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Initiation of high-frequency oscillatory ventilation and its effects upon cerebral circulation in pigs: an experimental study

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Background. Current practice at high-frequency oscillatory ventilation (HFOV) initiation is a stepwise increase of the constant applied airway pressure to achieve lung recruitment. We hypothesized that HFOV would lead to more adverse cerebral haemodynamics than does pressure controlled ventilation (PCV) in the presence of experimental intracranial hypertension (IH) and acute lung injury (ALI) in pigs with similar mean airway pressure settings.

Methods. In 12 anesthetized pigs (24–27 kg) with IH and ALI, mean airway pressure (P_{mean}) was increased (to 20, 25, 30 cm H_2O every 30 min), either with HFOV or with PCV. The order of the two ventilatory modes (cross-over) was randomized. Mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral blood flow (CBF) (fluorescent microspheres), cerebral metabolism, transpulmonary pressures (P_T), and blood gases were determined at each P_{mean} setting. Our end-points of interest related to the cerebral circulation were ICP, CPP and CBF.

Results. CBF and cerebral metabolism were unaffected but there were no differences between the values for HFOV and PCV. ICP increased slightly (HFOV median +1 mm Hg, $P<0.05$; PCV median +2 mm Hg, $P<0.05$). At P_{mean} setting of 30 cm H_2O, CPP decreased during HFOV (median −13 mm Hg, $P<0.05$) and PCV (median −17 mm Hg, $P<0.05$) paralleled by a decrease of MAP (HFOV median −11 mm Hg, $P<0.05$; PCV median −13 mm Hg, $P<0.05$). P_T increased (HFOV median +8 cm H_2O, $P<0.05$; PCV median +8 cm H_2O, $P<0.05$). Oxygenation improved and normocapnia maintained by HFOV and PCV. There were no differences between both ventilatory modes.

Conclusions. In animals with elevated ICP and ALI, both ventilatory modes had effects upon cerebral haemodynamics. The effects upon cerebral haemodynamics were dependent of the P_T level without differences between both ventilatory modes at similar P_{mean} settings. HFOV seems to be a possible alternative ventilatory strategy when MAP deterioration can be avoided.

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The ventilatory strategy to improve oxygenation in injured lungs includes recruitment of collapsed lung regions and maintenance of alveolar patency by means of increased airway pressures.[1] High-frequency oscillatory ventilation (HFOV) is a safe and effective technique in the treatment of patients' with acute respiratory distress syndrome (ARDS).[2–4] Atelectatic lung regions are reopened by continuous distending pressure (CDP) and superimposed pressure controlled oscillations provide alveolar gas exchange. Simultaneously, the applied oscillatory pressure amplitude (ΔP) surrounding CDP is damped during transmission to the alveolar level and results in very low tidal volumes (V_t) and low pressure changes, which reduce cyclic lung recruitment/derecruitment and lung overdistension.[5]

Despite a similar arithmetic mean airway pressure, the amplitude of pressure and volume excursions is substantially different between HFOV and CV. During CV, alveolar excursions occur around a greater gradient of pressures and volumes. In this context, haemodynamic effects of ventilation can be artificially grouped into interactions involving (i) lung inflation, where inspiration increases lung volume above end-expiratory volume, and (ii) positive-pressure ventilation increases intrathoracic pressure.[6] Depending on airway resistance and elastance of the respiratory system, high airway pressures elevates intrathoracic pressures and adverse haemodynamic effects occur. Inspiratory lung inflation can alter autonomic tone, pulmonary vascular resistance, ventricular filling by reduced venous return, and at high lung volumes interacts mechanically with the heart in the cardiac fossa to limit absolute cardiac volumes.[6 7]

Current practice of HFOV is an initial treatment protocol, which uses stepwise increases of CDP to identify recruitable lung compartments and to achieve optimal lung recruitment.[2–4] In a clinical scenario with elevated intracranial pressure (ICP) and acute lung injury (ALI), recruitment manoeuvres may lead to detrimental haemodynamic effects [hypotension, decreased cardiac output (CO), increased ICP] and increase the risk of secondary neuronal damage. We were concerned that HFOV would lead to more adverse cerebral haemodynamics than does PCV, and this was the hypothesis that we wished to test. Therefore, we (i) investigated the effect of a typical lung recruitment manoeuvre at initiation of HFOV (sequential increases of P_{mean} from 20 to 25 and to 30 cm H_2O) in the presence of experimental ALI and increased ICP upon cerebral haemodynamics and (ii) compared the effects of HFOV with effects of conventional pressure controlled ventilation (PCV) upon cerebral haemodynamics at similar mean airway pressures of 20, 25 and 30 mbar. Our cardinal measures of cerebral haemodynamics were ICP, CPP and cerebral blood flow (CBF).

Materials and methods

Animal preparation

The study protocol was approved by the institutional and state animal care committee and in accordance with the National Institutes of Health guidelines for the care and use of animals. Twelve pigs [median 25 (range 24–27) kg of body weight] were used. The animals were killed at the end of each experiment, according to the recommendations of the 'Report of the American Veterinary Medicine Association Panel on Euthanasia'. After premedication with azaperone the animals were anesthetized with fentanyl (Janssen-Cilag Pharmaceuticals, Neuss, Germany) 0.15 mg i.v., thiopentone (Altana Pharma, Konstanz, Germany) 10–15 mg kg^{-1} i.v., followed by a continuous infusion of fentanyl (5 μg kg^{-1} h^{-1}) and thiopentone (10 mg kg^{-1} h^{-1}). Neuromuscular block was achieved with repeated i.v. pancuronium bromide (0.1 mg kg^{-1}, Pancuronium Organon, Organon, Oberschleissheim, Germany). The trachea was intubated (inner diameter 8.0 mm) and the lung was mechanically ventilated in volume constant mode (Servo 900C, Siemens Elema, Solna, Sweden; $F_{I_{O_2}}$ 0.4, PEEP 5 cm H_2O, inspiratory to expiratory ratio 1:1, tidal volume (V_t) 12 ml kg^{-1}, ventillatory frequency (VF) was set to maintain normocapnia). Ringer's solution at a rate of 5 ml kg^{-1} h^{-1} was given throughout the experiment. The animals were instrumented with a left ventricular catheter (5F Sidewinder, Cordis, Germany), a central venous line (Cavafix MT, Braun Melsungen, Germany), an arterial catheter (18G arterial catheter, Arrow GmbH, Erding, Germany), an aortic catheter via the left axillary artery (Cavafix, Braun, Melsungen, Germany) and an arterial multiparameter sensor (Paratrend 7, Diametrics Medical Ltd, UK). The position of the left ventricular catheter was verified by typical waveforms. The femoral arterial catheter was used for continuous arterial blood pressure monitoring (S/5 Monitoring, Datex-Ohmeda, Duisburg, Germany), intermittent arterial blood gas analysis (ABL 500/OSM 3, Radiometer Copenhagen, Denmark) and measurement of arterial oxygen content (ABL 500/OSM 3, Radiometer Copenhagen, Denmark). Arterial blood gas results were used to calibrate the arterial multiparameter sensor. The animals were positioned in prone position and catheters were inserted into the right and left lateral cerebral ventricle. The left lateral cerebral ventricle catheter was connected to a fluid filled pressure transducer (referenced to the meatus acusticus externus) for ICP monitoring, and the right lateral cerebral ventricle catheter was connected to an infusion pump. An 18 G catheter was inserted into the superior sagittal sinus for determination of cerebrovenous haemoglobin, oxygen saturation and oxygen content (ABL 500/OSM 3, Radiometer Copenhagen, Denmark). Thereafter, the animals were repositioned to a supine position for the complete study protocol. Blood temperature was monitored via the arterial multiparameter sensor and actively maintained at 37–38°C using heating pads. For measurement of the oesophageal pressure a catheter with an inflatable balloon (Oesophagus Catheter, Jaeger-Toennies, Hoechberg, Germany) at its tip was inserted into the distal part of the oesophagus and filled with 1 ml of air connected to a pressure transducer. Adequate transmission of pleural pressures to the balloon was verified with an occlusion test. This test was performed by gentle squeezing of the chest and the abdomen while the airway was blocked, both after an inspiration and after expiration.

Animal models

ICP was increased (to achieve a steady state ICP between 25 and 30 mm Hg) by continuous infusion of normal saline (warmed to 38°C) into the right cerebral ventricle with an infusion pump, while ICP was continuously monitored

via the left cerebral ventricle catheter. The infusion was started at a rate of 10 ml h^{-1} and adjusted as needed. Once the ICP was increased to 25 and 30 mm Hg, the infusion rate was titrated to maintain that range of ICP before initiation of HFOV and PCV, and was then kept unchanged.

Lung injury by surfactant-depletion was applied by repetitive lung lavages with warmed Ringer's solution (20 ml kg^{-1}, 38°C). The tracheal tube was disconnected from the ventilator, and the fluid was instilled from a height of 70 cm above the tracheal tube. After 30 s of apnoea, the fluid was retrieved by gravity drainage followed by tracheal suctioning. The lavage process was repeated until a Pa_{O_2}/FI_{O_2} ratio of <20.4 kPa was achieved and maintained stable for 15 min. Thereafter all animals were ventilated in a volume constant mode for 2 h. A continuous infusion of epinephrine was adjusted as needed to keep mean arterial pressure (MAP) between 70 and 80 mm Hg during the lung lavage process and the subsequent 2 h of volume constant ventilation.

Experimental protocol

The i.v. fluid administration and infusion of saline into the right lateral cerebral ventricle were kept unchanged during the subsequent procedures. The last dosage of the continuous infusion of epinephrine before the experimental protocol started was maintained during the following experiment and was not modified. Changes of arterial pressures because of variations of epinephrine dosage and fluid administration can therefore be excluded. Figure 1 illustrates the sequence of the experiment. Animals were ventilated with both ventilation modes (HFOV and PCV) during the experiment. The sequence of the first and second ventilator mode (HFOV–PCV or PCV–HFOV) was randomized. To achieve standardized conditions at initiation of HFOV or PCV, the tracheal tube was disconnected for 30 s and the volume constant ventilation mode was reestablished for 30 min before initiation of HFOV and PCV [FI_{O_2} 1.0, PEEP 5 cm H_2O, inspiratory to expiratory ratio 1:1, tidal volume (V_t) 12 ml kg^{-1} VF was set to maintain normocapnia]. A sequence of P_{mean} increases was performed in steps of 5 cm H_2O every 30 min from 20 to 25 and 30 cm H_2O with HFOV and PCV.

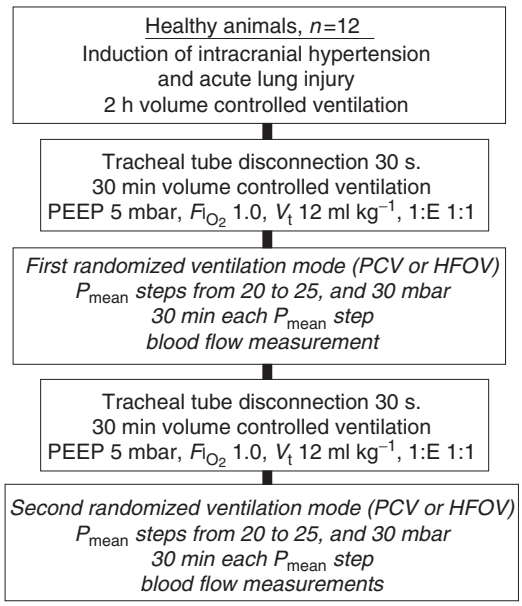

Fig 1 Illustration of the experiment.

Ventilatory parameters at HFOV (High-Frequency Oscillator Ventilator 3100 b, Sensor Medics, Yorba Linda, USA) were set as follows: CDP (=P_{mean}) was increased in steps of 5 cm H_2O every 30 min from 20 to 25 and 30 cm H_2O. FI_{O_2} was set to 1.0, bias flow 30 litre min^{-1}, oscillatory frequency (F) 5 Hz, T_{insp} 33% of the respiratory cycle. The oscillatory pressure amplitude (ΔP) was set to maintain normocapnia (Pa_{O_2} 4.9–5.7 kPa).

Ventilatory parameters at PCV (Servo 900c Ventilator, Siemens Elema, Erlangen, Germany) were set as follows: P_{mean} was increased from 20 to 25 and 30 cm H_2O by PEEP increases from 10 to 15 and 20 cm H_2O with a constant inspiratory pressure amplitude ($P_{endinsp}$=PEEP+20 cm H_2O) and a constant inspiration time (T_{insp}=50% of the respiratory cycle). The FI_{O_2} was 1.0 and the VF was set to maintain normocapnia (Pa_{CO_2} 4.9–5.7 kPa).

Measurements

After induction of intracranial hypertension (ICH) and lung injury, and 30 min after switching to a new P_{mean} (20, 25, and 30 cm H_2O) during ongoing HFOV or PCV, haemodynamics (HR, MAP, CVP), ICP, gas exchange (Pa_{O_2}, Pa_{CO_2}, Sa_{O_2}), haemoglobin (Hb), arterial oxygen content (Ca_{O_2}), superior sagittal sinus oxygen content (Css_{O_2}),and oxygen saturation (Sss_{O_2}) were obtained. Transpulmonary pressures (P_T) were calculated according the formula P_T=P_{mean} − oesophageal pressure, at each P_{mean} setting during HFOV and PCV. CBFs were measured with the fluorescent microsphere technique.[8] Microspheres were injected 30 min subsequent to each new P_{mean} setting during HFOV or PCV. For calculation of absolute blood flow rates, reference blood was sampled from the aortic catheter at a rate of 2 ml min^{-1} using a withdrawal pump (Genie, Kent Scientific Corporation, Torrington, USA). Withdrawal started 30 s before microsphere injection and was continued for 120 s after injection. To ensure that the time for reference blood sampling was sufficient, a separate blood sample of 1 ml was withdrawn immediately after completion of the 2-min reference blood withdrawal period, and fluorescence spectroscopy of this sample was performed separately. At the end of the experiment, the brain and kidneys were removed and weighed. Thereafter, microspheres were recovered from brain and kidney tissue and from blood by the sedimentation method.[9] The left and right renal blood flows were determined to verify a homogenous distribution

Table 1 Ventilatory variables, haemodynamics, blood gas analysis in healthy and injured animals (lung lavage and intracranial hypertension). Significant differences were found between healthy and injured animals, and no significant differences were found between injured animals before initiation of high-frequency oscillatory ventilation or pressure controlled ventilation. Data are given as median with IQ range. HFOV, high-frequency oscillatory ventilation; PCV, pressure controlled ventilation; $P_{Plateau}$, plateau airway pressure; P_{mean}, mean airway pressure, PEEP, positive end-expiratory pressure; C_{stat}, static lung compliance [$V_t/(P_{Plateau}-PEEP)$], VF, ventillatory frequency; V_t, tidal volume; MV, expiratory minute ventilation; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; Po_2, partial pressure of oxygen; Pco_2, partial pressure of carbon dioxide. $^{\#}P<0.01$ *vs* baseline

	Healthy	Injured animals before HFOV	Injured animals before PCV
$P_{plateau}$ (cm H_2O)	13 (11–15)	33$^{\#}$ (30–36)	32$^{\#}$ (29–37)
P_{mean}(cm H_2O)	8 (8–10)	12$^{\#}$ (13–16)	12$^{\#}$ (12–16)
PEEP (cm H_2O)	5 (5–5)	5 (5–5)	5 (5–5)
C_{stat} (ml cm H_2O^{-1})	31 (25–40)	9$^{\#}$ (8–10)	9$^{\#}$ (8–10)
VF (min^{-1})	18 (15–18)	18 (17–18)	18 (16–19)
V_t (ml kg^{-1})	10.3 (9.1–11.0)	10.2 (9.8–11.0)	10.4 (10.0–11.1)
MV (litre min^{-1})	4.5 (4.1–4.9)	4.5 (4.4–4.9)	4.6 (4.4–5.0)
HR (min^{-1})	113 (94–123)	121$^{\#}$ (104–143)	124$^{\#}$ (102–139)
MAP (mm Hg)	79 (73–85)	78 (75–83)	79 (74–87)
CVP (mm Hg)	12 (11–14)	12 (11–14)	13 (11–14)
ICP (mm Hg)	11 (10–12)	27$^{\#}$ (25–30)	28$^{\#}$ (26–30)
CPP (mm Hg)	63 (54–81)	49$^{\#}$ (46–55)	50$^{\#}$ (45–58)
Arterial Po_2 (kPa)	76.2 (70.6–77.7)	14.0$^{\#}$ (11.3–16.8)	13.8$^{\#}$ (11.4–16.5)
Arterial Pco_2 (kPa)	5.2 (5.1–5.7)	5.2 (5.1–5.5)	5.3 (5.1–5.6)

of microspheres. Blood flows were calculated using the formula blood flow $(ml\,min^{-1})=I_S*R$ $(ml\,min^{-1})*I_R{}^{-1}$, where I_S is the fluorescence intensity of sample, I_R is the fluorescence intensity in the reference blood sample and R is the reference withdrawal rate. Cerebral perfusion pressure (CPP) was calculated as CPP=MAP−ICP. Cerebral arteriovenous oxygen difference ($cAVD_{O_2}$) was calculated as $cAVD_{O_2}=Ca_{O_2}-Css_{O_2}$. Cerebral metabolic rate of oxygen (CMR_{O_2}) was calculated according to the formula CMR_{O_2}= CBF*($Ca_{O_2}-Css_{O_2}$). Cerebral oxygen extraction (cE_{O_2}) was calculated as $(Ca_{O_2}-Css_{O_2})*Ca_{O_2}{}^{-1}$.

Statistical analysis

Data are expressed as medians and interquartile range (IQ range) unless otherwise specified. In each animal (i) the sequence of the two ventilatory modes (HFOV, PCV) and (ii) the order of the six different colours of microspheres were randomized by statistical software (BIAS® Version 7.40, Epsilon-Verlag, Hochheim-Darmstadt, Germany). Intraindividual differences before and after induction of ICH and lung lavage was tested nonparametrically by Wilcoxon signed rank test for haemodynamics, ICP, CPP and blood gases. Friedman's ANOVA and multiple Wilcoxon–Wilcox tests's with Bonferroni's correction for multiple testing were used to analyse (i) the change of CPP, CBF, Sss_{O_2}, Css_{O_2}, $cAVD_{O_2}$, CMR_{O_2}, cE_{O_2}, ICP, MAP, CVP, HR, P_T and arterial blood gases in value over time during HFOV or PCV and (ii) differences of CPP, CBF, Sss_{O_2}, Css_{O_2}, $cAVD_{O_2}$, CMR_{O_2}, cE_{O_2}, ICP, MAP, CVP, HR, P_T and arterial blood gases between the ventilatory modes (HFOV and PCV). The question how closely P_T are associated to CPP and ICP, during lung recruitment by HFOV or PCV, were analysed by correlation analysis and linear regression analysis. A P-value of 0.05 was considered statistically significant.

Results

Induction of intracranial hypertension and lung injury

The study protocol was completed in 12 animals. The average (SEM) number of lung lavage procedures to induce lung injury was 3.4 (0.5) with a mean (SEM) lavage volume of 1665 ml (205 ml). An average (SEM) continuous infusion of epinephrine 0.3 (0.2–0.5) $\mu g\,kg^{-1}\,min^{-1}$ was administered to maintain the MAP between 70 and 80 mm Hg during lung lavages. The infusion rate [mean (SEM)] of saline into the right lateral cerebral ventricle was 5.9 (2.5) ml h^{-1} to maintain a steady state ICP between 25 and 30 mm Hg before transition to HFOV or PCV. There were no differences in gas exchange, systemic and cerebral haemodynamics between injured animals before initiation of HFOV or PCV (Table 1). The infusion rate of fluids and epinephrine was kept unchanged during recruitment by HFOV and PCV.

Effects of HFOV and PCV upon CBF, brain metabolism and haemodynamics

All data are demonstrated in Table 2. CBF, cerebral metabolic rate of oxygen and cerebral oxygen extraction were unaffected during HFOV or PCV and did not differ at similar P_{mean} levels. There were no differences between left and right renal blood flows (data not included). The sinus sagittalis oxygen saturation and oxygen content and arterio-sinus sagittalis DO_2 remained unchanged during HFOV and PCV, without differences between the two ventilatory modes. At P_{mean} levels of 30 cm H_2O MAPs and CPPs decreased during HFOV and PCV. Without changes of fluid management or additional vasopressor administration during lung recruitment, the CPP was <25 mm Hg at a P_{mean} of 30 cm H_2O in 3 out of 12 animals during HFOV and 4 out of 12 animals during PCV. ICPs

Table 2 Cerebral blood flow, haemodynamics and cerebral metabolism at increasing mean airway pressure with high-frequency oscillatory ventilation and pressure controlled ventilation. Data are given as median with IQ range. HFOV, high-frequency oscillatory ventilation; PCV, pressure controlled ventilation; P_{mean}, mean airway pressure; DO_2, difference of oxygen. $^{\#}P<0.05$ *vs* HFOV P_{mean} 20 cm H_2O; $^{\S}P<0.05$ *vs* PCV P_{mean} 20 cm H_2O

	HFOV P_{mean} 20 cm H_2O	PCV P_{mean} 20 cm H_2O	HFOV P_{mean} 25 cm H_2O	PCV P_{mean} 25 cm H_2O	HFOV P_{mean} 30 cm H_2O	PCV P_{mean} 30 cm H_2O
Cerebral blood flow (ml 100 g^{-1} min^{-1})	42 (32–51)	38 (23–51)	39 (28–57)	44 (33–57)	41 (28–48)	38 (30–52)
Cerebral perfusion pressure (mm Hg)	47 (41–56)	49 (43–59)	41 (31–48)	45 (36–48)	34$^{\#}$ (24–43)	32§ (21–39)
Mean arterial pressure (mm Hg)	75 (73–80)	75 (72–84)	69 (62–73)	71 (70–77)	64$^{\#}$ (57–70)	62§ (54–67)
Intracranial pressure (mm Hg)	29 (27–31)	28 (25–30)	30 (28–31)	29 (25–30)	30$^{\#}$ (28–32)	30§ (28–33)
Central venous pressure (mm Hg)	13 (12–15)	13 (12–14)	14 (13–16)	13 (12–16)	15$^{\#}$ (13–17)	16§ (14–17)
Heart rate (min^{-1})	150 (97–167)	140 (112–154)	145 (120–170)	138 (116–153)	166$^{\#}$ (128–170)	153§ (124–161)
Oxygen saturation sinus sagittalis (%)	39 (37–43)	40 (33–43)	38 (34–43)	37 (33–43)	38 (37–40)	37 (33–41)
Oxygen content sinus sagittalis (ml $litre^{-1}$)	4.0 (3.1–4.7)	3.9 (3.0–4.3)	3.9 (3.2–4.7)	3.8 (3.0–4.1)	4.1 (3.7–4.5)	4.0 (3.4–4.4)
Arterio-sinus sagittalis DO_2 (ml $litre^{-1}$)	7.2 (6.3–7.5)	6.9 (6.3–7.6)	7.1 (6.3–7.6)	6.8 (6.4–7.2)	7.0 (5.7–7.6)	6.9 (6.4–7.2)
Cerebral metabolic rate of oxygen (ml 100 g^{-1} min^{-1})	3.4 (2.7–3.8)	3.4 (2.9–3.7)	3.1 (2.5–3.6)	3.2 (2.5–3.6)	3.5 (2.0–4.0)	3.8 (2.6–3.9)
Cerebral extraction of oxygen (%)	65 (59–68)	64 (56–73)	63 (57–67)	64 (62–71)	63 (58–66)	67 (63–67)
Blood temperature (°C)	37.5 (36.9–38.2)	37.5 (36.9–38.1)	37.2 (36.9–37.9)	37.6 (37.0–38.3)	37.4 (36.9–38.0)	37.5 (36.9–38.2)

Table 3 Ventilatory variables at increasing mean airway pressure with high-frequency oscillatory ventilation and pressure controlled ventilation. Data are given as median with IQ range. HFOV, high-frequency oscillatory ventilation; PCV, pressure controlled ventilation; P_{mean}, mean airway pressure; na, not applicable. $^{\#}P<0.05$ *vs* HFOV P_{mean} 20 cm H_2O; $^{\S}P<0.05$ *vs* PCV P_{mean} 20 cm H_2O; $^{\&}P<0.05$ *vs* HFOV P_{mean} 25 cm H_2O; $^{\$}P<0.05$ *vs* PCV P_{mean} 25 cm H_2O

	HFOV P_{mean} 20 cm H_2O	PCV P_{mean} 20 cm H_2O	HFOV P_{mean} 25 cm H_2O	PCV P_{mean} 25 cm H_2O	HFOV P_{mean} 30 cm H_2O	PCV P_{mean} 30 cm H_2O
Transpulmonary pressure (cm H_2O)	14 (13–15)	13 (11–14)	17$^{\#}$ (15–19)	16§ (15–18)	22$^{\#\&}$ (19–24)	21$^{\$\S}$ (18–24)
Ventilatory frequency (min^{-1})	300 (300–300)	20 (15–26)	300 (300–300)	24 (15–30)	300 (300–300)	33§ (28–39)
End-inspiratory pressure (cm H_2O)	44 (34–58)	na	49 (35–57)	na	60$^{\#}$ (40–63)	na
Dynamic lung compliance (ml cm H_2O^{-1})	na	18 (16–19)	na	18 (14–21)	na	11$^{\$\S}$ (10–16)
Expiratory minute volume (litre min^{-1})	na	7.0 (5.1–9.8)	na	7.3 (4.4–8.1)	na	7.5§ (6.2–10.9)
Tidal volume (ml kg^{-1})	na	12.1 (9.4–12.9)	na	10.3 (9.3–12.0)	na	8.1$^{\$\S}$ (7.5–8.7)

at P_{mean} settings of 30 cm H_2O increased slightly (median +1 mm Hg during HFOV mm Hg and +2 mm Hg during PCV). During stepwise increases of P_{mean} by HFOV or PCV up to 30 cm H_2O heart rate and central venous pressures increased. There were no differences between HFOV and PCV at similar P_{mean} levels.

Association between P_T and CP, and between P_T and ICP during HFOV and PCV

The P_T increased with each ventilatory mode when P_{mean} was increased to 25 and 30 mbar (Table 3). The P_T showed a negative correlation to CPP. During HFOV and PCV, an increase of P_T was associated with a decrease of CPP (HFOV, Fig. 2A and PCV, Fig. 2B). No correlation was found between P_T and ICP (HFOV P=0.13, PCV P=0.16).

Effects of HFOV and PCV upon pulmonary gas exchange

Increasing P_{mean} from 20 to 25 and 30 cm H_2O improved oxygenation (Table 4) and normocapnia within the defined range was maintained (Table 4) with higher oscillatory pressure amplitudes (HFOV, Table 3) and higher ventilatory frequencies (PCV, Table 3). The increased ventilatory frequencies during PCV may have lead to intrinsic PEEP, but P_T during PCV was comparable to HFOV. When comparing Pa_{O_2} between HFOV and PCV at similar P_{mean} settings, HFOV was associated with a significantly higher Pa_{O_2} only at a P_{mean} of 20 cm H_2O (Table 4). Pa_{CO_2} was not different between HFOV and PCV at similar P_{mean} settings.

Discussion

The main finding of the present study was that HFOV produced effects on cerebral haemodynamics similar to those of PCV. We had been concerned to find more adverse effects of HFOV, but we did not detect these in the used scenario. We therefore conclude that HFOV is a suitable alternative to PCV in acute injured lungs and elevated ICP.

Comparison with other studies

Only few experimental data from small animal models and scarce clinical data in neonates focus on cerebral haemodynamics at initiation or during HFOV.[10–13] They reported decreased or unchanged cerebral haemodynamics when HFOV was applied, however, without differences when compared with conventional ventilatory modes. Recently,

we reported for the first time in five adult patients with ARDS and intracranial pathology no typical HFOV-related adverse events (tracheal tube obstruction by mucous obstruction, pneumothorax, tracheal injury) and no HFOV termination because of worsened CPP, ICP or deteriorated CO_2 clearance.[14] However, temporary effects upon CPP, ICP and Pa_{CO_2} were evident and required therapeutic interventions (fluid administration, change of vasopressor dosage and ventilator settings). The effects upon MAP and CO at HFOV initiation have been evaluated in previous experimental and clinical studies (pediatric and adult patients).[2–4 15–20] The reported main cause of declined MAP and CO during HFOV was reduced venous return dependent on the CDP setting. In addition, increases of lung volume can affect haemodynamics by direct mechanical compression of the cardiac fossa.

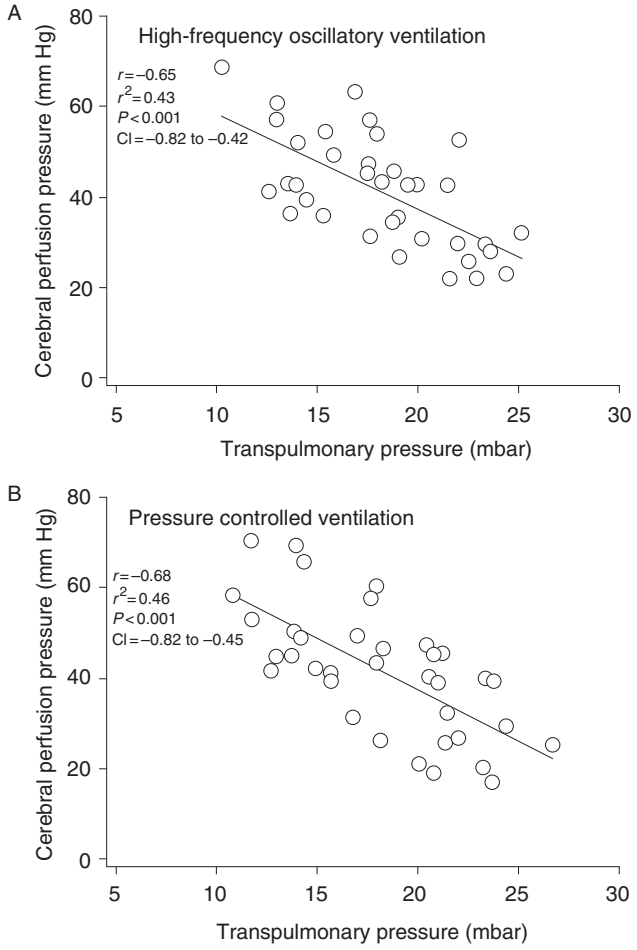

Fig 2 Regression analysis between transpulmonary pressure and cerebral perfusion pressure during high-frequency oscillatory ventilation (A) and pressure controlled ventilation (B). Data are given as correlation coefficient (r), r^2, transgression probability (P) and confidence interval (CI 0.95).

Despite decreased MAP and CPP during both ventilatory modes at high P_{mean} settings in the present study, cerebral oxygenation and CBF maintained stable indicating that CBF autoregulation was intact. However, in a clinical scenario with impaired autoregulation response of CBF, MAP and CPP are the most important factors to provide sufficient CBF and cerebral oxygenation.[21] In fact, investigation of CBF autoregulation (static or dynamic) in patients is possible (e.g. by means of transcranial Doppler velocities). However, this reflects only a short-term situation and may change over time. Therefore, in a clincial scenario a reduction of CPP as observed in the present study cannot be tolerated, because of the high risk of cerebral ischemia and secondary neuronal damage independent of the ventilatory mode used.

Another important factor is the potential adverse effect of hypercapnia upon cerebral circulation during lung recruitment. Lung recruitment in the present study was indicated by an increase of Pa_{O_2} at high P_T levels with both ventilatory modes. Simultaneously, when pulmonary hyperinflation is evident, dead space and consecutively Pa_{CO_2} increase, whereas oxygenation especially at higher oxygen fractions will show only slightly changes.[22] The steady state of CO_2 clearance was maintained in the present study, but at high P_T levels only with higher ΔP during HFOV and increased VF during PCV. The observed minor increase of ICP at P_{mean} settings of 30 cm H_2O was statistically significant but in a clinical context not relevant. The study was not designed to evaluate the specific causes of changes in ICP when lung recruitment manoeuvres were performed. However, we found no association between P_T and ICP. Other known factors may have influenced the minor increase of ICP: (i) cerebral vasodilatation because of CPP deterioration may increase the cerebral blood volume[23]; and (ii) impairment of cerebral venous outflow according to the Starling resistor model because of higher CVP.[24 25]

Table 4 Arterial blood gases, arterial haemoglobin and arterial oxygen content at increasing mean airway pressures with high-frequency oscillatory ventilation and pressure controlled ventilation. Data are given as median with IQ range. HFOV, high-frequency oscillatory ventilation; PCV, pressure controlled ventilation; P_{mean}, mean airway pressure; na, not available; P_{O_2}, partial pressure of oxygen; P_{CO_2}, partial pressure of carbon dioxide. $^{\#}P<0.05$ *vs* HFOV P_{mean} 20 cm H_2O; $^{\S}P<0.05$ *vs* PCV P_{mean} 20 cm H_2O; $^{\&}P<0.05$ *vs* HFOV P_{mean} 25 cm H_2O; $^{\$}P<0.05$ *vs* PCV P_{mean} 25 cm H_2O

	HFOV P_{mean} 20 cm H_2O	**PCV P_{mean} 20 cm H_2O**	**HFOV P_{mean} 25 cm H_2O**	**PCV P_{mean} 25 cm H_2O**	**HFOV P_{mean} 30 cm H_2O**	**PCV P_{mean} 30 cm H_2O**
Arterial P_{O_2} (kPa)	27.2 (25.5–29.8)	23.9$^{\#}$ (20.0–26.7)	54.5$^{\#}$ (42.7–65.8)	44.2§ (40.5–54.0)	77.8$^{\#\&}$ (72.4–83.9)	73.7$^{\$\$}$ (66.0–79.5)
Arterial P_{CO_2} (kPa)	5.3 (5.2–5.6)	5.2 (5.1–5.6)	5.5 (5.2–5.6)	5.2 (5.1–5.5)	5.5 (5.3–5.7)	5.3 (5.2–5.6)
Arterial oxygen content (ml litre^{-1})	10.6 (9.6–11.8)	10.8 (10.1–11.7)	11.1 (9.6–11.5)	10.2 (9.7–10.9)	11.4 (9.5–11.8)	10.5 (10.1–11.5)
Arterial haemoglobin (g litre^{-1})	79 (71–88)	79 (74–88)	82 (70–85)	79 (71–82)	84 (70–87)	80 (74–84)

Limitations of the study

The present study is an experimental study and the results can therefore not directly be extrapolated to patients with lung injury and intracranial pathology. The response to lung recruitment procedures upon gas exchange of saline lavaged animal lungs reflects early stages of ARDS. After complete recruitment of a saline lavaged lung, the model does not really reflect a diseased lung, but rather a healthy lung. If consolidated lung compartments are evident in severe ARDS, increases of P_{mean} may lead to higher dead space ventilation and consecutively to worsened CO_2 clearance. Measurement of lung volumes during HFOV is difficult and we have no direct data to support the hypothesis of pulmonary hyperinflation. We performed no CO measurement to further analyse why MAP decreased in the presence of increased P_{mean}. However, the relationship between high airway pressures and haemodynamic effects has well been reported during HFOV and PCV and MAP deterioration was shown to be caused by impaired cardiac filling as a result of reduced venous return.[2–6 14–17] We recently reported in humans that HFOV in severe ARDS with increasing P_{mean} increased RAP and PAOP, but decreased end-diastolic and end-systolic left ventricular cross-sectional area indices as determined by transoesophageal echocardiography.[17]

We obtained a 'negative result' in the sense that comparisons between HFOV and PCV were not statistically significant. This could have been a type 2 statistical error. We did not conduct a formal prior power analysis as this was a physiological study, rather than a clinical trial of therapy, but we feel a type 2 error unlikely as we did detect substantial changes in many of our cardinal variables during both HFOV and PCV.

Conclusions

Our animal study suggests that the use of HFOV in concomitant ALI and elevated ICP had no specific effects upon cerebral circulation and seems to be a possible alternative ventilatory strategy when MAP deterioration can be avoided.

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