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TRANSLATIONAL RESEARCH

Effects of High-frequency Oscillatory Ventilation on Systemic and Cerebral Hemodynamics and Tissue Oxygenation: An Experimental Study in Pigs

Jan Florian Heuer · Philip Sauter · Jürgen Barwing · Peter Herrmann · Thomas A. Crozier · Annalen Bleckmann · Tim Beißbarth · Onnen Moerer · Michael Quintel

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Abstract
Background In this study, we compare the effects of high frequency oscillatory ventilation (HFOV) with those of lung-protective volume-controlled ventilation (VCV) on cerebral perfusion, tissue oxygenation, and cardiac function with and without acute intracranial hypertension (AICH).
Methods Eight pigs with healthy lungs were studied during VCV with low tidal volume (V_T: 6 ml kg^{-1}) at four PEEP levels (5, 10, 15, 20 cmH_2O) followed by HFOV at corresponding transpulmonary pressures, first with normal ICP and then with AICH.
Systemic and pulmonary hemodynamics, cardiac function, cerebral perfusion pressure (CPP), cerebral blood flow (CBF), cerebral tissue oxygenation, and blood gases were measured after 10 min at each level. Transpulmonary pressures (TPP) were calculated at each PEEP level. The measurements were repeated with HFOV using continuous distending pressures (CDP) set at TPP plus 5 cmH_2O for the corresponding PEEP level. Both measurement series were repeated after intracranial pressure (ICP) had been raised to 30–40 cmH_2O with an intracranial balloon catheter.
Results Cardiac output, stroke volume, MAP, CPP, and CBF were significantly higher during HFOV at normal ICP. Systemic and cerebral hemodynamics was significantly altered by AICH, but there were no differences attributable to the ventilatory mode.
Conclusion HFOV is associated with less hemodynamic compromise than VCV, even when using small tidal volumes and low mean airway pressures. It does not impair cerebral perfusion or tissue oxygenation in animals with

J. F. Heuer (✉) · P. Sauter · J. Barwing · P. Herrmann · T. A. Crozier · O. Moerer · M. Quintel
Department of Anaesthesiology, Emergency- and Intensive Care Medicine, University of Göttingen Medical School, Göttingen, Germany
e-mail: jheuer@med.uni-goettingen.de

P. Sauter
e-mail: philip.sauter@med.uni-goettingen.de

J. Barwing
e-mail: jbarwing@med.uni-goettingen.de

P. Herrmann
e-mail: pherrmann@med.uni-goettingen.de

T. A. Crozier
e-mail: tcrozier@med.uni-goettingen.de

O. Moerer
e-mail: omoerer@gwdg.de

M. Quintel
e-mail: mquintel@med.uni-goettingen.de

A. Bleckmann · T. Beißbarth
Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany
e-mail: a.bleckmann@med.uni-goettingen.de

T. Beißbarth
e-mail: tim.beissbarth@med.uni-goettingen.de

A. Bleckmann
Department of Hematology and Oncology, University Medical Center Göttingen, Göttingen, Germany

AICH, and could, therefore, be a useful ventilatory strategy to prevent lung failure in patients with traumatic brain injury.

Keywords Volume controlled ventilation · HFOV · Cerebral blood flow · Cerebral tissue oxygenation · Hemodynamics

Introduction

Up to 40% of the patients with an isolated head injury develop ARDS and require mechanical ventilation with high positive end-expiratory pressures (PEEP) [1, 2]. Volume-controlled ventilation with PEEP improves oxygenation and reduces pulmonary morbidity [3], but it can also increase intracranial pressure (ICP) and impair cerebral perfusion [4, 5]. A lung-protective ventilatory strategy with small tidal volumes at higher respiratory rates reduces the risk of pulmonary damage [6] and helps to avoid the detrimental effects of high airway pressures on cerebral perfusion [5].

High frequency oscillatory ventilation (HFOV) takes the lung-protective approach to an extreme with very low tidal volumes and very small pressure changes [7] around a higher continuous distending pressure (CDP). Studies have demonstrated the efficacy of HFOV in patients with ARDS [8–10], and there is an evidence that the outcome improves when HFOV is initiated earlier [11, 12]. It is therefore reasonable to hypothesize that it would be beneficial to implement HFOV immediately and not just use it as a rescue measure after lung failure has set in. This is supported by the data from a study in very-low-birth-weight infants [13]. There is some concern that the high constant mean airway pressures of HFOV might impair cerebral perfusion and brain tissue oxygenation [14, 15] or contribute to right ventricular failure. The results of the small case series have been encouraging [16, 17], and a direct comparison of HFOV and pressure-controlled ventilation in an animal model, albeit with clinically obsolete large tidal volumes, showed both methods to be equivalent with regard to cerebral hemodynamics [18]. However, there are no controlled studies comparing the effects of HFOV on cerebral and systemic hemodynamics with those of VCV using a lung-protective, low tidal volume mode in animals with intracranial hypertension and normal lung function.

The following hypotheses were tested:

(a) HFOV has a negative effect on cardiac function, ICP, cerebral perfusion pressure, and tissue oxygenation at higher CDP levels;
(b) There is a difference between the effects of HFOV and those of low tidal volume VCV on these parameters;
(c) The effects of VCV and HFOV respond differently to acutely induced intracranial hypertension.

Materials and Methods

The study was approved by our institutional animal study review board. Throughout the study, animals were handled according to the Helsinki convention for the use and care of animals.

Animal Preparation

Eight healthy pigs (Göttinger mini-pigs, mean weight 37.3 ± 4.2 kg) were premedicated with 40 mg i.m. azaperonium. An ear vein was cannulated, and anesthesia was induced with thiopental (3–5 mg kg^{-1} i.v.) and ketamine (4 mg kg^{-1} i.v.), and maintained with ketamine (10 mg kg^{-1} h^{-1}) and midazolam (1 mg kg^{-1} h^{-1}) infusions. Ringer acetate was infused at an average rate of 4–5 ml kg^{-1} h^{-1}.

A cuffed tracheal tube was inserted, and the lungs were ventilated (Servo I®, Maquet, Rastatt, Germany) in VCV mode (PEEP 5 cmH_2O; inspiratory:expiratory ratio I:E = 1:1.5; FiO_2 = 0.5; respiratory rate 15 min^{-1}; constant inspiratory flow; tidal volume V_T = 6 ml kg^{-1}). The respiratory rate was adjusted to maintain normocapnia with a maximum rate of 20 min^{-1}. End-tidal CO_2 (Datex Capnomac Ultima®, Finland), peripheral oxygen saturation, ECG, and non-invasive blood pressure were monitored continuously (Datex—Ohmeda S/3 patient monitor, GE, USA).

A thermistor-tipped fiberoptic catheter (Pulsiocath®, 4F FT PV 2024, Pulsion Medical System, Munich, Germany) was placed in a femoral artery. A pulmonary catheter (Volef®, Pulsion Medical System, Munich, Germany) was inserted through a 5 F sheath introducer in the right internal jugular vein, and the position of the catheter tip confirmed by pressure tracing. The catheters were connected to pressure transducers and to an integrated bedside monitor (PiCCO®, Volef, Pulsion Medical Systems).

Three burr holes were made in the right frontal region to insert an intracranial pressure catheter (Codman, Monitor: Codman ICP Express®, Catheter: Codman Microsensor™, Ryhnam, MA, USA), a Licox® micro oxygen electrode for measuring oxygen tension ($p_{ti}O_2$) in brain tissue (Integra Neuroscience, Integra GmbH, 40880 Ratingen, Germany), and a 22 F Fogarty catheter. The tips of the two microprobes were placed approximately 15 mm below the dura with a distance of 15 mm to each other. The Fogarty catheter was placed 20 mm lateral to the medial microprobe [19].

After the neuromonitoring was established, the animals were turned into the supine position for the remaining

duration of the experiment. Both carotid arteries were exposed, and two ultrasound flow sensors (Transonic systems Inc., model: T 106, Maastricht, Netherland) were placed on the arteries and calibrated according to the manufacturer's recommendation.

An esophageal balloon catheter (Spiegelberg-Sonde Typ 1, Spiegelberg KG, Hamburg, Germany) was inserted to measure esophageal pressure. The correct placement of the catheter was confirmed by gentle mechanical compression of the abdomen [20].

Experimental Protocol

Four sets of measurements were performed under the two ventilatory modes in the following order: (1) VCV and (2) HFOV in animals with normal ICP, then (3) VCV and (4) HFOV after induction of intracranial hypertension. It was not possible to randomize the order due to the nature of the study design.

For each series, baseline values were recorded at a PEEP of 5 cmH_2O after all parameters had been constant for 30 min. The animals were then ventilated at consecutive PEEP levels of 10, 15, and 20 cmH_2O. Final measurements at PEEP 5 cmH_2O were made at the end of each series to measure the effects of pressure release. Measurements were performed after 10 min ventilation at each PEEP level. Airway and esophageal pressures were recorded, and the mean transpulmonary pressure (TPP) was calculated.

At the end of the measurements at each PEEP level, the lungs were allowed to collapse by disconnecting the tracheal tube from the respirator for 30 s. A recruitment maneuver was then performed by inflating the lungs to a pressure of 40 cmH_2O for 40 s, and ventilation was started at the next PEEP level.

VCV was performed as described above. HFOV was performed with a CDP set at 5 cmH_2O over the TPP determined during VCV at the corresponding PEEP level as described by Talmor et al. [20]. The ventilator (SensorMedics®-Ventilator 3100B, Care Fusion, Hong Kong) was initially set with a bias flow of 20 l min^{-1}, a power of 70%, an inspiration time of 44%, and a frequency of 5 Hz.

Acute Intracranial Hypertension

Intracranial hypertension was induced by inflating the Fogarty catheter until the ICP was constant between 30 and 40 cmH_2O. Baseline ICP values are slightly elevated even during the control series, since ICP increased significantly when the animals were turned into the supine position.

Measurements and Data Acquisition

Cardiac output (CO), stroke volume, global ejection fraction, left and right end-diastolic volumes, right ventricular ejection fraction, systemic and pulmonary artery pressures, extravascular lung water index (ELWI), and intrathoracic blood volume index (ITBI) were measured. Cardiac output measurements were performed in triplicate by the same investigator using 20 ml ice-cold 0.9% saline.

Arterial and mixed venous samples were collected, and blood gases were analyzed immediately (ABL 510, Radiometer, Copenhagen, Denmark). ICP and $p_{ti}O_2$ were recorded continuously, and cerebral perfusion pressure (CPP) was calculated.

Data recording and analysis was performed using the Modular Intensive Care Data Acquisition System (MIDAS) developed by Herrmann and Nguyen (Institut für Biomedizinische Technik, Hochschule Mannheim, Germany).

Statistical Analysis

Data analysis was performed with the statistical software R (http://www.r-project.org). The influence of PEEP, Disease, and Treatment on each individual variable was assessed by ANOVA. A multivariate linear regression model (lm) of the form (Variable $\sim$ Animal + PEEP * Treatment * Disease) was individually fitted for each of the analyzed variables. Here "Animal" denotes the coefficients for the individual eight animals, "PEEP" denotes a factor variable for the different PEEP levels, "Treatments" are HFOV or VCV, and "Diseases" are the presence or absence of intracranial hypertension (AICH). The interactions of PEEP, Treatment, and Disease were modeled. The *P*-values computed for the variables were adjusted to control the family wise error rate using the Holm method. Changes from baseline in each individual series were assessed with the Wilcoxon-test for paired samples. Figures were performed with Statistica for Windows (9.0; StatSoft; Europe).

Results

Gas Exchange

Gas exchange parameters remained constant in the individual groups, except that PaO_2 was higher than baseline at a PEEP of 15 and 20 cmH_2O in group HFOV + AICH. Arterial oxygen tension was significantly higher and $PaCO_2$ significantly lower in the HFOV groups (Table 1). CDP based on transpulmonary pressure (TPP) was lower than a CDP based on mean airway pressure (Table 1).

Table 1 Pulmonary gas exchange, serum lactate, and airway pressures

	T_0 = PEEP 5	PEEP 10	PEEP 15	PEEP 20	PEEP 5
pHa$^{\#,\ +,\ -}$					
VCV	7.49 ± 0.08	7.49 ± 0.08	7.46 ± 0.07*	7.41 ± 0.07*	7.46 ± 0.05*
HFOV	7.48 ± 0.06	7.52 ± 0.08	7.48 ± 0.09	7.50 ± 0.06	7.47 ± 0.08
VCV + AICH	7.46 ± 0.09	7.46 ± 0.07	7.45 ± 0.05	7.41 ± 0.05	7.44 ± 0.04
HFOV + AICH^	7.45 ± 0.10	7.48 ± 0.10	7.49 ± 0.09*	7.45 ± 0.06	7.46 ± 0.04
$PaCo_2$, mmHg					
VCV	39 ± 4	38 ± 5	40 ± 3	39 ± 14	38 ± 2
HFOV°	36 ± 4	36 ± 8	37 ± 7	35 ± 7	38 ± 7
VCV + AICH	39 ± 7	39 ± 5	38 ± 3	42 ± 6	39 ± 3
HFOV + AICH^	40 ± 10	36 ± 8	35 ± 6	38 ± 5	36 ± 7
PaO_2, mmHg					
VCV	293 ± 28	292 ± 29	299 ± 29	302 ± 32	304 ± 32*
HFOV°	31 ± 11	313 ± 13	314 ± 12	311 ± 21	313 ± 14
VCV + AICH	301 ± 25	304 ± 28	305 ± 26	298 ± 24	300 ± 31
HFOV + AICH^	302 ± 1	311 ± 17	317 ± 14*	310 ± 13	321 ± 12*
pO_2/FiO_2					
VCV	587 ± 56	584 ± 59	598 ± 59	605 ± 64	608 ± 64*
HFOV°	623 ± 22	626 ± 26	627 ± 24	622 ± 43	627 ± 28
VCV + AICH	602 ± 59	608 ± 55	611 ± 53	596 ± 48	600 ± 63
HFOV + AICH^	604 ± 32	622 ± 34	634 ± 29*	620 ± 27*	641 ± 24*
Lactat, mmol $l^{-1\#}$					
VCV	2.2 ± 0.7	2.4 ± 0.8*	2.5 ± 0.8*	2.5 ± 0.7*	2.6 ± 0.7*
HFOV	2.4 ± 0.8	2.3 ± 0.8	2.3 ± 0.7	2.3 ± 0.7	2.3 ± 0.6
VCV + AICH	2.2 ± 0.7	2.2 ± 0.6	2.1 ± 0.6	2.0 ± 0.5*	2.1 ± 0.6*
HFOV + AICH	2.1 ± 0.6	2.2 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5
VCV					
Paw	7.1 ± 0.9	11.9 ± 0.8	17.3 ± 0.7	22.5 ± 0.9	6.6 ± 0.5
Esophageal pressure	2.0 ± 1.2	3.7 ± 1.4	5.8 ± 1.6	8.3 ± 1.7	1.7 ± 1.1
TPP	5.1 ± 1.1	8.2 ± 1.8	11.5 ± 1.7	14.2 ± 1.9	4.8 ± 1.2
CDP	10.1 ± 1.1	13.2 ± 1.8	16.5 ± 1.7	19.2 ± 1.9	9.8 ± 1.2
CDP conventional	12.1 ± 0.9	16.9 ± 0.8	22.3 ± 0.7	27.5 ± 0.9	11.6 ± 0.5
Delta CDP	2.0 ± 1.2	3.7 ± 1.4	5.8 ± 1.6	8.3 ± 1.7	1.7 ± 1.1
VCV + AICH					
Paw	6.8 ± 0.5	11.6 ± 0.6	17.4 ± 0.5	22.4 ± 1.0	6.6 ± 0.5
Esophageal pressure	2.2 ± 1.4	3.9 ± 1.7	5.5 ± 1.7	8.2 ± 2.0	2.6 ± 1.4
TPP	4.6 ± 1.4	7.7 ± 1.9	11.9 ± 2.1	14.2 ± 2.2	4.0 ± 0.9
CDP	9.6 ± 1.4	12.7 ± 1.9	16.9 ± 2.1	19.2 ± 2.2	9.0 ± 0.9
CDP conventional	11.8 ± 0.5	16.6 ± 0.6	22.4 ± 0.5	27.4 ± 1.0	11.6 ± 0.5
Delta CDP	2.2 ± 1.4	3.9 ± 1.7	5.5 ± 1.7	8.2 ± 2.0	2.6 ± 1.4

Values are mean (SD) of 8. *VCV* Conventional volume controlled ventilation group, *HFOV* high frequency oscillatory ventilation group, *VCV + AICH* conventional volume controlled ventilation + acute intracranial hypertension group, *HFOV + AICH* high frequency oscillatory ventilation + acute intracranial hypertension group, *PHa* arterial pH value, $PaCO_2$ partial arterial carbon dioxide pressure, PaO_2 partial arterial oxygen pressure *Paw* mean airway pressure, *TPP* transpulmonary pressure (TPP = Paw-esophageal pressure); *CD*P continuous distending pressure (TPP + 5 cmH_2O), *CDP conventional* continuous distending pressure (PAW + 5 cmH_2O), *Delta CPD* difference between CDP conventional and CDP. Levels of significance: * $P < 0.05$ vs. T_0/PEEP 5 (*Wilcoxon-test for paired samples); $^{\#}$ $P < 0.05$ influence of AICH; $^{+}$ $P < 0.05$ influence of PEEP without AICH; $^{-}$ $P < 0.05$ influence of PEEP with AICH; Inter-group comparison: ° $P < 0.05$ VCV vs. HFOV; ^ $P < 0.05$ VCV + AICH vs. HFOV + AICH; ($^{\#,\ +,\ -}$, °, ^assessed by ANOVA/multivariate linear regression model)

Hemodynamics

There was a significant reduction of MAP during VCV with a PEEP of 10 cmH_2O with both normal and elevated ICP (Table 2; Fig. 1). MAP was significantly reduced in all series at PEEP 15 cmH_2O and higher. Central venous pressure remained constant during HFOV but increased significantly under VCV and was significantly higher during VCV in animals with normal ICP. Mean pulmonary arterial pressure was significantly lower in HFOV + AICH compared with VCV + AICH. Pulmonary wedge pressure was higher ($P < 0.05$) in VCV in comparison to HFOV. ITBI decreased in both AICH groups at higher PEEP levels ($P < 0.05$).

Cardiac Function

Cardiac output decreased significantly during VCV at higher PEEP values with normal ICP but the changes were similar in both modes with elevated ICP (Table 2; Fig. 1). Stroke volume decreased significantly during VCV + AICH at PEEP 15 cmH_2O and with both ventilatory modes at PEEP 20 cmH_2O. It differed significantly between the groups with normal ICP. Intracranial hypertension significantly reduced global and right ventricular ejection fractions, and they were further decreased by VCV at PEEP 20 cmH_2O (Table 3). RVEDV differed significantly between VCV and HFOV. It increased during intracranial hypertension but was reduced at higher PEEP levels (Fig. 2). LHEDV was significantly lower in animals with increased ICP. End-diastolic volumes and ejection fractions increased sharply on the reduction of PEEP from 20 to 5 cmH_2O. The changes were not tested for significance.

Cerebral Blood Flow, Perfusion Pressure, Oxygenation, and ICP

CPP and mean cerebral blood flow (mCBF) were consistently higher under HFOV than under VCV (Table 4; Fig. 3). Cerebral tissue oxygen tension was higher under HFOV than under VCV at all PEEP levels in animals with normal ICP. This parameter decreased significantly with increased mean airway pressures in animals with intracranial hypertension, but there was no difference between the two ventilatory modes (Table 4). Reducing PEEP from 20 to 5 cmH_2O at the end of a series led to a surge in CPP, mCBF, and $P_{ti}O_2$, in some cases exceeding baseline values (Fig. 3).

Discussion

To our knowledge, this is the first study comparing the effects of low tidal volume, lung-protective ventilation (VCV), and HFOV on systemic and cerebral hemodynamics. This is a relevant issue since lung-protective ventilation is used prophylactically, whereas HFOV is usually initiated as a rescue measure in patients with severe ARDS when conventional ventilatory strategies with large tidal volumes and high PEEP have failed. A study comparing HFOV and high tidal volumes, and pressure-controlled ventilation in animals with acute lung injury revealed no differences between the two ventilatory methods with regard to the observed variables [18].

The main finding of the present study is that HFOV did not have detrimental effects on cerebral hemodynamics or right ventricular function in experimental animals, even in the presence of intracranial hypertension. The effects of increasing mean airway pressure on systemic hemodynamics, CBF, and $ptiO_2$ were similar to the two ventilatory methods. Gas exchange parameters and $ptiO_2$ were better under HFOV than under VCV. Similar effects were previously described in a small case series [17].

Many studies on HFOV employ a CDP that is set according to the mean airway pressure at each corresponding PEEP level [12, 14]. They also employ large tidal volumes of 10–12 ml kg^{-1} BW which give higher mean airway pressures. In this study, CDP during HFOV was based on mean transpulmonary pressures and not on mean airway pressures at the corresponding PEEP level. Talmor et al. [20] had demonstrated that TPP-guided ventilation was superior to the conventional algorithms for mechanical ventilation. The CDP levels in our study were, therefore, 25% lower at PEEP 15 cmH_2O and 30% lower at PEEP 20 cmH_2O than they would have been if they had been based on mean airway pressures. Mean airway pressures and subsequently mean TPP were, of course, lower due to the small tidal volumes. This leads to a further reduction of CDP that may be partially responsible for the less pronounced circulatory effects than those observed in a recently published study [14].

One factor limiting comparability of our study with most others was that we did not induce lung injury in our animals. The rationale for this study design was that we wished to test the feasibility of HFOV as a prophylactic measure because a large proportion of patients with traumatic brain injury develop lung failure during controlled ventilation [1, 2]. This has been shown to be due to the shear and distension stresses associated with large tidal volumes [3, 21]. The lung-protective ventilation strategy effectively reduces the incidence and the severity of lung damage by using small tidal volumes to minimize these injury mechanisms [3, 21]. HFOV takes the reduction of the tidal volume to an extreme and virtually eliminates the shear stresses involved in alveolar damage, and could therefore possibly be even more effective as a prophylactic measure.

Although HFOV compared favorably to conventional ventilation with high tidal volumes with regard to cerebral hemodynamics in animals with lung injury, it was not certain how it would compare, first of all, to small tidal

Table 2 Hemodynamic parameters

	T_0 = PEEP 5	PEEP 10	PEEP 15	PEEP 20	PEEP 5
HR, $min^{-1\#}$					
VCV	62 ± 15	60 ± 12	62 ± 15	56 ± 11	58 ± 13
HFOV	68 ± 22	68 ± 21	65 ± 23	64 ± 26	62 ± 22
VCV + AICH	89 ± 23	86 ± 17	90 ± 16	96 ± 18	96 ± 22
HFOV + AICH^	101 ± 22	103 ± 25	100 ± 27	98 ± 30	96 ± 28
MAP, $mmHg^{\#, +, -}$					
VCV	89 ± 20	78 ± 15*	69 ± 14*	62 ± 11*	99 ± 17
HFOV°	104 ± 17	101 ± 18	91 ± 16*	84 ± 17*	104 ± 19
VCV + AICH	109 ± 23	93 ± 18*	79 ± 17*	69 ± 13*	109 ± 28
HFOV + AICH^	111 ± 21	94 ± 17	79 ± 20*	75 ± 20*	102 ± 23
CVP, $mmHG^{+, -}$					
VCV	8.7 ± 4.6	12.5 ± 7.9	16.3 ± 7.4*	18.2 ± 7.6*	11.5 ± 5.8*
HFOV°	11.2 ± 6.3	11.5 ± 4.2	13.7 ± 9.5	13.6 ± 5.8	10.7 ± 5.8
VCV + AICH	13.5 ± 9.6	12.9 ± 7.0	13.7 ± 6.2*	15.1 ± 4.7*	11.6 ± 4.2*
HFOV + AICH	12.9 ± 9.1	13.3 ± 7.8	16.6 ± 1.9	16.7 ± 8.5	11.4 ± 7.2
mPAP, $mmHG^{\#, +, -}$					
VCV	17.6 ± 4.2	18.6 ± 3.7	21.8 ± 3.6*	25.8 ± 3.2*	20.7 ± 4.5*
HFOV	18.9 ± 4.8	20.1 ± 4.5	23.0 ± 4.3*	22.9 ± 5.3*	20.1 ± 4.9
VCV + AICH	19.7 ± 5.2	21.2 ± 4.3*	23.6 ± 3.2*	26.8 ± 4.1*	21.4 ± 5.4
HFOV + AICH^	19.8 ± 5.2	19.2 ± 4.8	20.9 ± 4.5	23.1 ± 5.0*	20.9 ± 6.3
PCWP, $mmHG^{+, -}$					
VCV	11.2 ± 2.7	12.6 ± 3.3*	13.4 ± 3.3*	15.4 ± 4.1*	14.3 ± 2.2*
HFOV°	13.6 ± 2.9	14.4 ± 4.0	15.1 ± 4.3	15.8 ± 3.1*	15.3 ± 2.8*
VCV + AICH	13.3 ± 3.6	13.0 ± 3.0	14.2 ± 2.7*	16.7 ± 3.3*	15.1 ± 3.5
HFOV + AICH	13.7 ± 3.4	13.1 ± 3.7	13.8 ± 4.0	14.1 ± 4.0	13.7 ± 4.0
CO, $l\ min^{-1\#, +, -}$					
VCV	2.9 ± 1.5	2.2 ± 0.8*	2.0 ± 0.4*	1.9 ± 0.4*	3.0 ± 0.4
HFOV°	3.0 ± 0.4	3.1 ± 0.5	2.7 ± 0.5	2.6 ± 0.6	3.0 ± 0.3
VCV + AICH	3.2 ± 1.1	2.9 ± 0.9*	2.5 ± 0.5*	2.3 ± 0.4*	3.4 ± 0.6
HFOV + AICH	3.7 ± 1.3	3.2 ± 1.0	2.5 ± 0.6*	2.4 ± 0.8*	3.4 ± 0.7
SV, $ml^{\#, -}$					
VCV	42 ± 15	39 ± 17	37 ± 14	36 ± 10	38 ± 10
HFOV°	43 ± 12	42 ± 11	43 ± 15	42 ± 10	47 ± 16
VCV + AICH	40 ± 10	36 ± 15	32 ± 12*	28 ± 8*	30 ± 13*
HFOV + AICH	35 ± 11	35 ± 14	29 ± 14	26 ± 9*	30 ± 9*
SVV, $\%^{\#, +, -}$					
VCV	10.1 ± 4.2	9.9 ± 3.3	12.1 ± 1.6	13.3 ± 2.2	8.5 ± 2.8
HFOV	9.5 ± 4.4	9.6 ± 4.4	10.7 ± 4.2	12.7 ± 4.5	8.4 ± 4.1
VCV + AICH	11.9 ± 4.1	11.4 ± 4.6	11.8 ± 3.5	14.7 ± 4.0*	8.9 ± 4.3
HFOV + AICH	10.6 ± 4.1	11.9 ± 4.3	12.5 ± 3.5	14.9 ± 3.6	8.9 ± 6.0
ITBI, $ml\ m^{2\#, -}$					
VCV	707 ± 378	555 ± 123	525 ± 86	530 ± 101	665 ± 125
HFOV	602 ± 100	656 ± 232	615 ± 18	606 ± 229	656 ± 174
VCV + AICH	589 ± 70	514 ± 96*	480 ± 91*	458 ± 100*	556 ± 83
HFOV + AICH	570 ± 106	525 ± 94*	472 ± 76*	454 ± 69*	559 ± 97
ELWI, ml/kg					
VCV	9.3 ± 6.0	6.8 ± 2.8	6.7 ± 3.3	6.1 ± 2.2	6.5 ± 1.7
HFOV	6.1 ± 2.3	7.5 ± 5.8	7.8 ± 6.6	7.9 ± 6.6	7.5 ± 4.0
VCV + AICH	5.7 ± 1.2	5.7 ± 1.4	5.6 ± 1.7	5.7 ± 1.8	5.6 ± 1.5
HFOV + AICH	6.7 ± 3.9	7.1 ± 4.5	7.1 ± 4.7	7.1 ± 5.3	6.9 ± 4.0

Values are mean (SD) of eight. See text or Table 1 for description of groups. *HR* Heart rate, *MAP* mean arterial pressure, *CVP* central venous pressure, *mPAP* mean pulmonary artery pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *SV* stroke volume, *SVV* stroke volume variation, *ITBI* intrathoracic blood volume index, *ELWI* extravascular lung water index. Levels of significance: * $P < 0.05$ vs. T_0/PEEP 5 (* Wilcoxon-test for paired samples); $^{\#}$ $P < 0.05$ influence of AICH; $^{+}$ $P < 0.05$ influence of PEEP without AICH; $^{-}$ $P < 0.05$ influence of PEEP with AICH; Inter-group comparison: ° HFOV vs. VCV; ^ HFOV + AICH vs. VCV + AICH, all $P < 0.05$; ($^{\#, +, -}$, °, ^assessed by ANOVA/multivariate linear regression model)

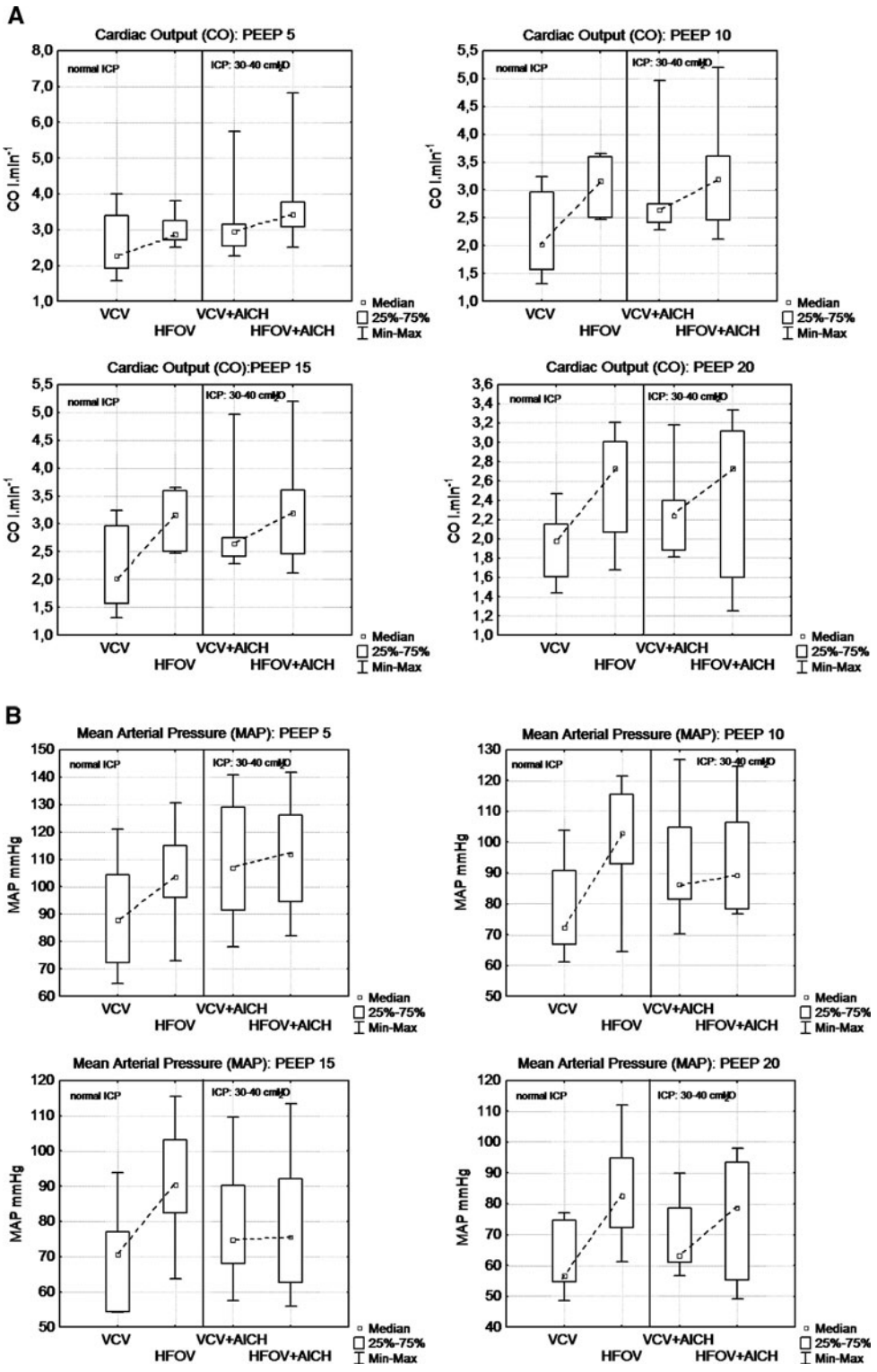

Fig. 1 Data are presented as median, 25 and 75% quartiles, minimum and maximum ($n = 8$). *VCV* Conventional volume controlled ventilation group, *HFOV* high frequency oscillatory ventilation group, *VCV + AICH* conventional volume controlled ventilation + acute intracranial hypertension group, *HFOV + AICH* high frequency oscillatory ventilation + acute intracranial hypertension group. **a** cardiac out in ml^{-1} during PEEP 5, 10, 15 and 20. **b** Mean arterial pressure in mmHg during PEEP 5, 10, 15, and 20

volume ventilation, and second, in animals with normal lungs.

At a PEEP of 10 cmH_2O and the corresponding CDP, HFOV had a significantly smaller impact on MAP, cardiac output, stroke volume, and cerebral blood flow than VCV. This difference disappeared at higher PEEP levels. In a study examining the effects of increased PEEP (5–20 cmH_2O) on cerebral perfusion and hemodynamics in healthy pigs,

Table 3 Cardiac function parameter

	T_0 = PEEP 5	PEEP 10	PEEP 15	PEEP 20	PEEP 5
GEF, %$^{\#,\ -}$					
VCV	30 ± 11	35 ± 11	31 ± 11	29 ± 9	38 ± 7*
HFOV	36 ± 11	34 ± 7	35 ± 7	35 ± 6	35 ± 10
VCV + AICH	33 ± 9	31 ± 10	29 ± 10	24 ± 10*	31 ± 11
HFOV + AICH	31 ± 7	31 ± 12	25 ± 12	26 ± 9	28 ± 8
RVEF, %$^{\#,\ +,-}$					
VCV	38 ± 14	33 ± 10	31 ± 9	27 ± 6	38 ± 8
HFOV	35 ± 10	36 ± 9	34 ± 9	33 ± 12	37 ± 9
VCV + AICH	32 ± 9	29 ± 10	27 ± 1	24 ± 7*	29 ± 8
HFOV + AICH	28 ± 9	26 ± 8	27 ± 6	26 ± 6	30 ± 8
RVEDV, ml$^{\#,\ -}$					
VCV	83 ± 25	80 ± 28	76 ± 24	80 ± 25	103 ± 39*
HFOV°	110 ± 48	94 ± 28	89 ± 30*	92 ± 36	183 ± 31*
VCV + AICH	103 ± 38	106 ± 43	104 ± 48	91 ± 40	110 ± 33
HFOV + AICH	122 ± 46	118 ± 46	90 ± 22*	84 ± 21*	110 ± 38*
RHEDV, ml					
VCV	172 ± 51	164 ± 57	157 ± 48	168 ± 53	216 ± 91
HFOV	223 ± 111	185 ± 39	171 ± 45*	183 ± 73	183 ± 31
VCV + AICH	193 ± 57	188 ± 70	192 ± 84	176 ± 88	198 ± 51
HFOV + AICH	220 ± 67	216 ± 80	167 ± 44*	157 ± 38*	196 ± 55
LHEDV, ml$^{\#,\ -}$					
VCV	431 ± 236	341 ± 172	285 ± 77*	281 ± 126*	479 ± 104
HFOV	328 ± 95	374 ± 219	350 ± 196	372 ± 210	372 ± 159*
VCV + AICH	305 ± 102	246 ± 122*	214 ± 133*	245 ± 109*	270 ± 83
HFOV + AICH	261 ± 134	227 ± 139	223 ± 91	227 ± 78	275 ± 113

Values are mean (SD) of eight. See text or Table 1 for description of groups. *GEF* Global ejection fraction, *RVEF* right ventricle ejection fraction, *RVEDV* right ventricle end-diastolic volume, *RHEDV* right heart end-diastolic volume, *LHEDV* left heart end-diastolic volume. Levels of significance: * $P < 0.05$ vs. T_0/PEEP 5 (*Wilcoxon-test for paired samples); $^{\#}$ $P < 0.05$ influence of AICH; $^{+}$ $P < 0.05$ influence of PEEP without AICH; $^{-}$ $P < 0.05$ influence of PEEP with AICH; Inter-group comparison: ° $P < 0.05$ VCV vs. HFOV; ^ $P < 0.05$ VCV + AICH vs. HFOV + AICH; ($^{\#,\ +,\ -}$, °, ^assessed by ANOVA/multivariate linear regression model)

Münch et al. [22] only observed an increase of central venous pressure. In their follow-up study in patients with subarachnoid hemorrhage, they observed a reduction of MAP and mCBF under VCV, which is consistent with the data of our study. One reason that these effects were not seen in their pig model is perhaps because their animals were studied in the prone position, whereas in our study they were supine. We observed a significant ICP increase when the animals were turned from the prone to the supine position, and this could have affected the starting conditions.

Cardiac output, stroke volume, and mean arterial pressure were significantly higher under HFOV in animals with normal ICP, but not after intracranial hypertension had been instituted. The acute elevation of ICP had a significant impact on global ejection fraction (GEF), right ventricle ejection fraction (RVEF), right ventricle end-diastolic volume (RVEDV), left heart end-diastolic volume (LHEDV), and heart rate. Intracranial hypertension significantly reduced ITBI and rendered it more sensitive to airway pressure changes in both ventilatory modes. The initial increase in sympathetic outflow [23] may have masked the hemodynamic effects of this relative hypovolemia, since there were no corresponding changes of MAP or CO. Cardiovascular instability is observed in brain dead patients with cessation of sympathetic outflow or in heart transplant recipients with cardiac sympathetic denervation [24, 25]. However, stroke volume was decreased by higher PEEP levels only during the series with intracranial hypertension, which could indicate a direct effect on ventricular function [26]. Clinical data supporting this possibility showed that left ventricular dysfunction occurs in up to 10% of patients with severe brain injury [27]. Attention should thus be given to adequate the fluid therapy during the intracranial hypertension and ventilation with higher airway pressures while not

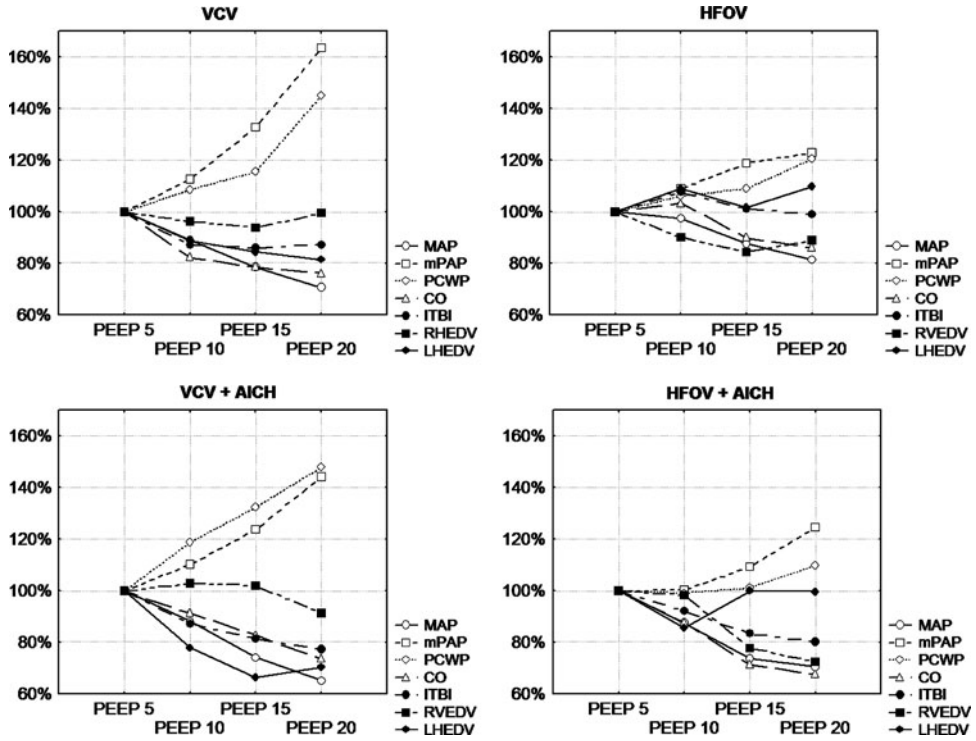

Fig. 2 The data shown are the median values of each parameter calculated as a percentage of the baseline at PEEP 5 (baseline = 100%). *VCV* Conventional volume controlled ventilation group, *HFOV* high frequency oscillatory ventilation group, *VCV + AICH* conventional volume controlled ventilation + acute intracranial hypertension group, *HFOV + AICH* high frequency oscillatory ventilation + acute intracranial hypertension group, *MAP* mean arterial pressure, *mPAP* mean pulmonary pressure, *PCWP* pulmonary capillary wedge pressure, *CO* cardiac output, *ITBI* intrathoracic blood volume, *RVEDV* right ventricular end diastolic volume, *LHEDV* left heart end diastolic volume, *PEEP 5* baseline value, *PEEP 10* value at PEEP 10 related to baseline, *PEEP 15* value at PEEP 15 related to baseline, *PEEP 20* value at PEEP level 20 related to baseline

Table 4 Cerebral hemodynamics and tissue oxygen tension

	T_0 = PEEP 5	PEEP 10	PEEP 15	PEEP 20	PEEP 5
mICP, $cmH_2O^{\#,+,-}$					
VCV	16.3 ± 5.0	16.6 ± 3.3	18.0 ± 2.9	19.7 ± 3.2	16.8 ± 3.07
HFOV	17.0 ± 4.0	17.4 ± 2.9	18.1 ± 2.8	18.8 ± 3.3	16.6 ± 3.27
VCV + AICH	35.1 ± 4.2	36.9 ± 6.9	36.3 ± 6.8	35.9 ± 7.2	39.4 ± 7.71
HFOV + AICH	37.4 ± 7.8	34.3 ± 7.8	33.5 ± 7.9	34.1 ± 7.2	36.8 ± 11.3
$PtiO_2$, mmHG					
VCV	48.4 ± 26.7	46.7 ± 27.8	48.1 ± 31.0	49.0 ± 33.4	52.7 ± 34.7
HFOV°	59.7 ± 39.7	60.5 ± 41.6	59.8 ± 42.9	59.7 ± 43.7	66.6 ± 36.3*
VCV + AICH	71.3 ± 27.2	63.7 ± 21.2*	52.8 ± 22.8*	43.6 ± 23.5*	47.1 ± 33.3*
HFOV + AICH	61.1 ± 13.7	60.8 ± 13.6	55.3 ± 16.3*	51.8 ± 20.0*	48.5 ± 33.4
mCBF, $ml/min^{-1\#,+,-}$					
VCV	428 ± 137	374 ± 135*	330 ± 101*	293 ± 73*	527 ± 122*
HFOV°	563 ± 173	532 ± 195	465 ± 181*	410 ± 168*	540 ± 194
VCV + AICH	544 ± 188	480 ± 139*	398 ± 120*	340 ± 97*	573 ± 187
HFOV + AICH	589 ± 202	510 ± 182*	404 ± 124*	379 ± 165*	559 ± 210
CPP, $mmHG^{\#,+,-}$					
VCV	70.7 ± 17.2	60.2 ± 13.8*	49.7 ± 13.1*	40.0 ± 9.4*	78.7 ± 17.5
HFOV°	85.3 ± 17.1	82.4 ± 18.3	71.7 ± 16.7*	64.2 ± 18.1*	83.4 ± 18.9
VCV + AICH	71.3 ± 20.5	55.7 ± 16.3*	42.0 ± 14.9*	32.7 ± 11.0*	62.5 ± 22.8
HFOV + AICH	68.5 ± 15.6	62.2 ± 15.1	48.2 ± 19.3*	42.7 ± 17.9*	69.6 ± 25.0

Values are mean and standard deviation of eight animals. See text or Table 1 for description of groups. *mICP* Mean intracranial pressure, $mPtiO_2$ partial brain tissue oxygen pressure, *mCBF* mean cerebral blood flow, *CPP* cerebral perfusion pressure. Levels of significance: * $P < 0.05$ vs. T_0/PEEP 5 (*Wilcoxon-test for paired samples); $^{\#}$ $P < 0.05$ influence of AICH; $^{+}$ $P < 0.05$ influence of PEEP without AICH; $^{-}$ $P < 0.05$ influence of PEEP with AICH; Inter-group comparison: ° $P < 0.05$ VCV vs. HFOV; ^ $P < 0.05$ VCV + AICH vs. HFOV + AICH; ($^{\#,+,-}$, °, ^assessed by ANOVA/multivariate linear regression model)

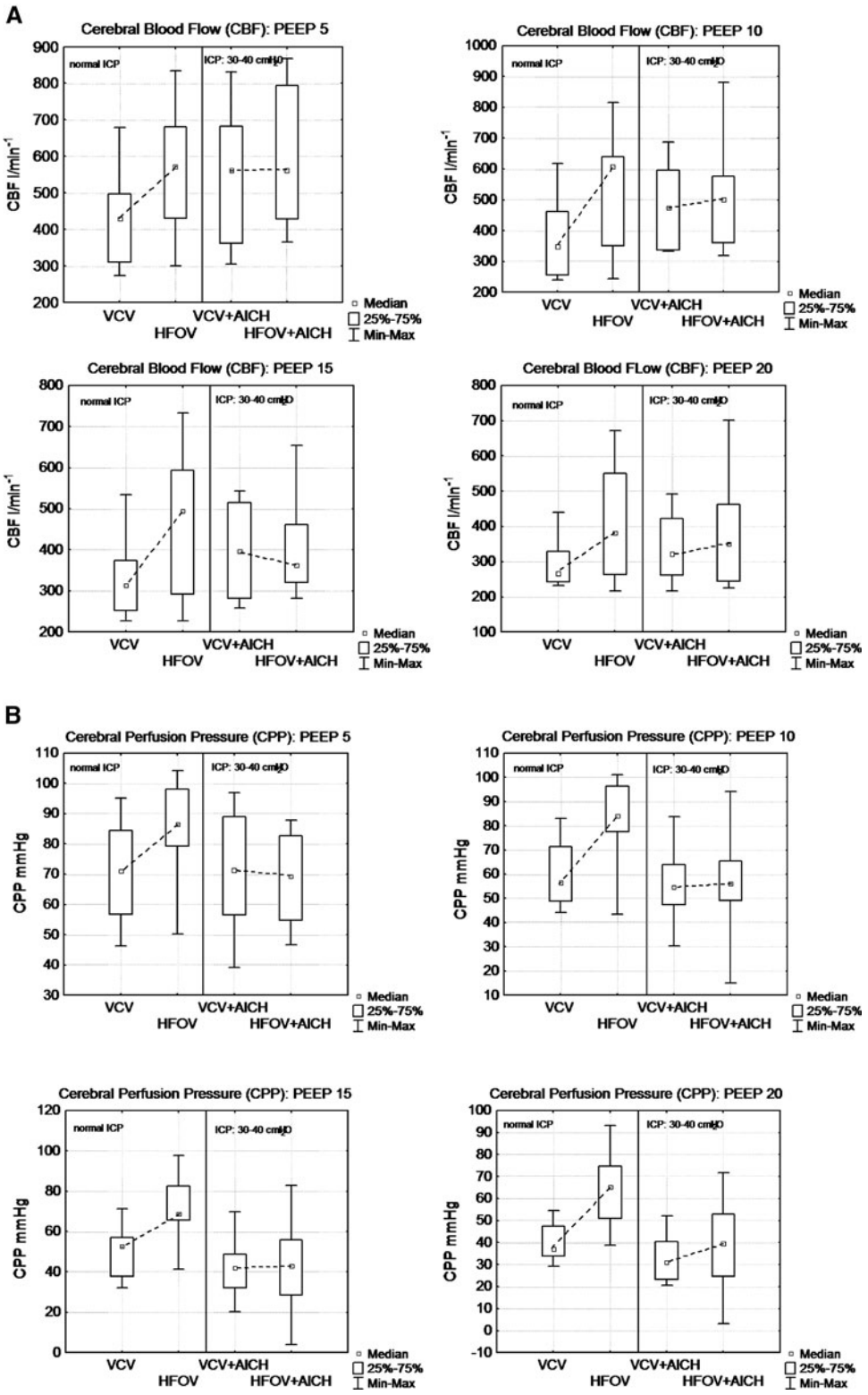

Fig. 3 Data are presented as median, 25 and 75% quartiles, minimum and maximum ($n = 8$). *VCV* Conventional volume controlled ventilation group, *HFOV* high frequency oscillatory ventilation group, *VCV + AICH* conventional volume controlled ventilation + acute intracranial hypertension group, *HFOV* + AICH high frequency oscillatory ventilation + acute intracranial hypertension group. **a** Cerebral blood flow in ml^{-1} during PEEP 5, 10, 15 1, and 20. **b** Cerebral perfusion pressure in mmHg during PEEP 5, 10, 15, and 20

neglecting the possible negative impact of volume overload on lungs and brain [28].

ITBI is considered one of the best parameters for assessing pre-load [29] and should therefore be measured in hemodynamically unstable patients with acute brain injury. The animals in our study seemed to be more prone to reduced venous return with decreased pre-load during VCV than during HFOV, although the observed difference

was not statistically significant. Mean PAP was higher during VCV than during HFOV with and without intracranial hypertension. This might have reduced left ventricular filling and could explain the moderate differences between the two groups in left and right end-diastolic volumes (Table 2).

Limitations

The primary limitation of this study was that we were unable to randomize the order of the applied ventilatory modes, since the transpulmonary pressures used for the HFOV settings were determined during the preceding phase with conventional ventilation. The sequence of PEEP settings could have been randomized, but we believe that the period of deflation and following alveolar recruitment was sufficient to minimize memory effects in the lung. There is the possibility that using each animal for all ventilator modes might induce factors relating to the history of the lung, which as a consequence might influence subsequent measurements. This could be reflected by differences seen in the baseline values. However, performing all measurements in a single animal has the advantage of reducing inter-individual variability and allows the use of paired-data analysis that gives a higher statistical power and reduces the risk of type II error.

We did not induce ARDS in the study animals, as has been done in other studies, because we were not interested in the effects of HFOV in the injured lung but in its effects before lung injury sets in.

Conclusions

The study results show that HFOV guided by transpulmonary pressure is equal or superior to conventional ventilatory regimens with regard to systemic and cerebral hemodynamics and cerebral tissue oxygenation in animals with increased ICP. It might therefore be useful as a prophylactic approach to also prevent lung failure, not only as a rescue strategy once lung failure has set in. The promising results in neonates and from small clinical studies justify large scale trials with HFOV initiated immediately after admission of the patient to the ICU.

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