterial blood pressure and pulmonary arterial pressure monitoring was performed by Nihon Kohden (Nihon Kohden Corporation, Tokyo, Japan). Cardiac output and mixed venous blood oxygen saturation were measured continuously by the Vigilance monitor (Edwards Lifesciences, Irvine, CA, USA). Arterial blood gases, i.e. PaO₂, partial pressure of carbon dioxide (PaCO₂) and pH, were continuously measured by CDI 500 (Terumo, Tokyo, Japan) with a sampling rate $f_s = 0.1675$ Hz. The arterio-venous extracorporeal circuit for CDI 500 monitor was established between the femoral artery and the femoral vein using a mechanical blood pump (peristaltic roller pump with a blood flow set to 400 mL/min).

All the signals were recorded synchronously using a LabChart system (ADInstruments, Oxford, UK). Animals were switched to the SensorMedics 3100B HFO ventilator (CareFusion, Yorba Linda, CA, USA).

Initial setting was as follows: mean initial CDP = 9 ± 2 cmH₂O (range 8–15 cmH₂O), oscillatory frequency 5 Hz, inspiration/expiration ratio 1:1, bias flow 40 L/min, and F₁O₂ = 0.21. Proximal pressure amplitude ΔP , that provides the ventilation, was set to maintain normocapnia ($40 \text{ mmHg} \pm 5 \text{ mmHg}$). Every 10 minutes, CDP was stepwise increased by 2 cmH₂O until the mean maximum CDP = 32 ± 5 cmH₂O (range 26–44 cmH₂O) was reached (ascending steps). Increase in CDP was stopped when severe signs of hemodynamics deterioration were observed. Then, CDP was stepwise decreased by 2 cmH₂O to its initial value (descending steps).

In order to mimic ARDS, surfactant deficiency was induced during a subsequent conventional mechanical ventilation by double or triple lung lavage with 30–40 mL/kg 37°C normal saline containing nonionic surfactant Triton X-100 (0.05%), followed by a 1 h stabilization period after each lavage. When normocapnia was reached, the animals were switched to HFOV with F₁O₂ = 1.0. Every 10 minutes, CDP was stepwise increased by 2 cmH₂O from 17 ± 4 cmH₂O (range 8–23 cmH₂O), but when an animal did not tolerate low CDP levels after the lung lavage, CDP was rapidly increased in order to prevent further deterioration in severe hypoxia. During the CDP steps, F₁O₂ was decreased to 0.65 ± 0.13 . The mean maximum CDP was 43 ± 6 cmH₂O (range 30–52 cmH₂O). Increase in

CDP was stopped when severe signs of hemodynamics deterioration appeared. Then, CDP was stepwise decreased by 2 cmH₂O to its initial value.

We performed CDP steps 10 minutes long, longer than in usual recruitment maneuvers and PEEP titration,^[20, 21] in order to allow PaO₂ sufficient time to settle in shape and amplitude.

Thus, two CDP stepwise maneuvers have been performed: one before the lung lavage (healthy lung pigs) and one after the lung lavage (ARDS lung model pigs).

Data analysis

The MATLAB environment was used for data processing (MATLAB 7.04, The Mathworks, Natick, USA).

In order to evaluate the shape of the course of PaO₂ following the CDP stepwise changes, we selected each CDP step performed and we fitted each correspondent PaO₂ segment with a one-term power series model as follows:

$$y = ax^b,$$

where x is the length of the CDP segment in terms of time, a is the amplitude of the model and the exponent b reflects the shape of the model. The coefficients were assessed using iterative Levenberg–Marquardt nonlinear least squares algorithm.

If b is between 0 and 1, PaO₂ follows a root function with respect to time, e.g. a square root when $b = 0.5$;
If $b = 1$, PaO₂ follows a linear function with respect to time;

If b is between 1 and 2, PaO₂ follows a function between linear and quadratic with respect to time;

If $b = 2$, PaO₂ follows a quadratic function with respect to time;

If b is between 2 and 3, PaO₂ follows a function between quadratic and cubic with respect to time.

If $b = 3$, PaO₂ follows a cubic function with respect to time.

When PaO₂ course was constant we set $b = 0$.

The exponent b is never negative, but for convenience, we have assigned the minus sign to b when the parameter a was negative. In this way, a positive value of b means that PaO₂ is growing and a negative value b means that PaO₂ is dropping.

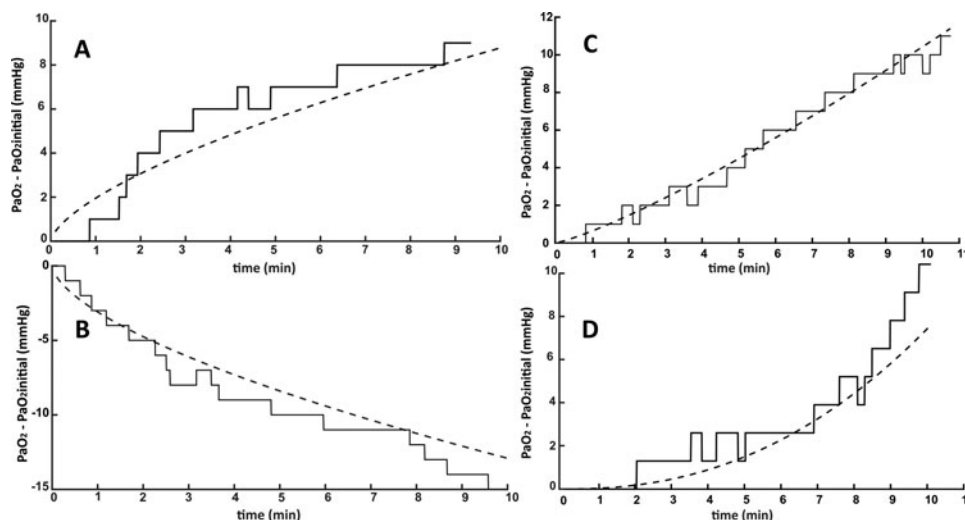


Figure 2. Representative shapes followed by PaO_2 in arterial blood during a single CDP step. Continuous line is the measured PaO_2 during one single CDP step, dotted line is the fitted model. From the original values of PaO_2 , their initial values have been subtracted. Values of the model parameters are: (A) $a = 1.95$ and $b = 0.65$; (B) $a = -3.09$ $b = 0.62$; (C) $a = 0.63$ and $b = 1.23$; (D) $a = 0.035$; $b = 2.31$.

Statistical analysis

The goodness of fitting of the one-term power model was assessed by calculating both coefficients of determination (r -squared) and root mean square error (RMSE).

In order to evaluate if the shape of the response in PaO_2 after a sudden CDP change is related to the CDP level at which the change was conducted, we performed a linear regression between values of the exponents b and the average values of CDP calculated for each CDP step and for all conditions considered (before and after the lung lavage, during the ascending and descending steps).

Results

Examples of the possible shapes that PaO_2 course can bear with respect to time are reported in Figure 2. Panel A shows a representative root function that PaO_2 can follow during its growing. In this particular case the model fitted has the following parameters $a = 1.95$ and $b = 0.65$ ($r^2 = 0.92$ and $\text{RMSE} = 0.79$). Panel B shows a representative root function that PaO_2 can follow during its decreasing with the following parameters: $a = -3.09$ and $b = 0.62$ ($r^2 = 0.97$ and $\text{RMSE} = 0.68$). Panel C shows a representative function between linear and quadratic that PaO_2 can follow with the following parameters: $a = 0.63$ and $b = 1.23$ ($r^2 = 0.98$ and $\text{RMSE} = 0.51$). Panel D shows a representative function between quadratic and cubic with the following parameters $a = 0.035$ and $b = 2.31$ ($r^2 = 0.98$ and

$\text{RMSE} = 0.57$). For each CDP step considered, we have subtracted the initial value from the original PaO_2 waveform in order to normalize the amplitude of the step response.

For all segments of PaO_2 fitted in each single CDP step, RMSE is less than 2 and the r -squared is more than 0.75.

Figure 3 shows values of exponents b respect to PaO_2 before the lung lavage (healthy lung pigs). Exponents b calculated during the ascending and descending CDP steps are plotted in the left and right panel, respectively. Values of PaO_2 have been calculated as average value during each single CDP step. It is interesting to note that, during both ascending and descending steps, for $\text{PaO}_2 > 110$ mmHg (underlined by the black dotted vertical line) exponents b assume exclusively values between 0 and 1 ($0 < b < 1$) (grey circles), whereas for $\text{PaO}_2 \leq 110$ mmHg exponents b can be as follows: $0 < b < 1$, $b = 1$, $1 < b < 2$, $b = 2$, $2 < b < 3$ and $b > 3$ (black square). The positive values of exponents b refer to the growing of PaO_2 , whereas those negative to the dropping of PaO_2 .

Figure 4 shows values of exponents b with respect to PaO_2 after the lung lavage (ARDS lung model pigs). Exponents b calculated during the ascending and descending CDP steps are plotted in the left and right panel, respectively. Values of PaO_2 have been calculated as average value during each single CDP step. It is possible to note that during both ascending and descending steps, for $\text{PaO}_2 > 200$ mmHg (underlined by the black dotted vertical line) exponents b assume

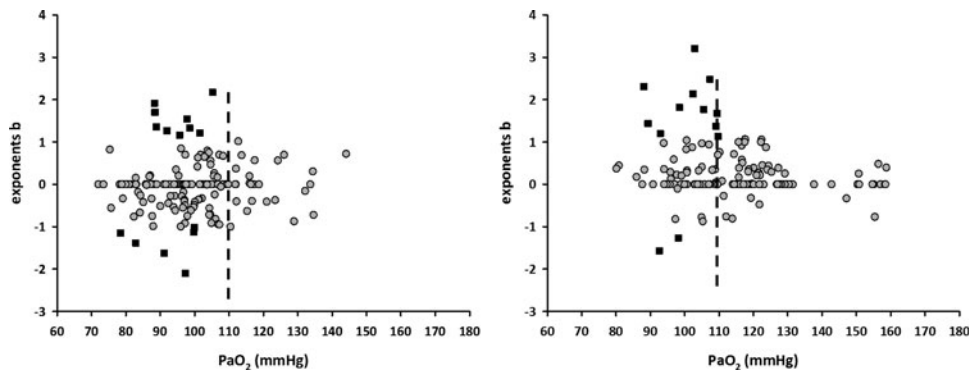


Figure 3. Values of exponents b in relation with the average value of PaO_2 in arterial blood before the lung lavage (healthy lung pigs). Exponents b are calculated for each ascending (left panel) and descending (right panel) CDP step for all the animals studied. In both cases, $0 < b < 1$ for $\text{PaO}_2 > 110$ mmHg (grey circles), whereas $0 < b < 1$, $b = 1$, $1 < b < 2$, $b = 2$, $2 < b < 3$ and $b > 3$ for $\text{PaO}_2 \leq 110$ mmHg (black square). The black dotted vertical line underlines the value of $\text{PaO}_2 = 110$ mmHg. For values greater than this, exponents b assume only values between 0 and 1.

exclusively values between 0 and 1 ($0 < b < 1$) (grey circles), whereas for $\text{PaO}_2 \leq 200$ mmHg exponents b can be as follows: $0 < b < 1$, $b = 1$, $1 < b < 2$, $b = 2$, $2 < b < 3$ (black square). The positive values of exponents b refer to the growing of PaO_2 , whereas those negative to the dropping of PaO_2 .

Figures 5 and 6 show the exponents b in relation with CDP, before and after the lung lavage, respectively. Values of CDP have been calculated as an average value during each single CDP step. In both healthy and ARDS lung model pigs, the exponents b and CDP levels are not related: the linear regression returned very low r^2 in all the cases considered. Before the lung lavage: $r^2 = 0.015$ ($\text{SE} = 0.80$) for the ascending steps (left panel), $r^2 = 0.131$ ($\text{SE} = 0.75$), for the descending steps (right panel). After the lung lavage: $r^2 = 0.0001$ ($\text{SE} = 0.54$) for the ascending steps (left panel), $r^2 = 0.008$

($\text{SE} = 0.88$), for the descending steps (right panel). We have removed the values of exponents b equal to zero because they could have affected the results of linear regression.

Discussion

In this study, we assessed the response of PaO_2 in arterial blood to a sudden change in CDP during HFOV in terms of its shape, in healthy and ARDS lung model pigs.

To the best of our knowledge, the data here presented are original and, therefore, the main strength of this study is that during HFOV the shape of the PaO_2 response of the organism to the CDP stepwise change have never been studied in healthy and ARDS model lung pigs before.

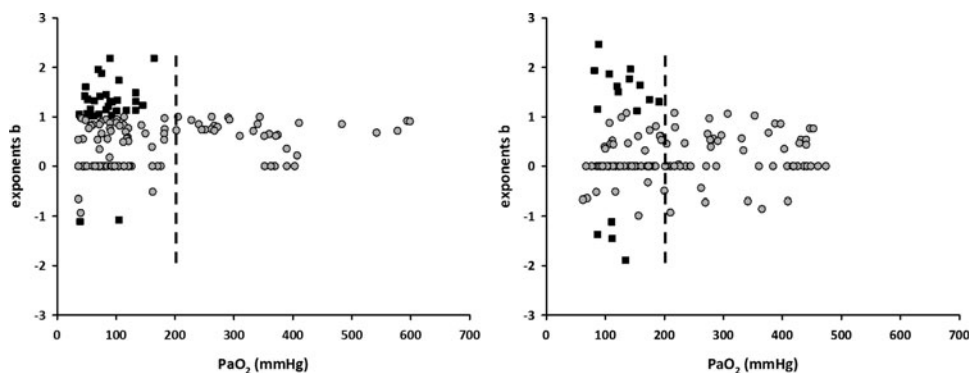


Figure 4. Values of exponents b in relation with the average value of PaO_2 in arterial blood after the lung lavage (ARDS lung model pigs). Exponents b are calculated for each ascending (left panel) and descending (right panel) CDP step for all animals studied. In both cases, $0 < b < 1$ for $\text{PaO}_2 > 200$ mmHg (grey circles), whereas $0 < b < 1$, $b = 1$, $1 < b < 2$, $b = 2$ and $2 < b < 3$ for $\text{PaO}_2 \leq 200$ mmHg (black square). The black dotted vertical line underlines the value of $\text{PaO}_2 = 200$ mmHg. For values greater than this, exponents b assume only values between 0 and 1.

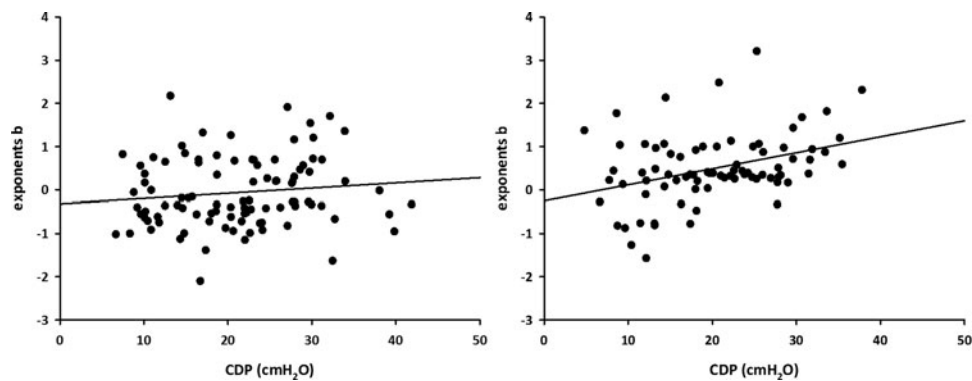


Figure 5. Exponents b in relation with the average value of CDP before the lung lavage (healthy lung pigs). Exponents b are calculated for each ascending (left panel) and descending (right panel) CDP step for all the animals studied. There is not a significant correlation between the exponents b and CDP value. Results of the linear regression are: $r^2 = 0.015$ (SE = 0.80) for the ascending steps (left panel), $r^2 = 0.131$ (SE = 0.75), for the descending steps (right panel) (SE—standard error).

The main finding of this study is that in healthy and ARDS model lung pigs, for each CDP step considered, the PaO_2 course follows several shapes that can be modeled by constant, root, linear, quadratic, and cubic functions. Indeed, for all segments of PaO_2 fitted in each single CDP step, RMSE, which reflects the precision of the prediction of the model, was excellent (< 2) and the r -squared was excellent as well (more than 0.75). The shape of PaO_2 depends on value of PaO_2 , but it is not possible to determine a relationship between the shape of PaO_2 response and the value of CDP.

In particular, in healthy lung pigs, as shown in Figure 3, for values of $\text{PaO}_2 \leq 110$ mmHg, the course of PaO_2 follows a shape that can be modeled by a root function, but also by a linear and/or quadratic and/or cubic functions, whereas for values of $\text{PaO}_2 > 110$ mmHg the course of PaO_2 follows a shape that can be modeled exclusively by a root function. In ARDS lung

model pigs, as shown in Figure 4, for values of $\text{PaO}_2 \leq 200$ mmHg the course of PaO_2 follows a shape that can be modeled by a root function, but also by a linear and/or quadratic and/or cubic functions, whereas for values of $\text{PaO}_2 > 200$ mmHg the course of PaO_2 follows a shape that can be modeled exclusively by a root function.

These findings could be explained considering the alveoli recruitment: when alveoli are not recruited at all or have not been fully recruited yet, oxygenation is more sensitive to changes in lung volume and aeration caused by a change in CDP, and thus PaO_2 grows or drops rapidly following linear and/or quadratic functions. Instead of, when alveoli are open and recruited, changes in PaO_2 are less sensitive to relatively minor changes in lung aeration and thus PaO_2 grows and drops slower, following only root function.

We did not find a relation between the shape of the course of PaO_2 and CDP level: the CDP does not

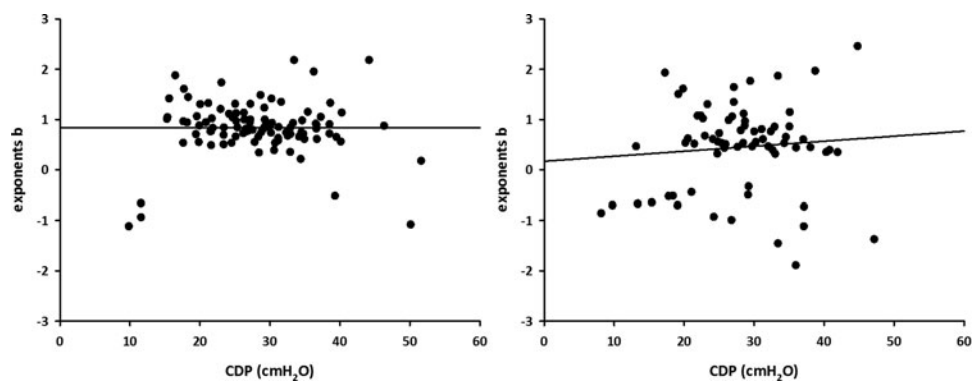


FIGURE 6. Exponents b in relation with the average value of CDP after the lung lavage (ARDS lung model pigs). Exponents b are calculated for each ascending (left panel) and descending (right panel) CDP step for all the animals studied. There is not a significant correlation between the exponents b and CDP value. Results of linear regression are: $r^2 = 0.0001$ (SE = 0.54) for the ascending steps (left panel), $r^2 = 0.008$ (SE = 0.88), for the descending steps (right panel) (SE—standard error).

affect the response of organism in terms of PaO₂ shape change. Indeed, the linear regression between values of the exponents *b* and the average values of each single CDP step returned very low *r*-squared values both before the lung lavage (ascending steps: $r^2 = 0.015$, SE = 0.80; descending steps: $r^2 = 0.131$, SE = 0.75) and after the lung lavage (ascending steps $r^2 = 0.0001$, SE = 0.54; descending steps: $r^2 = 0.008$, SE = 0.88). This is probably due to the fact that the recruitment occurs at different values in each pig and so, absolute value of CDP does not provide information about the recruitment. This result suggests individual CDP titration, rather than universal CDP (or high PEEP) strategies should be adopted. This our finding is also confirmed by a clinical study,^[22] in which authors found that some physiologic variables and individual patient physiology could be useful in predicting alveolar recruitment when applying higher-than-traditional PEEP. Although recruitment maneuvers may have a role to play in individual optimization of ventilation strategies in severely hypoxaemic patients, it remains to be elucidated how best to perform them and the optimal timing of their use.^[23]

Our study has several limitations. We used an animal model instead of real patients and also ARDS induced by lung lavage with saline may not represent ARDS patients' lung behavior, although there are studies that support the validity of large animal model, e.g., pigs, as model of ARDS.^[14, 15] The model reflects acute refractory hypoxemia, but not other pathophysiology commonly concomitant with clinical ARDS. It is also possible that the lung injury created by saline lavage may not induce lung behavior representative of the volutrauma and biotrauma typical of ARDS rescue. Evaluation of more than 14 pigs might have been able to detect effects in severity subgroups, although the general findings were consistent with those of the healthy pig.

In conclusion, the level of CDP does not affect the shape of the PaO₂ response to stepwise changes in CDP during HFOV in healthy lungs and in animal model of ARDS. We speculated that the shape of the PaO₂ curve as a response to a sudden change in CDP may give information about the level of recruitment of alveoli, but cannot be used for optimization of CDP level during HFOV in healthy and ARDS lung model pig.

Further studies are needed to fully elucidate the optimization of CDP in patients with ARDS.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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