Normocapnic High Frequency Oscillatory Hyperventilation Increases Oxygenation in Pigs

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Summary

High frequency oscillatory ventilation (HFOV), contrary to conventional ventilation, enables a safe increase in tidal volume (V_T) without endangering alveoli by volutrauma or barotrauma. The aim of the study is to introduce the concept of normocapnic high frequency oscillatory hyperventilation and to assess its effect upon oxygen gain under experimental conditions. Laboratory pigs (n=9) were investigated under total intravenous anesthesia in three phases. *Phase 1*: Initial volume controlled HFOV period. *Phase 2*: Hyperventilation – V_T was increased by (46 ± 12) % when compared to normocapnic V_T during phase 1. All other ventilatory parameters were unchanged. A significant increase in PaO_2 (by 3.75 ± 0.52 kPa, $p<0.001$) and decrease in $PaCO_2$ (by -2.05 ± 0.31 kPa, $p<0.001$) were obtained. *Phase 3*: Normocapnia during hyperventilation was achieved by an iterative increase in the CO_2 fraction in the inspiratory gas by a CO_2 admixture. All ventilatory parameters were unchanged. A significant increase in PaO_2 (by 3.79 ± 0.73 kPa, $p<0.001$), similar to that which was observed in phase 2, was preserved in phase 3 whereas normocapnia was fully re-established. The concept of high frequency normocapnic hyperventilation offers a lung protective strategy that significantly improves oxygenation whilst preserving normocapnia.

Key words

Hyperventilation • Normocapnia • Oxygenation • High frequency ventilation

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Introduction

Tidal volume (V_T) and rate of ventilation (f) are considered to be the main parameters that determine arterial CO_2 partial pressure ($PaCO_2$) throughout spontaneous breathing and also during controlled mechanical ventilation (CMV). Mean airway pressure (MAP) is one of the main parameters that determine arterial oxygen partial pressure (PaO_2). However, it should be noted that the tidal volume plays a specific role in oxygenation control, as it is one of the parameters that determine alveolar ventilation ($\dot{V}_A$). Insufficient alveolar ventilation leads to a drop in the oxygen partial pressure in the alveolar space (P_AO_2); this occurs regardless of the mean airway pressure. On the other hand, hyperventilation induced by an increase in V_T can cause an increase in P_AO_2 and consequently this leads to an increase in the oxygen pressure gradient across the alveolo-capillary membrane. It is this gradient which controls the diffusion of oxygen. The increase in alveolar oxygen concentration induced by the initiation of hyperventilation during the initial normocapnia leads to hypocapnia, i.e. to a decrease in $PaCO_2$. This effect can be prevented by admixing CO_2 into the inspiratory gas. This procedure defines "normocapnic hyperventilation", which could be beneficial during high frequency ventilation strategies. Low tidal volumes (V_T) of 1 to 3 ml/kg b.w. (Pachl *et al.* 2006, McLuckie 2004, Zimová-Herknerová *et al.* 2006) that are applied during HFOV allow a safe increase of V_T without increasing the risk of ventilator induced lung injury (VILI). The increased V_T remains significantly lower than the currently used values

of V_T which occur during conventional mechanical ventilation. Hypocapnia during hyperventilation may be prevented by controlled carbon dioxide supplementation into the inspiratory gas.

The aim of this study is to specify the effect of normocapnic hyperventilation during HFOV upon oxygen gain under experimental conditions.

Methods

The study was approved by the Committee for Protection of Animals Against Abuse of the Institute of Clinical and Experimental Medicine, Prague. It was conducted at the accredited experimental laboratory of the Institute of Clinical and Experimental Medicine, Prague, adhering to the valid regulations of the Czech Republic and European Guidelines on Laboratory Animal Care.

Nine healthy laboratory pigs (weight 30-42 kg) were included into the study. General anesthesia was maintained by combination of a continuous drip of remifentanil (Ultiva, GlaxoSmithKline) 1 mg/kg/min, propofol (Diprivan, AstraZeneca) 6 mg/kg/hour and midazolam (Dormicum, Roche) 1 mg/kg/hour. Neuromuscular blockade was maintained by vecuronium (Norcuron, Organon) 0.8 mg/kg/min.

Venous access was assured through 2 peripheral veins on both ears. The carotid artery was cannulated in the supine position to enable systemic blood pressure measurement and arterial blood sampling. A Swan-Ganz thermodilution catheter was introduced into the pulmonary artery through the internal jugular vein.

Haemodynamic parameters: mean arterial pressure (APmean), systolic pressure (APsyst), central venous pressure (CVP), pulmonary capillary wedged pressure (PCWP), cardiac output (CO), pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were recorded by a BSS 9800 K monitor (Nihon Kohden). Tracheal tube No. 8.0 (Portex) was introduced via tracheostomy. The tracheal tube contained an integrated sampling channel in its wall which was used to obtain the HFOV pressure parameters. Arterial blood gases were sampled and analyzed (ABL 4, Radiometer Copenhagen, Denmark) 15 minutes after any change in ventilatory regimen. A constant body temperature of 37 °C was maintained by a heated mattress and an external radiator.

A custom-made high frequency ventilator was used throughout the experiment. Scheme of the ventilator is depicted in Figure 1. The ventilator consists of a nozzle permanently connected to an adjustable source of high pressure inspiratory gas. The nozzle opens into an intake channel that is periodically occluded and released at its opposite side by a flexible membrane. The membrane is supported by a metal spring and is controlled by pressure changes generated by a pneumatic pulse generator. During inspiratory phase (Figure 1A), the pneumatic pulse generator delivers a positive pressure pulse into the chamber behind the membrane. As a result, the membrane seals the intake channel of the nozzle. In this case, the inspiratory gas from the nozzle flows through the flow and pressure sensors and ETC port into a ventilated animal. Gas in the high pressure gas inlet in front of the nozzle has a relatively high and constant
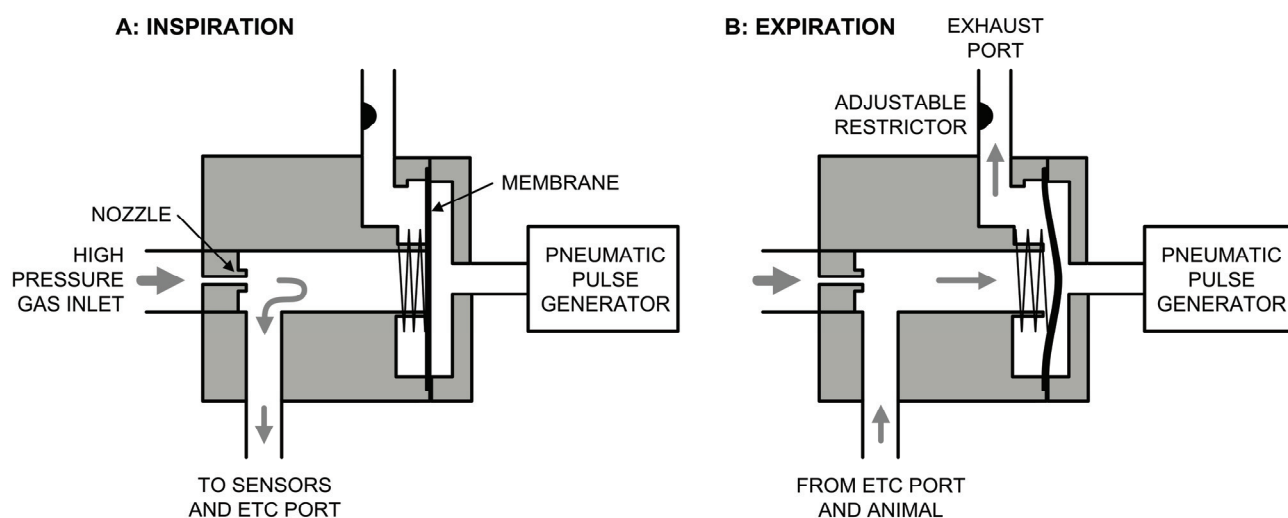

Fig. 1. Functional scheme of the ventilator. **A** – Condition and gas flow during inspiratory phase. **B** – Condition and gas flow during expiratory phase.
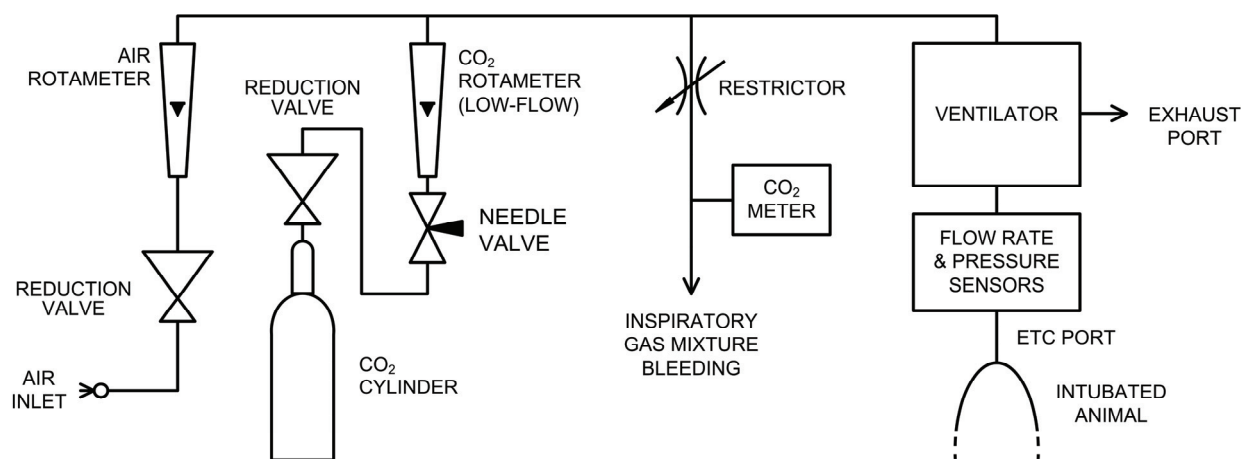
Fig. 2. Schematic drawing of the experimental setup during the study.

value of pressure. As the nozzle has a very small aperture representing a high pneumatic resistance, the combination of the high pressure gas source with the pneumatic resistance constitutes a source of a constant gas flow. Therefore, this ventilator could be considered a volume-controlled high frequency ventilator, as the tidal volume is an accurately adjustable parameter. The generated flow rate and duration of inspirium directly determine the tidal volume delivered into the respiratory system of an animal.

Active expirium is assured by a jet-like system equipped with a PEEP (positive end-expiratory pressure) control valve. During expirium, the pneumatic pulse generator provides zero pressure and the membrane is deflected from its straight position by the metal spring (Figure 1B). As a consequence, the nozzle intake channel is opened directly into the exhaust port. High-velocity gas from the nozzle generates a negative pressure in the intake channel. As the ventilated animal is connected to the side of this channel, the negative pressure assures the active expirium. Gas from the nozzle, enriched with the gas expired from the animal, flows out of the ventilator through the exhaust port equipped with a pneumatic restrictor representing an adjustable flow resistance to the gas flow. The pressure developed on the restrictor is used for adjustment of PEEP. The ventilator is controlled by a microelectronic system which comprises all the standard security elements and alarms. The ventilatory frequency can be adjusted from 2 to 25 Hz and relative inspiratory time T_I/T from 20 to 80 %.

The overall experimental setup is presented in Fig. 2. Animals were ventilated either with pure air or with air enriched with CO_2. A regulated source of CO_2

flow for the defined admixture of CO_2 into the inspiratory air was constructed for hypocapnia compensation. The CO_2 generator consists of an adjustable high-pressure source of CO_2 from a cylinder and a high-resistance pneumatic resistor. A pressure-flow curve was used for the calculation of the CO_2 input pressure that was necessary to generate the required CO_2 flow rate. The actual flow rate was checked by a low-flow rotameter calibrated for carbon dioxide. In order to produce the inspiratory gas mixture, the delivered CO_2 was mixed with medicinal quality air, flowing from a pressure reduction valve and an air rotameter. Before entering the ventilator through the high pressure gas inlet, a pneumatic restrictor with a very high airflow resistance was connected to the inspiratory gas line providing a source of the inspiratory gas mixture at ambient pressure which is suitable for CO_2 concentration measurement (Anagas CD 98, Environmental Instruments, U.K.).

A special monitoring system for measurement of tidal volume, pressure values and mechanical parameters of the respiratory system during HFOV (Pachl *et al.* 2006) was connected between the ventilator and the tracheal tube of the ventilated animal. This system was used for independent confirmation of the adjusted HFO ventilatory parameters that were controlled by the HFO ventilator.

The protocol of the animal study was divided into three phases:

Phase 1 – normocapnic ventilation. HFOV with ventilatory frequency $f = 5$ Hz (300 min^{-1}), relative inspiratory time $T_i/T = 50$ %, mean airway pressure MAP = 0.8 kPa and initial tidal volume $V_T = 2$ ml/kg was started. Normocapnia with the target value of

$PaCO_2 = 5.33$ kPa (40 Torr) was achieved by iterative changes of V_T. Values of PaO_2, $PaCO_2$ and tidal volume V_T during phase 1 were considered as the reference values for the next phases of the experiment and for the evaluation of results.

Phase 2 – hyperventilation. Hyperventilation was achieved by V_T increase of 45 % when compared to the normocapnic V_T from phase 1. Mean airway pressure (MAP) as well as other ventilatory parameters were kept constant at the same values as in phase 1. Arterial blood sampling and analysis of PaO_2 and $PaCO_2$ were conducted 15 minutes after the increase of V_T.

Phase 3 – normocapnic hyperventilation. Normocapnia with preserved increase in V_T from phase 2 was achieved by regulation of the CO_2 flow rate, i.e. by iterative settings of the CO_2 fraction in the inspiratory gas, in order to restore the $PaCO_2$ values from phase 1. Mean airway pressure and other ventilatory parameters were kept constant at the same level as in phases 1 and 2. Arterial blood sampling and analysis of PaO_2 and $PaCO_2$ were conducted 15 minutes after each change in CO_2 flow rate.

Results of the experiment are presented as mean value ± standard deviation. The assessment of the statistical significance of the average change in values was conducted by the two-tail Student's t-test, always against the normocapnic values achieved in the first phase of the experiment. The symbol p stands for the statistical significance level. Values of $p < 0.01$ were considered to be statistically significant.

Results

All nine animals included in the study were subjected to all three phases of the experiment in accordance to the presented study design.

In the first phase of the study, normocapnia ($PaCO_2 = 5.48 \pm 0.35$ kPa, $PaO_2 = 11.3 \pm 1.6$ kPa) was achieved by iterative changes of V_T to the final normocapnic value of $V_T = 1.9 \pm 0.3$ ml/kg. Values of PaO_2, $PaCO_2$ and V_T during phase 1 were considered as reference values for the remaining phases (2 and 3) of the experiment and used for the subsequent analysis in the measured changes of the arterial blood gases. The monitored haemodynamic parameters were: mean arterial pressure APmean $= 86 \pm 18$ mm Hg, systolic arterial pressure APsyst $= 109 \pm 19$ mm Hg, central venous pressure CVP $= 7.4 \pm 2.6$ mm Hg, pulmonary capillary wedged pressure PCWP $= 7.4 \pm 1.8$ mm Hg, cardiac

output CO $= 2.3 \pm 0.68$ l/min, pulmonary vascular resistance PVR $= 408 \pm 154$ dyne·s/cm^5 and systemic vascular resistance SVR $= 2890 \pm 240$ dyne·s/cm^5.
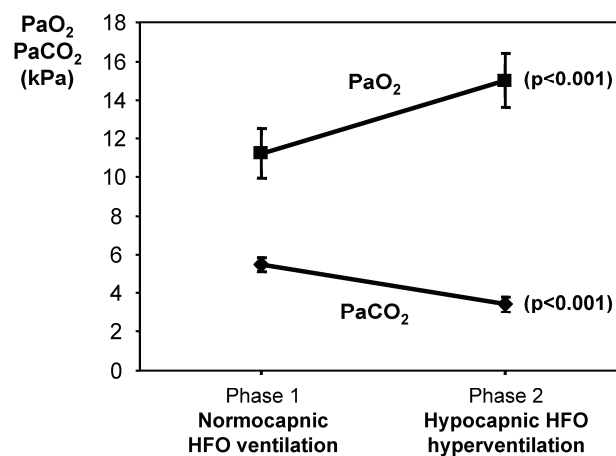

Fig. 3. Changes in PaO_2 and $PaCO_2$ after the introduction of HFO hyperventilation with an increased tidal volume compared to the normocapnic ventilation values established in the initial phase of the experiment.
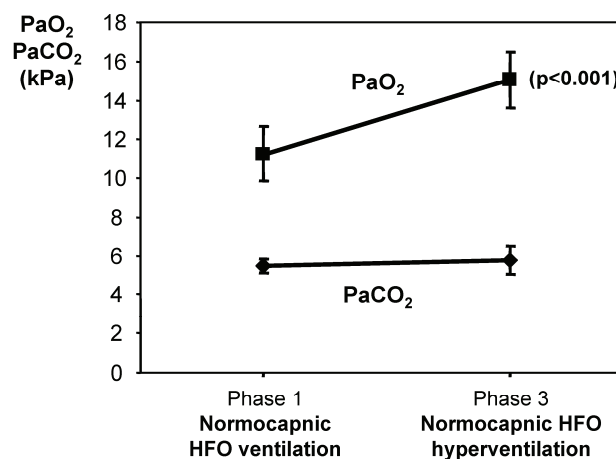

Fig. 4. Changes in PaO_2 and $PaCO_2$ after the introduction of normocapnic HFO hyperventilation with an increased tidal volume and supplementary carbon dioxide administration compared to the normocapnic ventilation values established in the initial phase of the experiment.

In the second phase, characterized by uncompensated (hypocapnic) hyperventilation, a statistically significant ($p < 0.001$) increase in PaO_2 (of 3.75 ± 0.52 kPa) was obtained. This was accompanied with a significant ($p < 0.001$) decrease in $PaCO_2$ (of -2.05 ± 0.31 kPa) (Figure 3). The tidal volume during HFO hyperventilation was increased by (46 ± 12) %.

During the third phase, the hyperventilation with the increased tidal volume was preserved as in phase 2

but the induced hypocapnia was compensated ($PaCO_2 = 5.76\pm0.69$ kPa) by adding carbon dioxide into the inspiratory gas. Despite the hypocapnia compensation, the oxygen gain in phase 3 (PaO_2 increased by 3.79 ± 0.73 Torr, $p<0.001$) was similar to the oxygen gain in phase 2 (Figure 4). The flow rate of carbon dioxide, as a part of the inspiratory gas, was within the range 0.9 to 1.4 l/min; this flow rate assured the full compensation of hypocapnia.

Only the desired alterations in V_T were observed throughout the experiment; other ventilatory parameters such as mean airway pressure (MAP), ventilatory frequency (f), F_IO_2 and Ti/T ratio did not change significantly. The values of haemodynamic parameters: mean arterial pressure (APmean), systolic pressure (APsyst), central venous pressure (CVP), pulmonary capillary wedged pressure (PCWP), cardiac output (CO), pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were not seen to fluctuate significantly throughout the experiment either.

Discussion

The results of the presented experimental study show that high frequency oscillatory hyperventilation causes a significant oxygen gain of over 33 % when a very low tidal volume is used. The final tidal volume used during the hyperventilation was less than 3 ml/kg. The oxygen gain of over 33 % was preserved even when the hypocapnia was fully re-established to the original normocapnic value by admixing carbon dioxide into the inspiratory gas.

The effect of increased tidal volume, and therefore increased minute ventilation, upon carbon dioxide clearance is well known both within conventional mechanical ventilation and high frequency oscillatory ventilation. The effect of hyperventilation upon CO_2 elimination is expected to be stronger than its effect upon oxygenation. Throughout our experiment, the same effects were observed. Even though the absolute value of PaO_2 gain was higher (3.75 ± 0.52 kPa) than the absolute decrease in $PaCO_2$ (2.05 ± 0.31 kPa), the relative increase in PaO_2 was lower (33 %) than the relative decrease in $PaCO_2$ (37 %). The relatively high effect of hyperventilation upon oxygenation during HFOV can be explained by different mechanisms of gas exchange taking place during HFOV than those acting during conventional ventilation. Effect of V_T upon alveolar ventilation $\dot{V}_A$ during conventional ventilation is often described by the conventional

ventilation equation $\dot{V}_A = (V_T - V_D) \cdot f$, which was derived under the simplified condition that the gas exchange is assured solely by bulk gas flow in the respiratory system. Bulk flow is the predominant mechanism of gas exchange during conventional ventilation, but it cannot be significant during high frequency ventilation where tidal volumes are comparable or even less then the anatomical dead space volume. In this case, other more complex gas exchange mechanisms take place in gas exchange (Pillow 2005). A simple universal equation similar to the conventional ventilation equation cannot be derived easily. The existing ventilation equations valid for HFOV were derived either theoretically, e.g. Brychta's eucapnic ventilation equation (Brychta and Javorka 1990), or empirically (Venegas *et al.* 1986) based on results of numerous animal studies. Regardless of the origin of the ventilation equation, a strong effect of dead space volume on gas exchange is expressed in all of these equations in the form of V_T/V_D ratio. When considering the fact that tidal volume during high frequency oscillatory ventilation is similar to or less than the anatomical dead space volume V_D, it may be expected that the tidal volume has a significant effect not only on carbon dioxide elimination, but also on oxygenation. This idea is in concordance with our clinical experience with HFOV application in adults and supports the presumption that tidal volume significantly affects the alveolar gas exchange with a consequent higher sensitivity in PaO_2 to changes in tidal volume when compared to conventional mechanical ventilation. This presumption was also tested prior to the study using a gas exchange model (Kopelent *et al.* 2004). The model performs a numerical solution of the convection-diffusion equation for the oxygen transport in the respiratory system and confirms the higher effect of tidal volume upon the alveolar gas composition during HFOV when compared to conventional mechanical ventilation.

During conventional mechanical ventilation, positive end-expiratory pressure (PEEP) is applied to assure alveolar stability. PEEP helps to maintain a stable lung surface for gas exchange and to prevent dangerous repetitive closure and reopening of alveoli during each breath cycle that cause significant shear forces exerted to the alveolar walls. In HFOV, extremely small tidal volumes are used. These small tidal volumes cause significantly lower volume and pressure changes in the alveolar space. Therefore, mean airway pressure is the only parameter acting throughout the entire breath cycle that prevents both cyclic and permanent alveolar collapse.

In our study, MAP was kept constant assuring the same level of lung recruitment and a constant lung surface for gas exchange in all the three experimental phases. Furthermore, MAP directly affects partial pressure of oxygen in the alveolar space, P_AO_2, and hence MAP affects oxygenation. Keeping MAP constant within all the three phases of the experiment allows eliminating the effect of MAP upon the experimental study results. The other ventilatory parameters except for V_T, i.e. ventilatory frequency and F_IO_2, were kept constant during the whole experiment as well. There were no significant variations in haemodynamic parameters during the experiment. In our opinion the only explanation of the observed oxygen gain of more than 33 % is that hyperventilation positively influences the composition of the alveolar gas. Increased V_T causes an improvement of alveolar ventilation and consequently leads to an increase in the fresh air delivery into the alveolar space.

Admixing of small amount of CO_2 into the inspiratory gas decreases the fraction of oxygen in the inspiratory gas, F_IO_2, slightly. To evaluate this effect, the CO_2 flow rate should be compared with the minute ventilation. In phases 2 and 3, the ventilatory frequency was 5 Hz, i.e. 300 breaths per minute, and the average tidal volume was 100 ml (36 kg × 2.78 ml/kg), which yields a minute ventilation of 30 l/min. The average flow rate of CO_2 during the compensation of hypocapnia was 1.15 l/min which represents 3.8 % of the minute ventilation. The original fraction of air in the inspiratory gas was 100 % when CO_2 was not administered. It dropped to a value of 96.2 % during the phase of hypocapnia compensation when the flow rate of CO_2 represented 3.8 % of the minute ventilation. As a result, fraction of oxygen in the inspiratory gas decreased from its original value of 20.9 % to 20.1 % within the normocapnic hyperventilation. This calculated change in F_IO_2 is relatively small and is much less than the effects of hyperventilation upon oxygenation observed in this experimental study.

Normocapnic hyperventilation is a strategy that, besides increasing MAP and F_IO_2, can positively influence partial pressure of oxygen in the alveolar space. An increase in tidal volume during conventional ventilation can induce a dangerous excessive mechanical load on the lungs. It causes not only direct damage to the lung tissue, which is known as acute lung injury, but it also induces an inflammatory response and negatively affects performance of other healthy organs (Carney et al. 2005, Kobr et al. 2010). High frequency ventilation is a

ventilatory technique utilizing extremely low tidal volumes. The reduction of tidal volume belongs to the major principles of protective lung ventilation (Malhotra 2007, The Acute Respiratory Distress Syndrome Network 2000). According to the lung protective strategies, the target tidal volume in conventional mechanical ventilation is around 6 ml per kilogram of predicted body weight (Malhotra 2007), whereas tidal volumes used during HFOV are only 1-3 ml/kg. Therefore, alveolar ventilation can be improved considerably by the increase of V_T during HFOV; the increased V_T during high frequency hyperventilation will remain significantly lower than the current V_T used during conventional ventilation.

In many instances, applying the recommendations of lung protective ventilation may lead to an elevation of arterial carbon dioxide tension, referred to as permissive hypercapnia (Fan 2005). Although acute hypercapnic respiratory acidosis has many potential adverse effects, some evidence indicates that permissive hypercapnia is not only relatively benign (Laffey et al. 2004), but it may also be considered a therapeutic method (Chovanec et al. 2009) and is another central component of the current protective ventilatory strategies. To the contrary, hyperventilation leads to hypocapnia due to the increased alveolar ventilation. The admixture of carbon dioxide into the inspiratory gas may be used to regulate PaCO$_2$ to a level required according to the current protective ventilatory strategy. The disadvantage of this method is due to its relative complexity in comparison to solely HFOV. The requirement for specialized equipment that assures precise and stable carbon dioxide administration is another disadvantage of the method.

Conclusions

Normocapnic hyperventilation established during high frequency oscillatory ventilation leads to a significant improvement of oxygenation without negative effects associated with the increase in tidal volume or respiratory alkalosis. The oxygen gain can be explained by an increase in the partial pressure of oxygen in the alveolar gas due to increased alveolar ventilation. The admixture of CO_2 into the inspiratory gas provides an efficient tool for the re-establishment of normocapnia during hyperventilation, whereas the acquired oxygen gain is preserved. The concept of high frequency normocapnic hyperventilation may be used as a lung protective strategy significantly improving oxygenation.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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