Models of a PaO_2 course during a stepwise change of Continuous Distending Pressure in HFOV

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***Abstract* — Acute respiratory distress syndrome (ARDS) is an acute severe lung disease commonly encountered in intensive care units. High-frequency oscillatory ventilation (HFOV) could offer effective lung protective ventilation by delivering very low tidal volumes around constant relatively higher continuous distending pressure (CDP) at frequencies of 3 to 15 Hz. The rapid ventilatory rate can provide adequate gas exchange, the higher CDP and lower tidal volumes limit alveolar derecruitment and overdistension, respectively. 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 if the level of CDP affects the shape of the PaO_2 response of the organism to the CDP stepwise changes. Ten pigs were used in this study. In order to mimic ARDS, surfactant deficiency was induced by a double or triple lung lavage normal saline containing nonionic surfactant. When normocapnia was reached, the animals were switched to HFOV with FIO_2=1.0. Every 10 minutes, CDP was stepwise increased by 2 cmH_2O from 17±4 cmH_2O, 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. The mean maximum CDP was 43±5 cmH_2O and then CDP was stepwise decreased by 2 cmH_2O to its initial value. In order to calculate the shape that PaO_2 course follows during the CDP stepwise, for each CDP step performed, we fitted PaO_2 with a one-term power model as follows: $y = a \cdot x^b$, where *x* is the length of CDP in terms of time, *a* is the amplitude of the model, exponents *b* reflects the shape of the model. PaO_2 course can follow several shapes modelled by constant, root, linear and quadratic functions. For values of PaO_2<200 mmHg, PaO_2 course follows shapes modelled mainly by root, but also, linear and quadratic functions. For values of PaO_2>200mmHg PaO_2 course follows a shape modelled exclusively by a root function. It is not possible to describe a relationship between the shape of the PaO_2 course and the values of CDP. 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 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. The CDP level does not affect the response of organism in terms of shape change of PaO_2, probably due to the fact that the recruitment occurs at different values in each pig.**

Keywords—high frequency oscillatory ventilation, HFOV, continuous distending pressure, ARDS, pig model, lung lavage, oxygenation; PaO_2

I. 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 hypoxaemia, which is refractory to oxygen treatment and requires assisted ventilation [1]. The severity of the condition was defined by the ratio of the arterial oxygen tension (PaO_2 measured in mmHg) to the inspiratory oxygen fraction (FIO_2; where room air is 0.21 and pure oxygen is 1.0). Mild ARDS: 300mmHg > PaO_2/FIO_2>200 mmHg; moderate ARDS: 200mmHg>PaO_2/FIO_2>100 mmHg and severe ARDS: $PaO_2/FIO_2 \leq 100$ mmHg [1, 2].

The acute phase of ARDS is characterized by injury to the alveolar–capillary membrane, with disruption leading to increased permeability. The consequent respiratory failure is aggravated by severe ventilation/perfusion mismatching, with some perfused alveoli no longer receiving any ventilation, while others are ventilated but not perfused [3].

Mechanical ventilation is major components of the treatment of ARDS as it keeps the patient alive and ensures gas exchange despite patients with ARDS exhibit a highly inhomogeneous, compliance dependent distribution of regional ventilation during conventional mechanical ventilation (CMV) [4].

High-frequency oscillatory ventilation (HFOV) can theoretically offer effective lung protective ventilation by delivering very low tidal volumes (1 to 3 mL/kg) around constant relatively higher, compared to CMV, continuous distending pressure (CDP, i.e. mean airway pressure during HFOV) at frequencies of 3 to 15 Hz.

Thus, while the rapid ventilatory rate can provide adequate gas exchange, the higher CDP and lower tidal volumes limit alveolar derecruitment and overdistension, respectively [5].

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 to prevent of ventilator-induced lung injury [6, 7, 8].

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HFOV may be beneficial, mostly as a rescue therapy in oxygenation failure [9]. A substantial improvement in oxygenation [10], safety of HFOV [11] and a more effective CO_2 elimination [12] has been shown.

During our former ventilatory experiments with HFOV, we noticed that the response of PaO_2 to a sudden change in CDP varied significantly not only in amplitude but also in its shape. We hypothesize that this shape of the PaO_2 response to the sudden change in CDP depends on the target CDP level. Furthermore, we expect that the shape of the response is related to a certain CDP level, above which a higher CDP level starts to have a significant adverse effect on hemodynamic and starts to compromise the systemic circulation.

The aim of this study is to investigate if the level of CDP affects the shape of the PaO_2 response of the organism to the CDP stepwise changes.

II. Material and Methos

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

Ten crossbred Landrace female pigs (*Suss crofa 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 atropine sulphate (0.02 mg/kg IM) and ketamine hydrochloride (20 mg/kg IM) followed by initial boluses of morphine (0.1 mg/kg IV) and propofol (2 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. A vein and arterial cannulation for central venous pressure and arterial blood pressure monitoring was performed. Cardiac output, mixed venous blood oxygen saturation and pulmonary artery pressure were measured continuously by Vigilance (Edwards Lifesciences, Irvine, CA, USA) monitor. Arterial blood gases, i.e. partial pressure of oxygen (PaO_2), carbon dioxide ($PaCO_2$) and pH, were continuously measured by CDI 500 (Terumo, Tokyo, Japan) with a sampling rate fs=0.033 Hz. All the signals were recorded synchronously using a LabChart system (ADInstruments, Oxford, UK). Animals were switched to a SensorMedics 3100B HFO ventilator (CareFusion, Yorba Linda, CA). Fig 1. shows representative pictures of pig experiments performed in Charles University in Prague (Czech Republic).

In order to mimic ARDS, surfactant deficiency was induced by a 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 (40 mmHg ± 3 mmHg) was reached, the animals were switched to HFOV with FIO_2=1.0. Every 10 minutes, CDP was stepwise increased by 2 cmH_2O from 17±4 cmH_2O (range 8 ÷ 23 cmH_2O), 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. The mean maximum CDP was 43±5 cmH_2O (range 38÷52 cmH_2O). Then, CDP was stepwise decreased by 2 cmH_2O to its initial value.

Fig. 2 shows an experimental and representative CDP stepwise and the PaO_2 course during the ascending (top panel) and descending bottom panel) CDP steps.

B. Data Analysis

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

In order to evaluate the shape that the course of PaO_2 follows during the CDP stepwise, for each CDP step performed we fitted PaO_2 with a one-term power model as follow:

$$y = a \cdot x^{b}$$

where x is the length of CDP in terms of time, a is the amplitude of model, exponents b reflects the shape of model.

If $b = 0 \div 1$, PaO_2 follows a root function respect to time, e.g. a square root when b=0.5;

If $b = 1$, PaO_2 follows a linear function respect to the time;

If $b = 1 \div 2$, PaO_2 follows a function between linear and quadratic respect to the time;

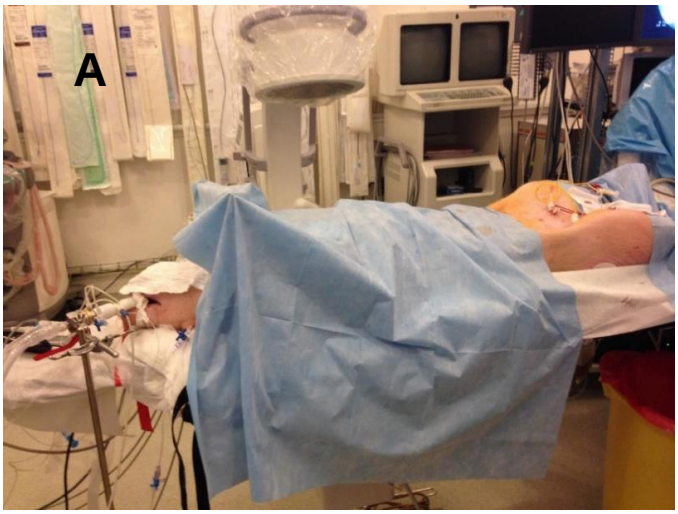
If $b = 2$, PaO_2 follows a quadratic function respect to the time;

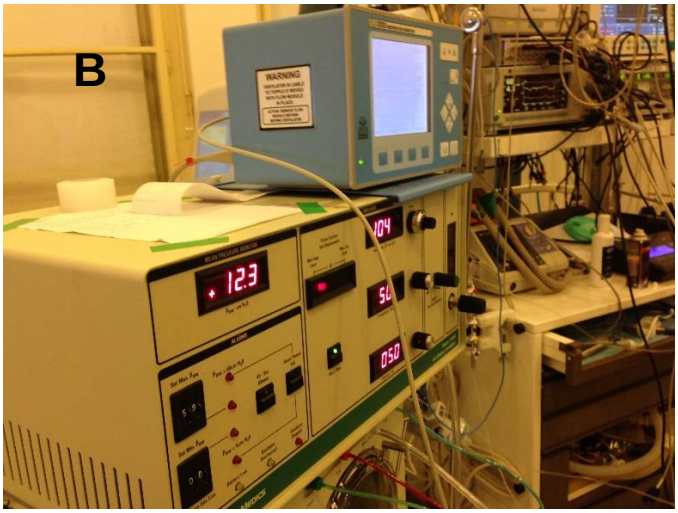
If b 2÷ 3 PaO_2 follows a function between quadratic and cubic respect to the time.

For all other values of b, e.g. PaO_2 course is constant we set $b = 0$.

The exponent b is never negative. We have assigned to b negative values when the parameter a is negative. In this way, when b is positive, it means that PaO_2 is growing and when b is negative it means that PaO_2 is falling.

We have considered only exponents b with $r^2 > 0.75$.





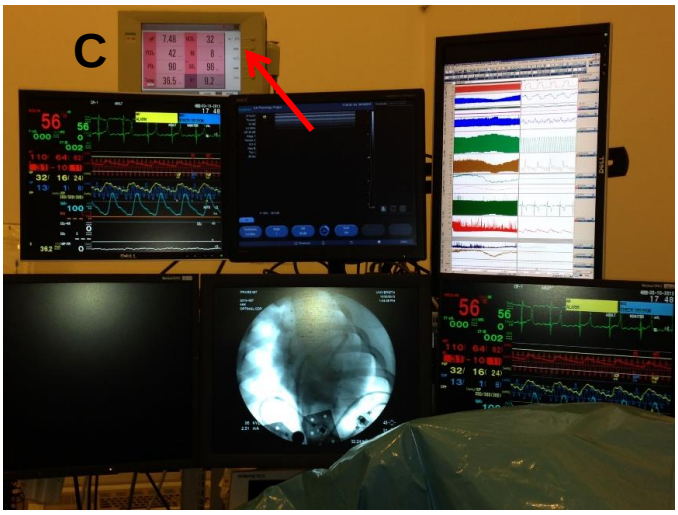


Fig. 1 Representative pictures of pigs experiments. *A)* Pig after preparation and intubated; *B)* HFO ventilator; *C)* Some monitor devices used during experiment, as CDI 500 Terumo used for the measurement of PaO_2 (indicated by a red arrow).

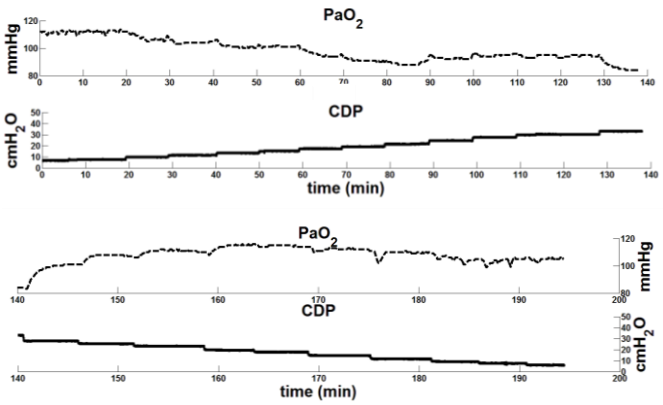


Fig. 2 Representative CDP stepwise and PaO_2 course during the ascending and descending CDP steps.

III. RESULTS

Some of the possible shapes that PaO_2 course can bear with respect to time are reported in Fig. 3. Panels *A*) and *B)* show the root function that PaO_2 can follow during its growing and dropping, respectively. In particular in the panel *A*), the model has the following parameters a=1.95 and b=0.65, r^2=0.92 and RMSE=0.79 and in the panel *B*), the model has the following parameters: a=–3.09, b=0.62, r^2=0.97 and RMSE=0.68. Panels *C)* and *D)* show representative linear and quadratic÷cubic functions, respectively, that PaO_2 can follow. In particular, in the panel *C)* the model has the following parameters: a=0.63; b=1.23; r^2=0.98 and RMSE=0.51 and in the panel *D)* a=0.035; b=2.31 r^2=0.98 and RMSE=0.57. At original values of PaO_2 in the CDP step considered, we have subtracted its initial value in order to have just the amplitude of it.

Fig. 4 shows values of exponents b respect to PaO_2 (calculated as average during the single CDP step) during the ascending (upper panel) and descending (bottom panel) CDP stepwise. It is interesting to note that for values of PaO_2>200 mmHg b=0÷1, whereas for values of PaO_2< 200 mmHg b=1; b=1÷2; b=2 and b=2÷3. Also during the descending CDP steps for values of PaO_2 >200 mmHg, b = 0 ÷ 1, whereas for values of PaO_2<200 mmHg b=1; b=1÷2, b=2 and b=2÷3. The positive values of exponents b refer to rising of PaO_2, whereas those negative to decrease of PaO_2.

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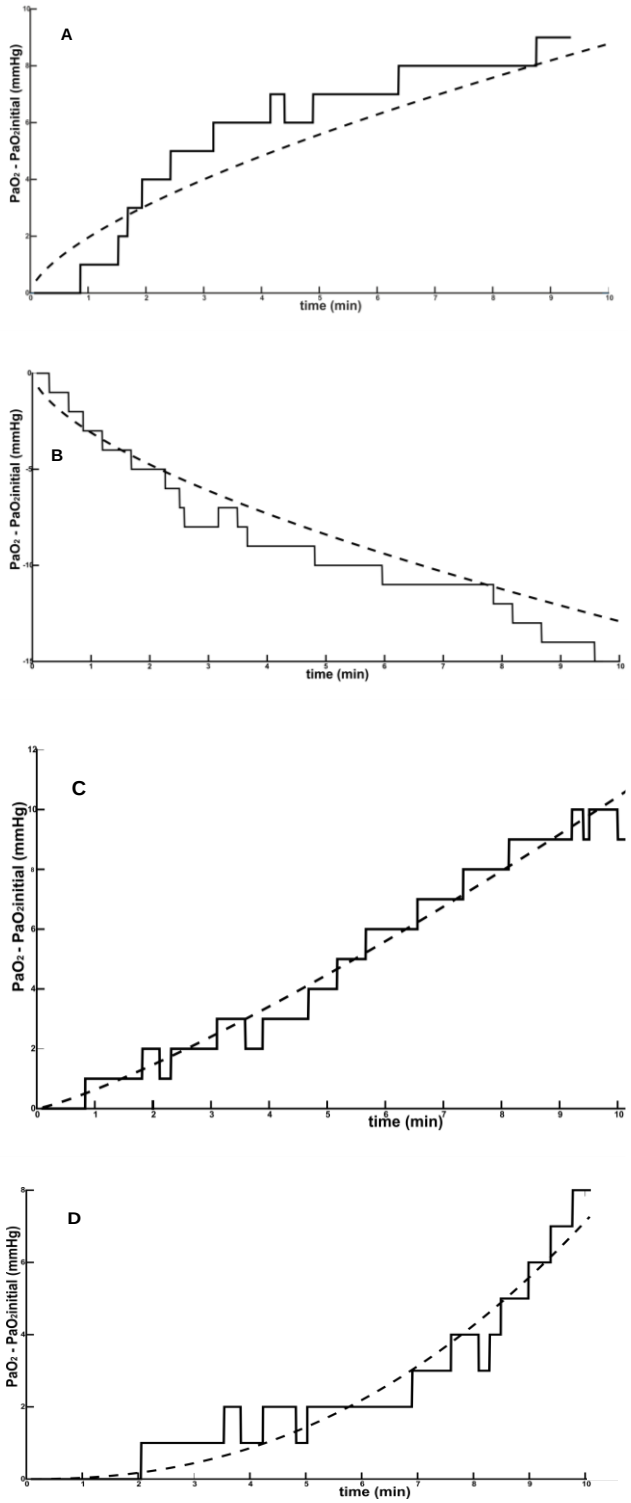

Fig. 3 Representative shapes followed by PaO_2 during a single CDP steps. Continuous line is the measured PaO_2 during one single CDP step, dotted line is the fitting model. For values of PaO_2 in the CDP step considered, its initial value was subtracted. Values of model parameters: *A)* a =1.95 and 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.

Fig. 5 shows values of exponents *b* respect to CDP (calculated as an average during the single CDP step) during the ascending (upper panel) and descending (bottom panel) CDP steps. It is possible to notice that values of exponents *b* are not related with the CDP steps. The positive values of exponents *b* refer to rising of PaO_2, whereas those negative to decrease of PaO_2.

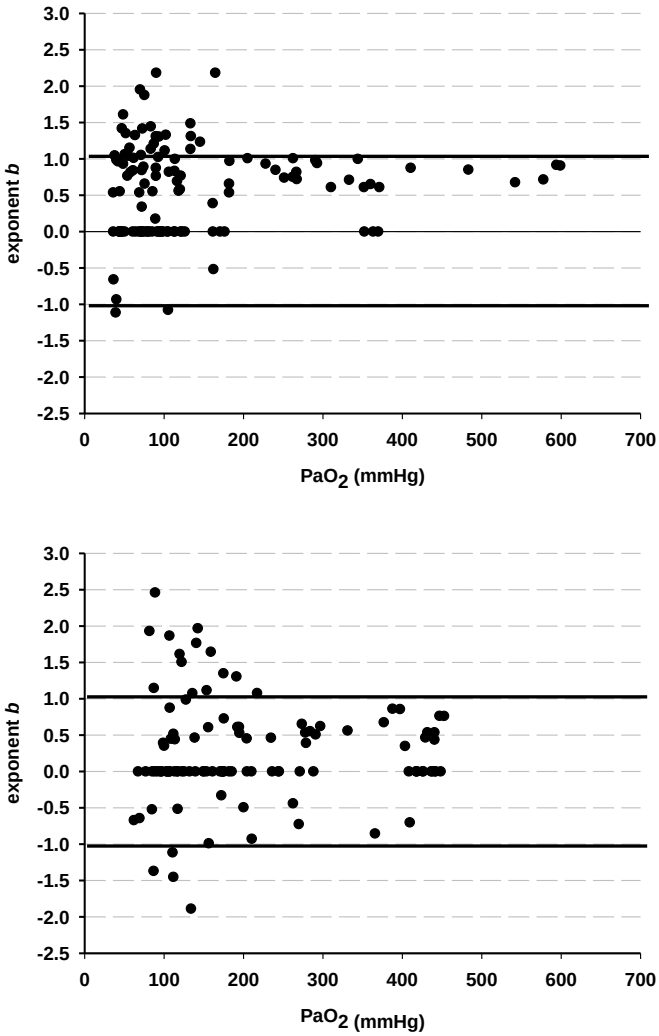

Fig. 4 Values of exponents *b* in relation with the average value of PaO_2 calculated for each ascending (upper panel) and descending (bottom panel) CDP steps. The black lines underline the upper and lower limit for a root function (b= 0 ÷ 1). For values of PaO_2 > 200 mmHg exponents b=0 ÷ 1.

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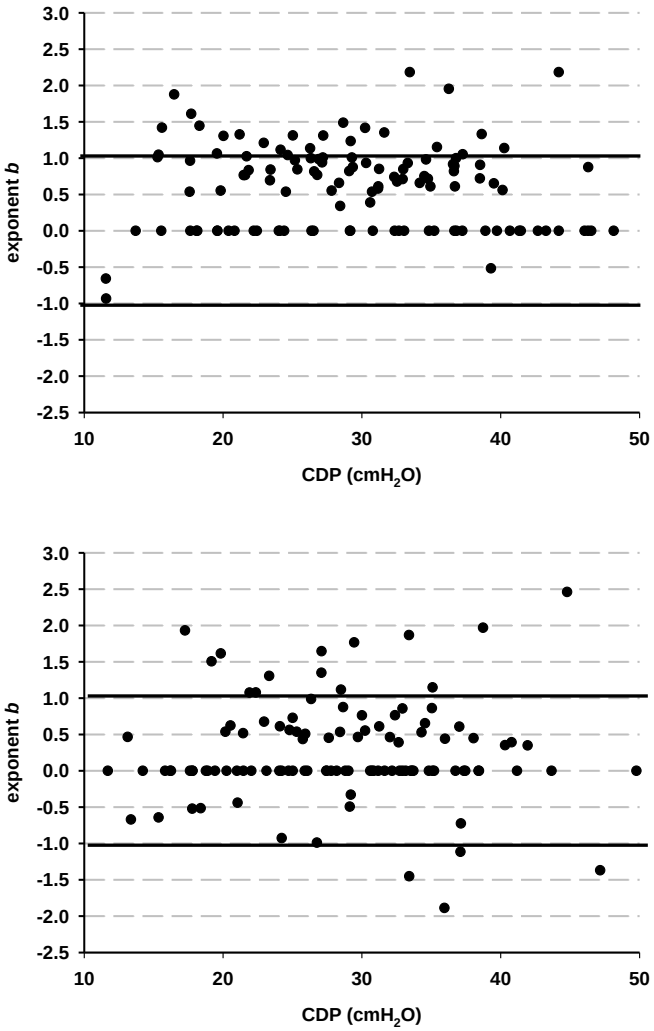

Fig. 5 Values of exponent *b* in relation with the continuous distending pressure CDP calculated for each ascending (upper panel) and descending (bottom panel) CDP steps. The black lines underline the upper and lower limit for a root function (b=0 ÷ 1).

IV. DISCUSSION

The main findings of this study are: *a)* during both the ascending and the descending of CDP steps, the PaO_2 course follows several shapes that can modelled mainly by the following functions: constant, root, linear and quadratic; *b)* for values of PaO_2<200mmHg the course of PaO_2 follows a shape can be modelled by a root function, but also by linear and/or quadratic functions; *c)* for values of PaO_2>200mmHg the course of PaO_2 follows a shape can be modelled exclusively by a root function; *d)* it is not possible to determine a relationship between the shape of PaO_2 response and the values of CDP.

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 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.

There is no relation between the shape of the course of PaO_2 and CDP level. The continuous distending pressure does not affect the response of organism in terms of PaO_2 shape change. 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.

V. CONCLUSIONS

There is no relation in the CDP level and shape of PaO_2 response to the sudden change in CDP during high frequency oscillatory ventilation in animal model of ARDS.

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