Continuous distending pressure effects on variables contributing to oxygenation in healthy and ARDS model pigs during HFOV

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Abstract. **Introduction.** High frequency oscillatory ventilation (HFOV) is an alternative form of mechanical ventilation. HFOV has been shown to provide adequate ventilation and oxygenation in acute respiratory distress syndrome (ARDS) patients and may represent an effective lung-protective ventilation in patients where conventional ventilation is failing. The aim of this study is to evaluate effects of continuous distending pressure (CDP) on variables that contribute to the oxygenation in healthy and ARDS lung model pigs. **Methods.** In order to simulate a lung disease, lung injury was induced by lavage with normal saline with detergent in three pigs. HFOV ventilation was applied before and after the lung lavage. CDP was stepwise increased by 2 cmH_2O, until the maximum CDP (before the lung lavage 32 cmH_2O and after the lung lavage 42 cmH_2O) and then it was stepwise deceased by 2 cmH_2O to the initial value. In this paper we analyzed the following parameters acquired during our experiments: partial pressure of oxygen in arterial blood (PaO_2), cardiac output (CO) and mixed venous blood oxygen saturation (SvO_2). In order to find how both PaO_2 and CO affected SvO_2 during the increase of CDP before and after lavage, a nonlinear regression fitting of the response in SvO_2 on the predictors (PaO_2 and CO) was implemented. **Results.** Before the lavage, with increasing of CDP, PaO_2 remained constant, CO strongly decreased and SvO_2 slightly decreased. After the lavage, with increasing of CDP, PaO_2 strongly increased, CO decreased and SvO_2 increased. So, development of SvO_2 followed the PaO_2 and CO trends. Changes in PaO_2 and CO occur at decisive CDP step and it was much higher after the lung lavage compared to the healthy lungs. The implemented nonlinear model gives a good goodness of fitting in all three pigs. The values of PaO_2 and CO estimated coefficients changed at the same decisive step of CDP identified by the trends. Also the algorithm identified a CDP step much higher after the lung lavage. **Conclusions**. From these preliminary results, it is possible to identify a certain level of CDP (higher in ARDS model pigs) at which the contribution of PaO_2 and CO to SvO_2 course changes their weights. Above this value, PaO_2 plays a major role in SvO_2 developments. This is in concordance with the clinical experience that HFOV is suitable for patient with more severe lung diseases when much higher CDP levels are required to assure an adequate oxygenation.
Keywords: high frequency oscillatory ventilation, HFOV, continuous distending pressure, ARDS, oxygenation.
PACS: 87.19.ug Heart and lung dynamics

INTRODUCTION

Mechanical ventilation (MV) is an effective technique for the management of patients with respiratory insufficiency or failure. Nevertheless, numerous studies have shown that MV itself can initiate as well as exacerbate lung injury and negatively affect other body organs[1,2]. This is known as ventilator-induced lung injury, which is the major cause of still persisting high mortality during MV. High frequency oscillatory ventilation (HFOV) is an alternative form of MV that can be delivered on critical care units. Unlike MV, HFOV relies on the rapid delivery of tidal volumes that are smaller than dead space (around 1-2 ml/kg), preventing volutrauma caused by alveolar over-distension. HFOV achieves CO_2 clearance without the large cyclical pressure changes required during MV, preventing atelectotrauma associated with cyclical alveolar collapse and reopening. HFOV delivers pressure oscillations of 3–15 Hz around a constant relatively high continuous distending pressure (CDP, i.e. mean airway pressure during HFOV) improving oxygenation via improved alveolar recruitment. HFOV has been successfully used in neonates and paediatrics. HFOV has been shown to provide adequate ventilation and oxygenation in acute respiratory distress syndrome (ARDS) patients and may represent an efficient lung-protective ventilation in patients where MV is failing[3,4].

The aim of this work is to analyze effects of continuous distending pressure (CDP) on variables contributing to the body oxygenation in order to explain different responses and tolerance to the CDP levels in healthy and ARDS lung model in pigs.

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MATERIAL AND METHOS

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 laboratory in accordance with Act No. 246/1992 Coll., on the protection of animals against cruelty.
Three 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 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 (CVP, *v. femoralis*) and arterial blood pressure (ABP, *a. femoralis*) monitoring was performed. Cardiac output (CO), mixed venous blood oxygen saturation (SvO_2) and pulmonary artery pressure (PAP) 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 f_s=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). Initial setting was as follows: initial CDP=8-10 cmH_2O, proximal pressure amplitude ΔP was set to maintain normocapnia, oscillatory frequency 5 Hz, inspiration/expiration ratio 1:1, fresh gas flow 40 L/min, and F_IO_2=0.21. Every 10 minutes, CDP was stepwise increased by 2 cmH_2O (rising steps, RS), until the maximum CDP (32 cmH_2O, maximum steps, MS) was reached. Then, CDP was stepwise deceased by 2 cmH_2O (decreasing steps, DS) to its initial value. Then, animals were switched back to CV. 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 F_IO_2=0.1. The same stepwise increase and decrease in CDP was performed; the initial CDP level was 10 cmH_2O, but when an animal did not tolerate low CDP levels after the lung lavage, we increased CDP rapidly in order to prevent further deterioration in severe hypoxia. The maximum CDP was 42 cmH_2O.

Data analysis

A MATLAB environment was used for data processing (MATLAB 7.04, The Mathworks, Natick, USA). All data considered (CO, SvO_2, PaO_2 and CDP) were resampled at f_s=250 Hz and noise was removed using a low-pass filter. In order to find how both PaO_2 and CO affected SvO_2 during the RS till MS of CDP before and after the lavage, a nonlinear regression fitting of the response in SvO_2 on the predictors (PaO_2 and CO) was implemented. PaO_2 and CO coefficients were assessed using iterative least squares estimation using the whole recorded RS signals and then in the moving windows 30 min long.

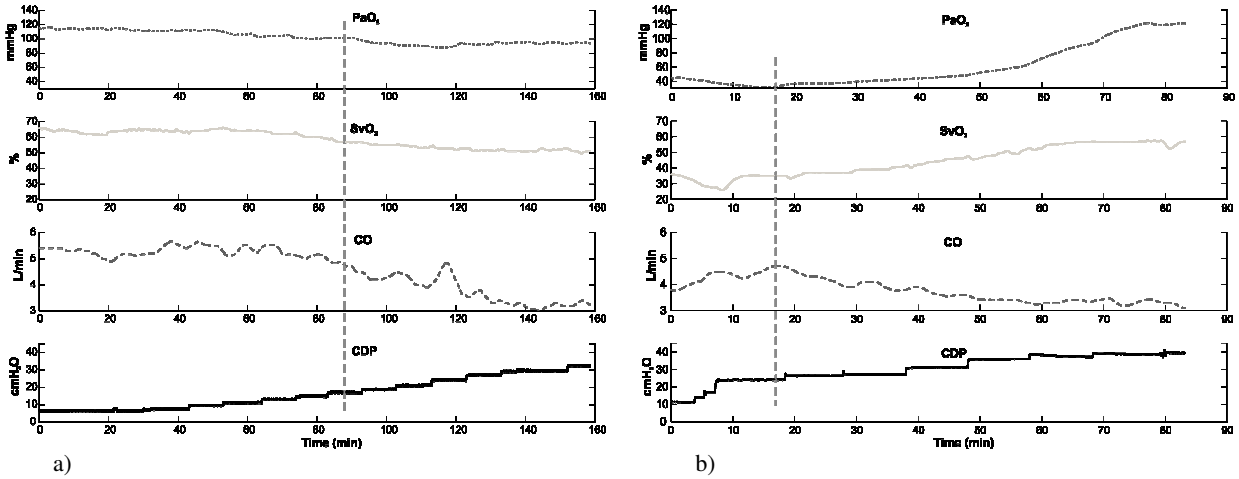
Statistical analysis

To test the goodness of fit, r^2 and mean square error (MSE) were evaluated. The r^2 values were determined by using the equation $1-(SS_{residual}/SS_{total})$, where $SS_{residual}$ is the sum of squares of the residuals and SS_{total} is the sum of square between the data points and their mean square. Paired T-test was used for comparison between the CDP values before and after the lung lavage. Data are expressed as mean ±standard deviation (SD).

RESULTS

In Figure 1, representative trends of PaO_2, SvO_2 and CO are shown during the RS till the MS of CDP before (a) and after (b) the lung lavage. Before the lavage, in all 3 pigs, with increasing of CDP, PaO_2 remains quite constant

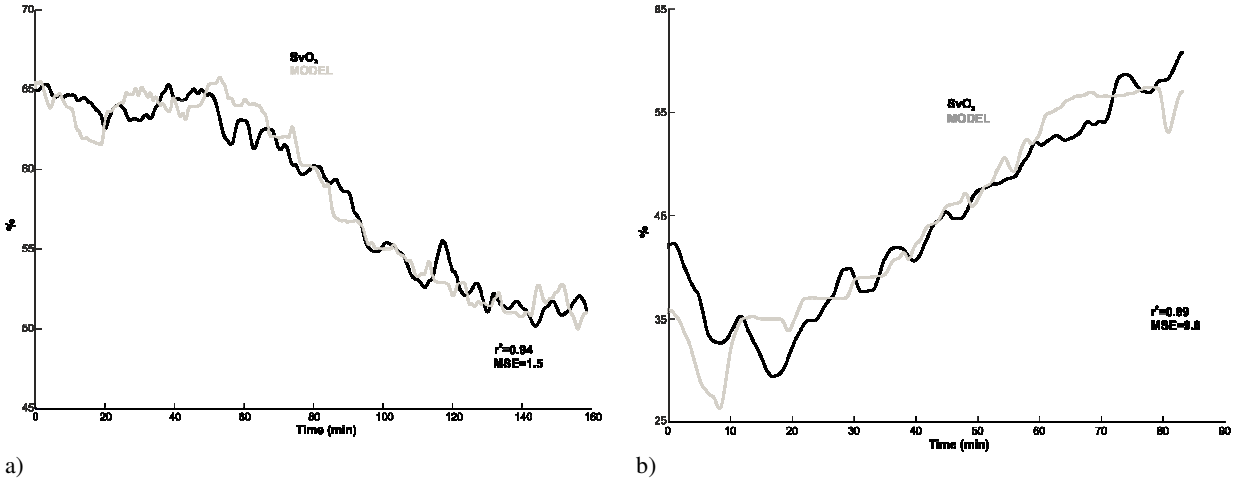
(mean value 94.2±7.2 mmHg, range 117÷77 mmHg), CO strongly decreases (4.5 ±0.2 L/min, range 5.7÷ 3.4 L/min) whereas SvO_2 slightly decreases (mean value 71.8 ±13.4%, range 88÷49%).
After the lung lavage, with increasing CDP, PaO_2 strongly increases (mean value 81.8±30.8 mmHg, range 192÷32 mmHg), CO slightly decreases (mean values 4.2±0.6 L/min, range 7.0÷3.1 L/min) and SvO_2 slightly increases (mean value 67.4±22.2% range 93÷26%). The vertical line underlines the decisive CDP step at which PaO_2, SvO_2 and CO started to change. In all cases, the decisive CDP was much higher after the lung lavage compared to the healthy lungs (p=0.04) (see Table 1). Trends in Figure 1 show how SvO_2 follows the behavior of both PaO_2 and CO.



a) b)

FIGURE 1. Representative trends in one pig of arterial partial pressure of oxygen (PaO_2), mixed venous blood oxygen saturation (SvO_2) and cardiac output (CO) during rising step of CDP, before (a) and after (b) the lung lavage. The dotted vertical line underlines the decisive CDP step at which PaO_2, SvO_2 and CO started to change.

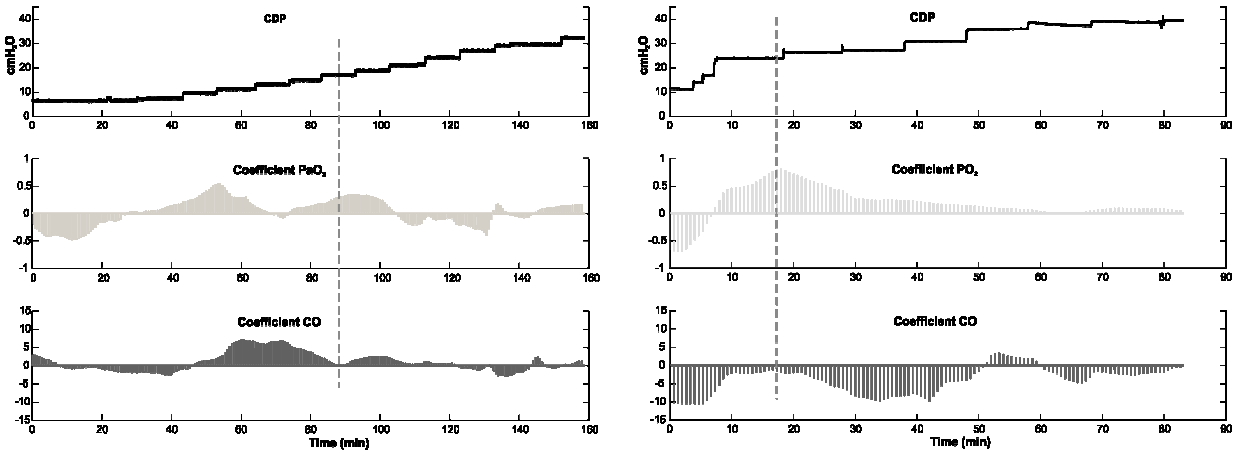
For this reason, we have implemented a nonlinear regression model of SvO_2 using PaO_2 and CO as predictors. We tested this model on all 3 pigs, before and after the lung lavage, finding a good fitting for each pig (*pig1*: before lung lavage r^2=0.45 MSE=0.79, after lung lavage r^2=0.73 MSE=4.6; *pig2*: before lung lavage r^2=0.83 MSE=5.1, after lung lavage r^2=0.64 MSE=1.30; *pig3*: before lung lavage r^2=0.94 MSE=0.94, after lung lavage r^2=0.89 MSE=9.8). Figure 2 shows the fitting model (gray line) and real data of SvO_2 (black line) in over the whole RS manuever before (a) and after (b) the lung lavage in one representative pig.



a) b)

FIGURE 2. Mixed venous blood oxygen saturation (SvO_2) (black line) and model (gray line) in whole recorded signal during rising CDP steps in one representative pig before (a) and after (b) the lung lavage.

Figure 3 shows the values of PaO_2 (middle panel) and CO (lower panel) predictor coefficients during the RS of CDP (upper panel) calculated over 30 min long moving window before (a) and after (b) the lung lavage. It is important to note that the values of PaO_2 coefficients are almost equal to zero and they increase their values when the CO coefficients decrease (this point is underlined by a vertical line). The algorithm identifies the same decisive step of CDP as identified from the trends in Figure 1. With this analysis, the decisive CDP was much higher after the lung lavage (p= 0.01) (see Table 1).



a) b)

FIGURE 3. Coefficient of partial pressure of oxygen (PaO_2) and cardiac output (CO) during rising steps of CDP in one representative pig before (a) and after (b) the lung lavage. The dotted vertical line underlines the decisive CDP step at which PaO_2 coefficients increase its value and CO coefficients decrease. This happens at the same decisive CDP found with analysis of trends shown in Figure 1.

TABLE 1: Values of decisive CDP calculated from trends of PaO_2, CO and SvO_2 and from nonlinear model (before versus after the lung lavage, *p<0.05)

	Decisive CDP (cmH_2O) in Trends		**Decisive CDP (cmH_2O) in Model**	
	Before lavage	**After lavage**	**Before lavage**	**After lavage**
pig #1	20.7	28.3	19.9	28.5
pig #2	17.1	21.3	15.6	21.6
pig #3	15.4	24.1	16.9	24.0
mean±SD	17.7±2.7	24.6±3.5*	17.5±2.2	24.7± 3.5*

CONCLUSIONS

After the lung lavage as a model of ARDS, pigs required a much higher CDP during HFOV to maintain an adequate oxygenation. It is possible to identify a certain level of CDP at which the contribution of PaO_2 and CO to SvO_2 development changes their weights. Above this value, PaO_2 plays a major role in SvO_2 course. Before the lung lavage, SvO_2 slightly decreases even though CO decreases rapidly while PaO_2 remains almost constant. On the other hand, after the lung lavage SvO_2 increases, despite decrease in CO, because PaO_2 increases rapidly.
This is in concordance with the clinical experience that HFOV is suitable for patient with more severe lung diseases when much higher CDP levels are required to assure an adequate oxygenation.

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