



Impact on cerebral hemodynamics of the use of volume guarantee combined with high frequency oscillatory ventilation in a neonatal animal respiratory distress model

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Abstract

High-frequency oscillatory ventilation (HFOV) is an alternative to conventional mechanical ventilation (CMV). Recently, the use of volume guarantee (VG) combined with HFOV has been suggested as a safe strategy capable of reducing the damage induced by ventilation in immature lungs. However, the possible impact of this new ventilation technique on cerebral hemodynamics is unknown. To evaluate the cerebral hemodynamics effect of HFOV combined with VG in an experimental animal model of neonatal respiratory distress syndrome (RDS) due to surfactant deficiency compared with HFOV and CMV+VG (control group). Eighteen newborn piglets were randomized, before and after the induction of RDS by bronchoalveolar lavage, into 3 mechanical ventilation groups: CMV, HFOV and HFOV with VG. Changes in cerebral oxygen transport and consumption and cerebral blood flow were analyzed by non-invasive regional cerebral oxygen saturation (CrSO₂), jugular venous saturation (SjO₂), the calculated cerebral oxygen extraction fraction (COEF), the calculated cerebral fractional tissue oxygen extraction (cFTOE) and direct measurement of carotid artery flow. To analyze the temporal evolution of these variables, a mixed-effects linear regression model was constructed. After randomization, the following statistically significant results were found in every group: a drop in carotid artery flow: at a rate of -1.7 mL/kg/min (95% CI: -2.5 to -0.81; $p < 0.001$), CrSO₂: at a rate of -6.2% (95% CI: -7.9 to -4.4; $p < 0.001$) and SjO₂: at a rate of -20% (95% CI: -26 to -15; $p < 0.001$), accompanied by an increase in COEF: at a rate of 20% (95% CI: 15 to 26; $p < 0.001$) and cFTOE: at a rate of 0.07 (95% CI: 0.05 to 0.08; $p < 0.001$) in all groups. No statistically significant differences were found between the HFOV groups.

Conclusion: No differences were observed at cerebral hemodynamic between respiratory assistance in HFOV with and without VG, being the latter ventilatory strategy equally safe.

What is Known:

- Preterm have a situation of fragility of cerebral perfusion which means that any mechanical ventilation strategy can have a significant influence. High-frequency oscillatory ventilation (HFOV) is an alternative to conventional mechanical ventilation (CMV). Recently, the use of volume guarantee (VG) combined with HFOV has been suggested as a safe strategy capable of reducing the damage induced by ventilation in immature lungs. Several studies have compared CMV and HFOV and their effects at hemodynamic level. It is known that the use of high mean airway pressure in HFOV can cause an increase in pulmonary vascular resistance with a decrease in thoracic venous return.

What is New:

- The possible impact of VAFO + VG on cerebral hemodynamics is unknown. Due the lack of studies and the existing controversy, we have carried out this research project in an experimental animal model with the aim of evaluating the cerebral hemodynamic repercussion of the use of VG in HFOV compared to the classic strategy without VG.

Keywords Neonatal respiratory distress syndrome · High frequency ventilation · Volume guarantee · Cerebral blood flow · Near-infrared spectroscopy

Abbreviations

A-aDO₂ Alveolar-arterial difference of oxygen
BAL Bronchoalveolar lavage

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BE	Base excess
BPD	Bronchopulmonary dysplasia
CBF	Cerebral blood flow
Cdyn	Dynamic compliance
cFTOE	Cerebral fractional tissue oxygen extraction
CMV	Conventional mechanical ventilation
COEF	Cerebral oxygen extraction fraction
CrSO ₂	Non-invasive regional cerebral oxygen saturation
CSOR	Cerebral-somatic ratio
DO ₂	Oxygen delivery
FiO ₂	Inspired oxygen fraction
Hb	Hemoglobin
HFOV	High-frequency oscillatory ventilation
HFOV + VG	High-frequency oscillatory ventilation with volume guarantee
HR	Heart rate.
Hz	Frequency
MAP	Mean arterial pressure
mPaw	Mean airway pressure
NIRS	Near-infrared spectroscopy
P _a CO ₂	Arterial partial pressure of carbon dioxide
P _a O ₂	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure
PIP	Peak inspiratory pressure
PSV+VG	Pressure support ventilation with volume guarantee
RDS	Respiratory distress syndrome
RrSO ₂	Somatic regional oxygen saturation
SatO ₂	Transcutaneous oxygen saturation
sFTOE	Somatic fractional tissue oxygen extraction
SjO ₂	Jugular venous saturation
SO ₂	Oxyhemoglobin saturation
T ^a	Temperature
VG	Volume guarantee
VO ₂	Oxygen consumption
VThf	High-frequency tidal volume
Vt	Tidal volume
ΔPhf	Oscillation pressure amplitude

Introduction

Respiratory distress syndrome (RDS) continues to be the main causes of morbidity and mortality in prematurity, with the risk of bronchopulmonary dysplasia (BPD) being high [1]. Although the pathogenesis of BPD is multifactorial, invasive mechanical ventilation is one of the most relevant etiological factors [2–4].

An alternative to conventional mechanical ventilation (CMV) is **high-frequency oscillatory ventilation (HFOV)**. In recent years, the possibility of directly controlling high-frequency tidal volume (VThf) by incorporating volume

guarantee (VG) represents a new alternative with the theoretical advantage of keeping the volumes generated at high frequency constant and reducing them to the minimum, thus avoiding exposure of the most immature lungs to large volumes [5–7].

Several studies have compared CMV and HFOV and their effects at hemodynamic level. It is known that the use of high mean airway pressure (mPaw) in HFOV can cause an increase in pulmonary vascular resistance with a decrease in thoracic venous return [8–10]. However, some studies that used optimal mPaw reported no decrease in ventricular function or cardiac output [11–13].

Premature infants have a high risk of long-term neurological sequelae; the etiology being multifactorial [14]. One important point is the **impaired cerebral blood flow (CBF) autoregulation**, making them especially vulnerable to changes in blood pressure [15, 16].

This situation of this fragility of cerebral perfusion means that any mechanical ventilation strategy can have a significant influence, so this new HFOV with VG could have a potential effect on cerebral perfusion. However, no studies have evaluated this effect. To better analyzed this new ventilatory strategy on cerebral hemodynamics, HFOV with or without VG were compared in an experimental model of neonatal RDS due to surfactant deficiency.

Materials and methods

Study subjects

Eighteen healthy at term *Landrace-Large White* piglets of 24–96 h of life with an average body weight of 1500–2500 g. The minimum sample size was used to find significant differences. In the preparation of the experimental model, 6 animals which were not included in the study were used. This study was approved by the Institutional Animal Care and Use Committee (Ethical Committee CEEA/OH 002-002/2019 Ref. PROEX 169/19) and carried out in accordance with the terms authorized by the European and National Regulations on the Handling of Experimental Animals (2010/63/UE and Royal Decree 53/2013). ARRIVE guidelines have been followed.

Anesthesia

Induction of general anesthesia was performed with 8% sevoflurane vaporized in oxygen, morphine (1 mg/kg) and muscle relaxant (rocuronium 0.6 mg/kg) as a bolus; general anesthesia was subsequently maintained by continuous intravenous infusion of propofol (5–30 mg/kg/hour).

Animal preparation

Once an adequate level of anesthesia was achieved, endotracheal intubation by tracheostomy and tracheal ligation was done, using a 3 mm diameter endotracheal tube, to prevent any air leaks. A peripheral intravenous line was placed (24G polyethylene catheter) for continuous perfusion of isotonic saline solution (10 ml/kg/hour) and propofol.

Piglets were connected to the respirator (*Babylog VN500*, *Dräger*[®], *Lübeck, Germany*), set to CMV using pressure support ventilation (PSV), in VG mode, with the following initial settings: a positive end-expiratory pressure (PEEP) of 6 cmH₂O, inspired oxygen fraction (FiO₂) of 40% to maintain a transcutaneous oxygen saturation (SatO₂) of 90–95%, a respiratory rate of 60 rpm and a tidal volume (Vt) 7 ml/kg to achieve an arterial partial pressure of carbon dioxide (P_aCO₂) of 40–55 mmHg. Peak inspiratory pressure (PIP) was defined to enable automatic adjustment by the respirator to achieve the Vt set.

Monitoring

To monitor cerebral hemodynamics, the following were used:

- Ultrasonic flow probe in the left carotid artery (*Transonic*[®] Flowprobe, *Transonic Systems INC, NY, USA*) to measure cerebral blood flow using a flow meter (*T206 blood flow meter, Transonic Systems INC, NY, USA*).
- *INVOS 5100 Monitor*[®] (*Covidien, Dublin, Ireland*) with two neonatal near-infrared spectroscopy sensors placed in the frontomedial region to monitor cerebral regional oxygen saturation (CrSO₂) and another in the thoracolumbar region to monitor somatic regional oxygen saturation (RrSO₂).
- Right femoral artery (20G polyethylene catheter) and right jugular vein (22G polyethylene catheter) with retrograde cannulation to the jugular bulb: for measurement of cerebral oxygen consumption by difference between arterial and venous blood gases (*IL 1306 ph/Blood Gas Analyzer, Allied Instrumentation*) and continuous monitoring of blood pressure through a calibrated pressure transducer

- Continuous monitoring of the electrocardiogram and heart rate, as well as SatO₂ (using a pulse oximeter placed on the leg) and rectal temperature (maintained between 37 and 39 °C).

Experimental protocol

After an initial 60-min stabilization period and once adequate CMV ventilation was achieved, bronchoalveolar lavage (BAL) was performed with 5 aliquots of 10 ml/kg of isotonic saline solution warmed to body temperature (38 °C), to decrease lung compliance due to surfactant depletion. Before and after BAL, pulmonary dynamic compliance (C_{dyn}) was noted, and the alveolar-arterial difference of oxygen (A-aDO₂) was calculated (moderate disease 200–500 mmHg) (Fig. 1) [17].

After BAL, FiO₂ increased to 100% and HFOV (mPaw 10 cm H₂O, at a frequency of 10 Hz and VThf 2.5 ml/kg) was initiated to perform a lung recruitment maneuver to ensure alveolar re-expansion and avoid the appearance of atelectasis [5].

After lung recruitment, animals were randomized, and the ventilation strategy was initiated in accordance with the protocol assigned to each group (Fig. 2), with data collection for a period of 2 h from stabilization after lung recruitment. Random numbers were generated using the standard=RAND() function in Microsoft Excel[®]. At the end of the study, animals were sacrificed with an overdose of propofol, followed by potassium chloride bolus (10 mEq/kg).

Since this was a strict experimental model, the confusion variables were reduced to a minimum.

Data collection

Arterial and venous blood samples were taken blood gas analysis, initially every 20 min until the target P_aCO₂ was reached and, subsequently, at one hour and at 2 h after the start of the assigned strategy. Ventilator and regional oxygen

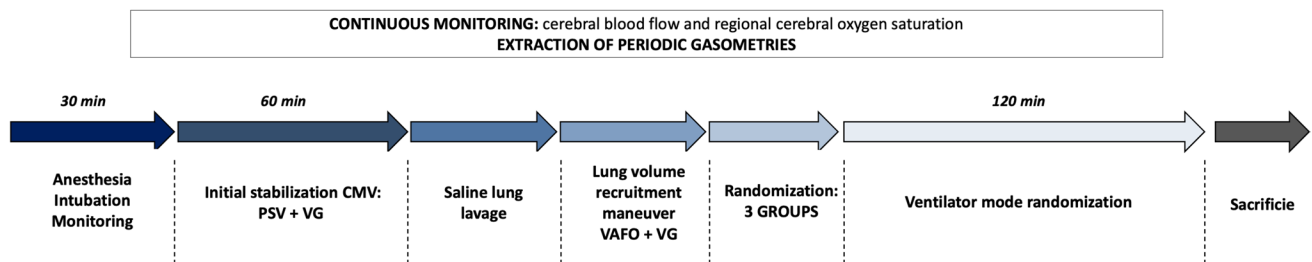


Fig. 1 Timeline of the experimental model. PSV + VG: Pressure support ventilation with volume guarantee

saturation data were obtained from the ventilator and the INVOS devices through an USB port. Data on carotid artery flow and other hemodynamic and respiratory variables, temperature, and sedation were collected. Data were collected every 10 min. Calculations were performed for cerebral fractional tissue oxygen extraction (cFTOE): $(\text{satO}_2 \text{ pulse oximetry} - \text{CrSO}_2) / \text{satO}_2 \text{ pulse oximetry}$; somatic fractional tissue oxygen extraction (sFTOE): $(\text{satO}_2 \text{ pulse oximetry} - \text{RrSO}_2) / \text{satO}_2 \text{ pulse oximetry}$; cerebral oxygen extraction fraction (COEF): $(\text{arterial SO}_2 - \text{SjO}_2) / \text{arterial SO}_2 \times 100$; cerebral-somatic ratio (CSOR): $\text{RrSO}_2 / \text{CrSO}_2$.

The evolution of arterial blood gases was analyzed at 4 moments: in the 1st hour of stabilization and after randomization (at 20, 60 and 120 min, prior to animal sacrifice). The data on the COEF and jugular venous saturation (SjO_2) were analyzed at 3 moments: in the 1st hour of stabilization and after randomization (at 60 and 120 min). Other hemodynamics were evaluated at 5 moments: pre-randomization and post-randomization (at 20, 60, 90 and 120 min).

Statistics

Descriptive statistics were calculated according to their nature. The median and interquartile range for the quantitative variables were reported. The possible association between the non-longitudinal quantitative variables of the study and the experimental groups was studied using the Wilcoxon signed-rank

test. To analyze the temporal evolution of the quantitative variables, a mixed-effects linear regression model was constructed, in which time, the experimental group, and the interaction between the two were considered as fixed effects. A random effect was included to account for the variability of repeated measures over time for each animal. A p -value threshold of 0.05 was used to determine statistical significance. All analyses were performed with R Statistical Software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

The median body weight of the piglets was 2.05 kg (IQR 1.80-2.20) with a median age of 3 days of life (IQR 2-4). 16 of the 18 animals were male (88%).

Initial stabilization and saline lung lavage

All animals were adequately ventilated and oxygenated. No differences were observed in hemodynamic parameters during the first 60 min. Similar respiratory distress occurs after BAL in all the animals without differences between groups ($p=0.2$). The median of the $A-a \text{ DO}_2$ after BAL was: PSV+VG group, 382 mmHg (IQR 330-413); HOFV group, 358 mmHg (IQR 282-434); HOFV + VG group, 308 mmHg (IQR 240-378).

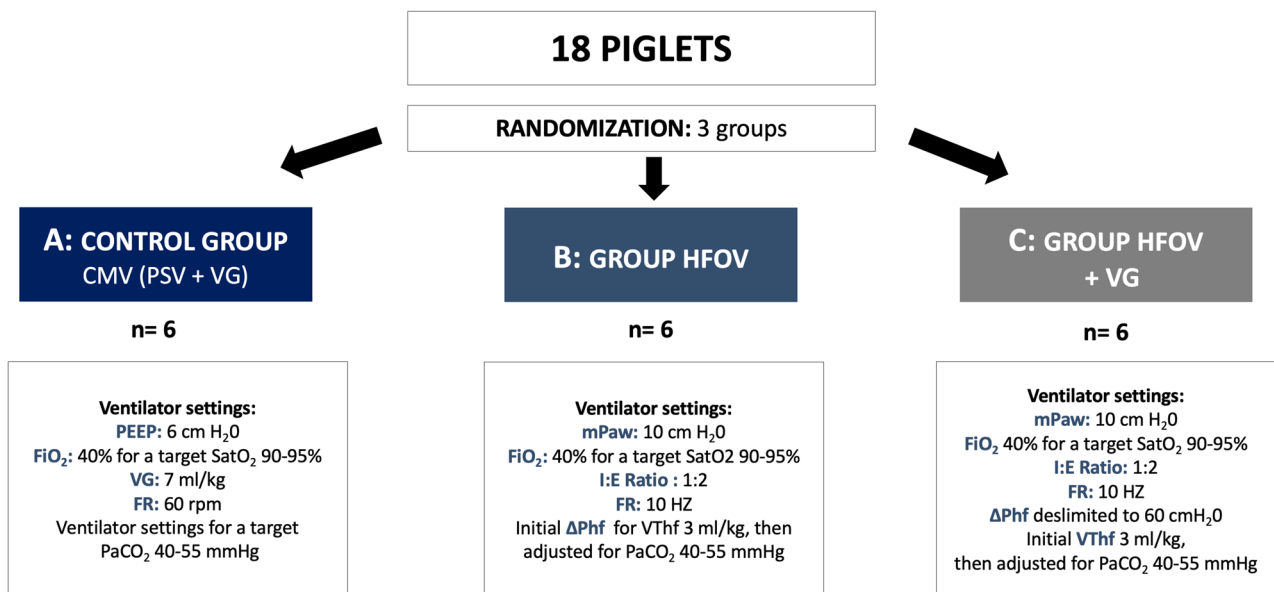


Fig. 2 Randomization groups of the experimental model. FiO_2 : inspired oxygen fraction; CMV: conventional mechanical ventilation; PSV+VG: pressure support ventilation with volume guarantee; HFOV: high-frequency oscillatory ventilation; HFOV + VG: high-frequency oscillatory ventilation with volume guarantee; PaCO_2 : arte-

rial partial pressure of carbon dioxide; I:E ratio: inspiration: expiration ratio; ΔPhf : oscillation pressure amplitude; Hz: frequency; VThf : high-frequency tidal volume; mPaw : mean airway pressure; SatO_2 : oxygen transcutaneous saturation; PEEP: positive endexpiratory pressure; VG: volume guarantee

Pre-randomization situation

The baseline situation prior to randomization after BAL and lung recruitment was similar in all piglets, with no significant differences found between groups, except for *carotid artery flow* (Table 1). All animals at that moment were ventilated on HFOV+VG.

Ventilator settings and parameters

After randomization, the ΔPhf , $VThf/kg$ and DCO_2 values were modeled using linear mixed-effects regression without detecting differences between the 2 groups ventilated with HFOV. When comparing the medians, no significant differences were found either: ΔPhf 44 (IQR 41-78) vs 39 (IQR 34-55), $p > 0.9$; $VThf/kg$ 3.2 (IQR 3-3.33) vs 3.19 (IQR 3.04-3.2), $p > 0.9$; DCO_2 120 (IQR 90-113) vs 120 (IQR 93-102), $p > 0.9$, for HFOV with VG and HFOV without VG, respectively. A $mPaw$ of 10 cmH_2O with 10 Hz remained constant in both groups after randomization.

Hemodynamic and cerebral blood flow changes:

1. Comparison between PSV+VG vs HFOV and HFOV+VG:
 - a. Changes in arterial blood gas analyses:

No significant differences were found between groups in pH , pO_2 , pCO_2 , *oxyhemoglobin saturation* (SO_2) and *glucose* at the 4 moments studied. However, significant differences were detected over time in the 18 animals, with no differences between the study groups in 3 variables. *Hemoglobin (Hb)*: Constant decrease at a rate of -0.27 g/dl (95% CI: -0.5 to -0.03; $p = 0.028$); *Lactic acid*: constant increase at a rate of 0.52 mmol/L (95% CI: 0.29 to 0.75; $p < 0.001$); *Base excess (BE)*: constant decrease at a rate of -1.9 mmol/L (95% CI: -2.7 to -1.1; $p < 0.001$) (Table 2).
 - b. Changes in hemodynamic parameters:

Mean arterial pressure (MAP) steadily decreased at a rate of -2.6 mmHg (95% CI: -4.1 to -1.1; $p < 0.001$) over time regardless of the treatment group. The HFOV with VG group had on average 16

Table 1 Baseline characteristics of the 3 groups at pre-randomization situation

	GROUPS		
	A: PSV+VG ^a	B: HFOV ^a	C: HFOV + VG ^a
CrSO₂ (%)	64 (62, 68)	72 (62, 78)	72 (66, 75)
RrSO₂ (%)	51 (43, 62)	44 (37, 49)	43 (42, 50)
cFTOE	0.31 (0.28, 0.37)	0.28 (0.21, 0.37)	0.29 (0.25, 0.34)
sFTOE	0.47 (0.38, 0.55)	0.55 (0.51, 0.63)	0.56 (0.50, 0.58)
CSOR	0.81 (0.64, 0.88)	0.65 (0.61, 0.72)	0.64 (0.61, 0.69)
Carotid artery flow/Kg (ml/kg/min)	13.9 (13.3, 15.3) ^{b*,**}	23.9 (18.6, 27.8)	20.9 (18.8, 24.9)
HR (bpm)	207 (188, 242)	212 (196, 236)	238 (237, 240)
MBP (mmHg)	61 (54, 62)	63 (57, 68)	68 (66, 72)
SatO₂ (%)	96 (94, 99)	99 (99, 100)	100 (99, 100)
T^a (°C)	37.9 (37.68, 38.12)	37.70 (37.15, 38.25)	37.90 (37.58, 38.22)
Propofol dose (mg/Kg/hour)	15 (14, 26)	22 (18, 27)	31 (23, 37)

CrSO₂ Cerebral regional oxygen saturation, *RrSO₂* Renal regional oxygen saturation, *cFTOE* cerebral fractional tissue oxygen extraction, *sFTOE* somatic fractional tissue oxygen extraction, *CSOR* Cerebro-splanchnic oxygenation ratio, *HR* heart rate, *MAP* mean arterial pressure, *SatO₂* oxygen transcutaneous saturation, *T^a* temperature, *PSV+VG* pressure support ventilation with volume guarantee, *VAFO* high-frequency oscillatory ventilation, *VAFO+VG* high-frequency oscillatory ventilation with volume guarantee

* $p = 0.045$ vs HFOV; ** $p = 0.005$ vs HFOV + VG

^aMedian (IQR)

^bWilcoxon rank sum test

mmHg higher MAP than PSV + VG group, these differences being significant (95% CI: 3.8 to 27; $p = 0.011$) (Table 3).

c. Changes in cerebral oxygenation: (Fig. 3)

$CrSO_2$ (%) decreased steadily at a rate of -6.2% (95% CI: -7.9 to -4.4; $p < 0.001$) over time regardless of the treatment group. At 60 minutes after randomization, a drop in $CrSO_2 > 20\%$ in 5 animals per group was observed (5/6; 83%); at 120 minutes after randomization, in 5 animals in the groups ventilated with HFOV (5/6; 83%) and in all animals in the PSV+VG group (6/6; 100%) with no significant differences between groups. *cFTOE* increased steadily at a rate of 0.07 (95% CI: 0.05 to 0.08; $p < 0.001$) over time regardless of the treatment group. *Carotid artery flow* fell steadily at a rate of -1.7 mL/kg/min (95% CI: -2.5 to -0.81; $p < 0.001$) over time regardless of the treatment group. *COEF* increased steadily at a rate of 20%

(95% CI: 15 to 26; $p < 0.001$) over time regardless of the treatment group. SjO_2 decreased steadily at a rate of -20% (95% CI: -26 to -15; $p < 0.001$) over time regardless of the treatment group.

d. Changes in systemic tissue oxygenation:

$RrSO_2$ (%) decreased steadily at a rate of -2.5% (95% CI: -3.7 to -1.3; $p < 0.001$) over time regardless of the treatment group. At 60 minutes after randomization, a drop in $RrSO_2 > 20\%$ in one animal per group was observed (1/6; 17%); at 120 minutes after randomization, in 2 animals per group (2/6; 33%), without finding significant differences between groups. *cFTOE* increased steadily at a rate of 0.03 (95% CI: 0.02, to 0.04; $p < 0.001$) over time regardless of the treatment group. *CSOR* increased consistently at a rate of 0.06 (95% CI: 0.03 to 0.10; $p < 0.001$) over time regardless of the treatment group.

Table 2 Changes in arterial blood gases prior to bronchoalveolar lavage and after randomization

	A: PSV + VG ^a	B: HFOV ^a	C: HFOV + VG ^a
pH			
<i>Moment 1</i>	7.36 (7.31, 7.39)	7.42 (7.41, 7.43)	7.36 (7.35, 7.38)
<i>Moment 2</i>	7.22 (7.16, 7.27)	7.33 (7.26, 7.37)	7.22 (7.20, 7.36)
<i>Moment 3</i>	7.29 (7.27, 7.32)	7.34 (7.33, 7.36)	7.32 (7.30, 7.36)
P_aO₂ (mmHg)			
<i>Moment 1</i>	122 (118, 124)	116 (98, 127)	148 (122, 162)
<i>Moment 2</i>	83 (76, 138)	141 (116, 162)	146 (119, 162)
<i>Moment 3</i>	92 (86, 120) ^{b*}	129 (104, 150)	138 (111, 152)
P_aCO₂ (mmHg)			
<i>Moment 1</i>	51.5 (51.0, 52.8)	50.5 (48.2, 52.8)	49.5 (49.0, 50.0)
<i>Moment 2</i>	66 (62, 76)	53 (47, 63)	62 (50, 65)
<i>Moment 3</i>	48.5 (46.5, 49.0)	45.0 (43.5, 48.0)	47.5 (42.5, 50.2)
Hb (g/dl)			
<i>Moment 1</i>	8.05 (7.17, 8.93)	8.10 (7.27, 8.40)	7.60 (6.43, 8.33)
<i>Moment 2</i>	8.70 (8.25, 9.38)	7.80 (7.40, 8.70)	7.25 (7.10, 7.40)
<i>Moment 3</i>	7.60 (6.72, 8.02)	7.95 (6.60, 8.55)	7.40 (6.50, 7.70)
Base excess (mmol/L)			
<i>Moment 1</i>	4.20 (0.15, 5.70)	7.15 (3.62, 7.60)	2.95 (1.53, 4.07)
<i>Moment 2</i>	-0.55 (-4.42, 2.65)	0.00 (-0.10, 1.10)	-1.25 (-2.58, 1.80)
<i>Moment 3</i>	-2.85 (-4.70, -0.03)	-0.80 (-1.73, 1.18)	-2.85 (-3.08, 0.08)
Lactate (mmol/L)			
<i>Moment 1</i>	1.70 (0.95, 2.08)	1.35 (1.15, 1.55)	1.30 (1.08, 1.68)
<i>Moment 2</i>	1.45 (1.25, 1.88)	1.85 (1.80, 2.05)	1.85 (1.58, 2.12)
<i>Moment 3</i>	3.10 (2.08, 3.53)	2.30 (2.03, 2.72)	2.35 (2.03, 2.98)

Times (1: during initial stabilization in the first hour; 2: 20 min after randomization; 3: 120 min after randomization, prior to animal sacrifice)

PaO₂ arterial partial pressure of oxygen, *PaCO₂* arterial partial pressure of carbon dioxide, *Hb* hemoglobin, *PSV+VG* pressure support ventilation with volume guarantee, *VAFO* high-frequency oscillatory ventilation, *VAFO+VG* high-frequency oscillatory ventilation with volume guarantee

* $p = 0.045$ vs HFOV + VG

^aMeridan (IQR)

^bWilcoxon rank sum test

Table 3 Evolution of mean arterial pressure

	A: PSV+VG ^a	B: HFOV ^a	C: HFOV + VG ^a
Mean blood pressure (mmHg)			
Pre-randomization	61 (54, 62)	63 (57, 68)	68 (66, 72)
60 min	54 (52, 56) ^{b*}	62 (54, 69)	66 (60, 68)
120 min	51 (40, 55)	48 (44, 49)	54 (45, 63)

PSV+VG pressure support ventilation with volume guarantee, VAFO high-frequency oscillatory ventilation, VAFO+VG high-frequency oscillatory ventilation with volume guarantee

*p=0.006 vs HFOV + VG group

^aMedian (IQR)

^bWilcoxon rank sum test

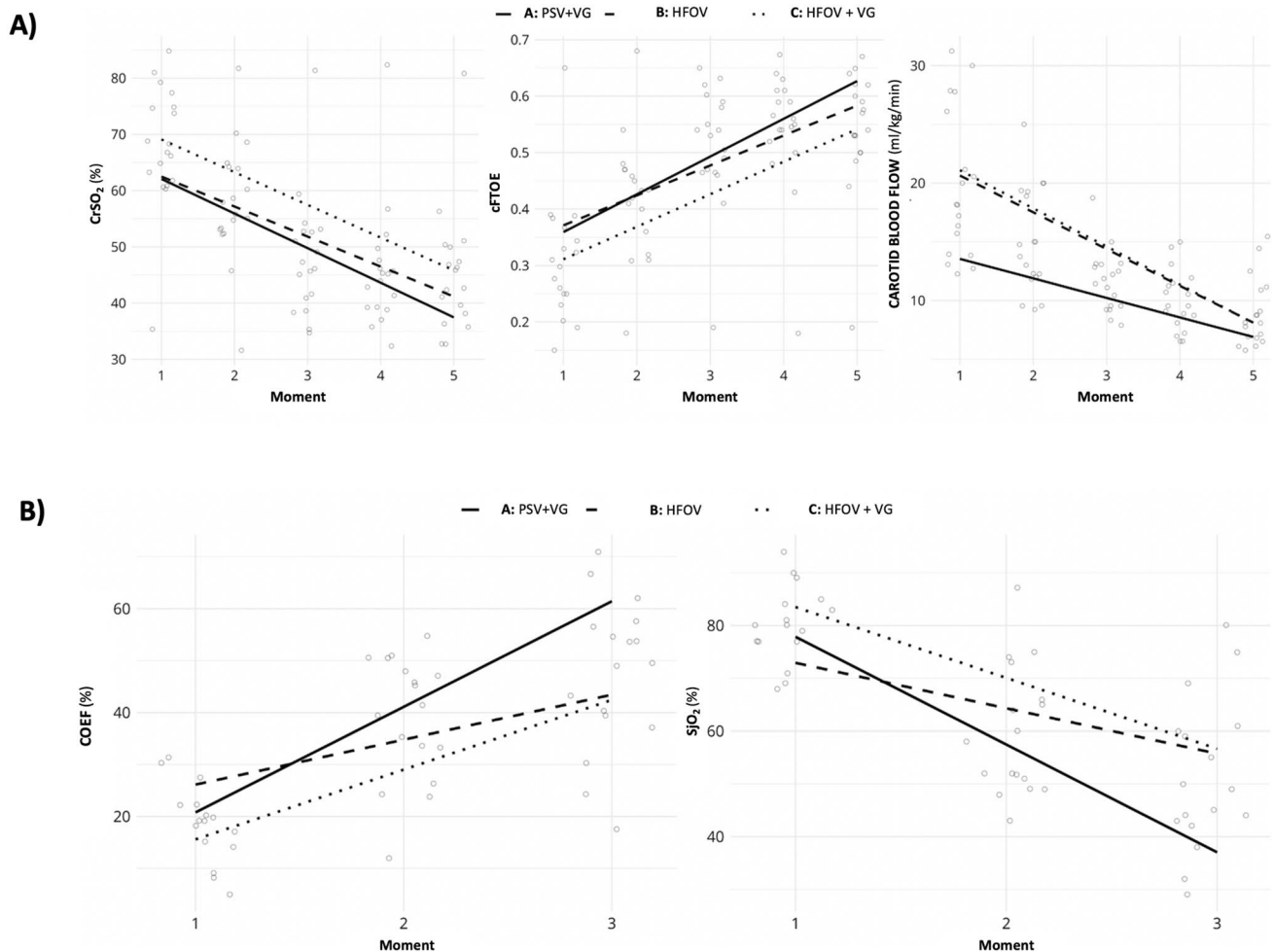


Fig. 3 **A** Linear mixed-effects model. Changes in cerebral regional oxygen saturation, cerebral fractional tissue oxygen extraction and carotid artery flow. The HFOV groups exhibited a sharper reduction in carotid flow. In the HFOV with VG group, this fell at a rate of -1.6 ml/kg/min compared to the PSV+VG group (95%CI: -2.8, -0.38; p=0.011) and in the HFOV without VG group, the decrease was at a rate of -1.5 ml/kg/min compared to the PSV+VG group (95%CI: -2.7, -0.26; p=0.011). Times (1: pre-randomization; 2: 20 min post-randomization; 3: 60 min post-randomization; 4: 90 min post-randomization; 5: 120 min post-randomization, prior to animal sacrifice). **B** Linear mixed-effects model. Changes in the cerebral oxygen extraction fraction and jugular venous oxygen saturation. The HFOV without VG group presented

a less pronounced increase in COEF, being -12% compared to the PSV+VG group (95% CI: -19, -3.9; p=0.004). The HFOV without VG group exhibited a less pronounced decrease in SjO₂, being 12% higher compared to the PSV+VG group. (95% CI: 4.1,20; p=0.004). Times (1: in the 1st hour of stabilization; 2: 60 min post-randomization; 3: 120 min post-randomization, prior to animal sacrifice). CrSO₂: Cerebral regional oxygen saturation; cFTOE: cerebral fractional tissue oxygen extraction; COEF: cerebral oxygen extraction fraction; SjO₂: jugular venous saturation PSV+VG: pressure support ventilation with volume guarantee; VAFO: high-frequency oscillatory ventilation; VAFO+VG: high-frequency oscillatory ventilation with volume guarantee

e. Changes in other factors:

No statistically significant variations were observed in *temperature* throughout the study. As regards *propofol infusion (mg/kg/hour)*, no significant differences were found either: PSV + VG group median 19 (IQR 14, 24); HFOV without VG group 18 (IQR 13, 22); HFOV without VG group 22 (IQR 18, 27).

2. Comparison between HFOV vs HFOV + VG:

a. Changes in arterial blood gas analyses:

No significant differences were found in *pH*, *pO₂*, *pCO₂*, *SO₂*, *glucose* and *hemoglobin* in terms of global values at the 4 moments studied. However, we observed significant differences in 2 variables over time in the 12 animals included, with no differences between the two groups. *Lactic*: steady increase at a rate of 0.39 mmol/L (95% CI: 0.17 to 0.62; *p* = 0.001); *BE*: this decreased constantly at a rate of -2 mmol/L (95% CI: -2.8 to -1.1; *p* < 0.001). (Table 2).

b. Changes in hemodynamic parameters:

MAP steadily decreased at a rate of -3.2 mmHg (95% CI: -4.9 to -1.6; *p* < 0.001) over time regardless of the treatment group. (Table 3)

c. Changes in cerebral oxygenation: (Fig. 3)

CrSO₂ (%) decreased steadily at a rate of -5.3% (95% CI: -7.1 to -3.6; *p* < 0.001) over time regardless of the treatment group. *cFTOE* increased steadily at a rate of 0.05 (95% CI: 0.04 to 0.07; *p* < 0.001) over time regardless of the treatment group. *Carotid artery flow* fell steadily at a rate of -3.1 mL/kg/min (95% CI: -4.2 to -2.1; *p* < 0.001) over time regardless of the treatment group. *COEF* increased steadily at a rate of 8.7% (95% CI: 2.6 to 15; *p* < 0.007) over time regardless of the treatment group. *SjO₂* decreased steadily at a rate of -8.6% (95% CI: -15 to -2.7; *p* < 0.001) over time regardless of the treatment group.

d. Changes in systemic tissue oxygenation:

RrSO₂ (%) decreased constantly at a rate of -1.4% (95% CI: -2.6 to -0.22; *p* < 0.021) over time regardless of the treatment group. *sFTOE* increased steadily at the rate of 0.01 (95% CI: 0.00 to 0.03; *p* < 0.022) over time regardless of the treatment group.

SjO₂ accompanied by an increase in *COEF* and *cFTOE*. These same changes were observed in the two groups of HFOV with no significant differences between them (Fig. 3).

Brain oxygenation depends on oxygen delivery (*DO₂*), that is arterial oxygen content (which, in turn, depends on Hb concentration, its saturation status, and its affinity for *O₂*) and blood flow (which is influenced by cardiac output and vascular resistance). *O₂* extraction and consumption (*VO₂*) by tissues is mostly related to oxygen transport and the metabolic status [18]. Under normal conditions, *VO₂* does not depend on *DO₂* since *O₂* transported is greater than *VO₂*. When an imbalance occurs, normally due to a decrease in *DO₂*, a number of compensation mechanisms are activated, notably the increase in *COEF* to keep *VO₂* constant [19]. If this situation is maintained over time, a maximum point of extraction (critical oxygen transport point) will be reached, where *VO₂* will depend on *DO₂* and new decrease in *DO₂* will reduce *VO₂*, resulting in anaerobiosis and acidosis [20].

There are different techniques to monitor cerebral hemodynamics. One is *jugular oximetry* [21], with blood gas extraction through a catheter positioned retrograde through the internal jugular vein into the jugular bulb to calculate *COEF*, which provides an indirect estimate of *CBF* [22]. Another method is by means of *cerebral oximetry with near-infrared spectroscopy* (NIRS) [23], which measures *CrSO₂*, analyzing the balance between *O₂* supply and demand. The degree of saturation is measured at the level of the exchange vessels where 75–80% correspond to the venous and tisular compartment. It therefore reflects the amount of *O₂* not extracted by tissues. The changes will be directly proportional to the supply and metabolic demand of cerebral [16, 24, 25].

During the 120 min of the study protocol, a decrease was observed in *CrSO₂* and *SjO₂* with an increase in the cerebral *COEF* and *cFTOE*. Why does this decrease in *CBF* occur in the 3 modalities of ventilatory support? The three main metabolic factors that can affect *CBF* are *pCO₂*, *pO₂* and hydrogen ions. Hypercapnia, hypoxemia, and acidosis cause cerebral vasodilatation with increased in *CBF*. Initially, *VO₂* should remain constant. *DO₂* depends on cardiac output and arterial *O₂* content, which in turn depends on Hb content and its *O₂* saturation. No significant differences were observed for these previously described values in the 3 groups. Although there seemed to be a statistically significant decrease in Hb, we did not consider this to be clinically relevant. Nor did we find factors that might have shifted the oxyhemoglobin dissociation curve, resulting in a lower affinity of Hb for *O₂* (increases in *pCO₂*, hydrogen ion or temperature) [26]. Despite the statistically significant increase in lactic acid and *BE*, we consider that this was not a clinically significant change, with arterial blood gases being maintained at *pH* > 7.20 (Table 2).

Discussion

This experimental study in a neonatal animal respiratory distress model suggests to us that the use of VG in HFOV does not have any impact on cerebral hemodynamics compared to the classic strategy of HFOV without VG.

In the control CMV group after BAL there was a gradual drop in *CBF*: a decrease in carotid artery flow, *CrSO₂* and

Sedation is also a conditioning factor in CBF. In our study, a continuous infusion of propofol was maintained. This drug produces a decrease in CBF and in cerebral metabolic oxygen demand, preserving autoregulation and performing a neuroprotective role [27, 28]. No significant differences were found in the doses administered between groups after randomization.

Another important point to evaluate is the **autoregulation of CBF**. In the immature brain of a newborn, especially of a premature one, CBF regulation capacity is altered, resulting in fluctuations in perfusion and cerebral oxygenation [16, 29]. This loss of autoregulation in the first days of life has been associated with brain damage, namely decreased CBF with silent ischemic lesions such as periventricular leukomalacia [29, 30] and the increase in CBF with cerebral hyperperfusion with risk of germinal matrix hemorrhage or intraventricular hemorrhage [29, 31, 32]. It is therefore important to determine the degree of involvement of the different MV strategies in variations in CBF. Little has been described so far regarding HFOV with VG.

In 2021 Bhogal et al. [33] published an experimental study in piglets with RDS in which they concluded that animals ventilated with HFOV+VG presented a significant drop in CBF with a decrease in $CrSO_2$, compared to those ventilated with HFOV without VG and CMV. The explanation given for this finding was that the piglets assisted with HFOV + VG reached the end of the study with statistically lower blood pressure figures (MAP 35 mmHg), and they considered that, based on these figures, there was a loss of CBF autoregulation [34]. Other studies have demonstrated the persistence of CBF autoregulation in piglets with MAP values of around 30 and 100 mmHg [35]. In preterm newborns, Munro et al. [36] also reported persistent cerebral autoregulation with MAP values higher than this figure (30 mmHg). However, other authors been unable to define the optimal blood pressure for maintaining adequate cerebral perfusion in this population [15, 37].

We observed a decrease in cardiac output (gradual fall in MAP) with a decrease in CBF together with a progressive increase in COEF to maintain VO_2 without reaching the maximum extraction point. Additionally, we noted a greater impact on CBF than on somatic flow. There was a decrease of > 20% in $CrSO_2$ at 120 min in almost 100% of the animals. However, the decrease of > 20% in $RrSO_2$ was only observed in 33% of the animals. As regards the differences found between both groups, the 3 modes of respiratory assistance presented similar behavior, although a sharper drop in carotid artery flow was observed in piglets ventilated with HFOV (with and without VG) compared to the CMV group but maintaining adequate metabolic compensation with increased COEF. This was possibly due to the absence of expiration and maintained pressure, which reduced venous return in the thorax and most likely

interfered with carotid flow. The piglets in the CMV group started from a more compromised pre-randomization situation, which perhaps explains the greater increase in COEF with a sharper decrease in SjO_2 .

No significant differences were found in any of the parameters studied between HFOV with and without VG. Both groups remained normally ventilated with a constant mPaw (10 cm H_2O) and 10 Hz. This differs from the results reported by Bhogal et al., who found that piglets in the HFOV + VG group needed a significantly higher ΔPhf to achieve the same Vt/kg as in the group without VG. They theorized that this increase in ΔPhf would have caused a fluctuation in intrathoracic pressure, causing CBF to decrease. This result is also not consistent with other published studies which have shown that amplitude variations are not transmitted at the level of the distal airway [35, 38]. Furthermore, in Bhogal's study there were significant differences in pCO_2 values at 60 min among the three groups. However, in our study the most stable pCO_2 values were maintained.

Since this was an experimental model with term newborn piglets, the main limitation of our study is that it may not be possible to extrapolate the results to the extremely preterm population. In addition, the study period was limited to 120 min. Nor was surfactant administered, which is the current treatment indicated for RDS. Therefore, we do not know how this treatment could have influenced lung mechanics and, consequently, the repercussions at cerebral hemodynamic level.

Conclusions

In our experimental model of neonatal respiratory distress with invasive ventilation, a greater decrease was observed in CBF than in systemic flow, probably because of changes in thoracic pressure and lung compliance. No differences were observed at cerebral hemodynamic between respiratory assistance in HFOV without and with VG, being the latter ventilatory strategy equally safe. It is worth highlighting the importance that the modifications in CBF may have in RDS in this highly susceptible population.

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Authors' contributions Alba Pérez-Pérez, Noelia González-Pacheco and Manuel Sánchez-Luna designed the study. Martín Santos-González directed the experimental study in the neonatal animal model. Alba Pérez-Pérez, Noelia González-Pacheco, María Arriaga-Redondo, Cristina Ramos-Navarro, Elena Rodríguez-Corrales and Ana Rodríguez-Sánchez de la Blanca conducted the data collection. Pablo González-Navarro performed the statistical analysis of the data. All authors made contributions to the conception of the work, revised the work critically and approved the final version of the text.

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Declarations

Ethics approval This study was approved by the Institutional Animal Care and Use Committee (Ethical Committee CEEA/OH 002-002/2019 Ref. PROEX 169/19) and carried out in accordance with the terms authorized by the European and National Regulations on the Handling of Experimental Animals (2010/63/UE and Royal Decree 53/2013).

Competing interests MSL has received advisory board consulting fees from Dräger. The authors declare that they have no conflicts of interest.

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