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The Effects of Hyper- and Hypoventilation on Cerebral Physiology in a Healthy and Compromised Brain State: An Experimental Pig Model with State-of-the-Art Neuromonitoring

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Abstract

Arterial carbon dioxide (pCO_2) strongly affects cerebrovascular tone and cerebral physiology. While moderate hyperventilation is often used to reduce intracranial pressure (ICP) in acute brain injury, its broader physiological effects remain unclear. In this experimental study, 10 anesthetized pigs underwent multimodal neuromonitoring, including ICP, cerebral perfusion pressure, common autoregulatory indices (pressure reactivity index [PRx], cerebral blood flow index [CBFx], oxygen reactivity index), CBF, brain tissue oxygenation ($pbtO_2$), and microdialysis. Animals were exposed to four ventilatory intervals (normoventilation, moderate and severe hyperventilation, and hypoventilation), first in a healthy state and then following induction of intracranial hypertension (ICP 30–40 mmHg) via epidural balloon inflation. In the *healthy brain*, moderate and severe hyperventilation numerically, but non-significantly, reduced CBF without affecting $pbtO_2$ or cerebral energy metabolism, while hypoventilation increased CBF and $pbtO_2$. Under intracranial hypertension, moderate hyperventilation improved PRx and preserved CBF, $pbtO_2$, and metabolism, but severe hyperventilation reduced $pbtO_2$. Hypoventilation produced variable responses: Animals with higher baseline blood pressure showed improved perfusion and oxygenation, whereas those with lower pressure experienced reduced CBF, impaired oxygenation, and metabolic distress. These findings underscore the complex and context-dependent effects of pCO_2 on cerebral physiology, indicating that ventilatory strategies may both benefit and harm the injured brain depending on individual vulnerability and hemodynamic status.

Keywords: carbon dioxide; cerebral blood flow; hyperventilation; multimodal monitoring; neurointensive care

Introduction

Neurointensive care (NIC) aims to mitigate secondary brain injury by optimizing the cerebral environment following severe acute brain disorders.[1,2] This is achieved by controlling several key physiological parameters along the downstream cascade of cerebral hemodynamic and metabolic regulation, including arterial blood pressure (ABP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), cerebral autoregulation (CA; the capacity to regulate the blood flow to the brain over a wide range of CPPs), cerebral blood flow (CBF), and the arterial content of oxygen and glucose.[1–7] These parameters are highly interdependent, and therapeutic interventions that aim to optimize one aspect of cerebral physiology may inadvertently impair another. One physiological variable that exemplifies this complexity is arterial carbon dioxide tension (pCO_2).[8] pCO_2 modulates cerebrovascular tone primarily through pH-mediated mechanisms, though direct CO_2 effects may also contribute,[9,10] within a physiological range of approximately 2–10 kPa.[11] Hypocapnia induces cerebral vasoconstriction, whereas hypercapnia promotes vasodilation, both of which can influence multiple brain

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physiological variables such as ICP, CPP, CA, and CBF.[5,8,12–16] In the context of traumatic brain injury (TBI), early management has often prioritized treatment of elevated ICP, frequently employing hyperventilation-induced hypocapnia.[8,17–20] While this strategy lowers ICP and can prevent brain herniation,[8,21] it may do so at the cost of reduced CBF[19,20] and increased oxygen extraction,[19,20] while the effects on CA capacity remain elusive.[12,13,22–24] Interestingly, the energy metabolic state does not appear to be significantly affected overall,[13,19,20] although substantial variability has been observed across different brain regions and between patients in TBI.[19,20] A landmark clinical trial by Muizelaar et al. demonstrated that severe hyperventilation (target $pCO_2 \approx 3.3$ kPa) was associated with worse 6-month outcomes compared to more moderate levels (4.0–4.5 kPa).[17] However, the lack of clear evidence regarding optimal pCO_2 intervals, other than avoiding extremely low values, contributes to substantial variability in clinical practice across NIC units[18] Conversely, in other forms of acute brain injury, such as aneurysmal subarachnoid hemorrhage (aSAH), the primary challenge may be less related to elevated ICP and more to cerebral vasospasm causing critically reduced CBF.[1,25,26] Experimental strategies involving hypercapnia have shown some promise in improving CBF,[27,28] though elevated pCO_2 may also increase cerebral blood volume (CBV), raise ICP, and potentially reduce CPP.[29]

Despite its clinical relevance, the net physiological impact of pCO_2 modulation in both healthy and injured brain states remains insufficiently understood and incompletely studied.[8,12] To address this knowledge gap, we conducted this experimental, reverse translational study on the effects of hypo- and hyperventilation on brain physiology across a wide pCO_2 spectrum using a large-animal model with state-of-the-art neuromonitoring techniques, mirroring those used in modern NIC units. The aim was to explore the effects of certain pCO_2 targets on the downstream cascade of brain physiology, including ICP, CPP, CA, $pbtO_2$, and cerebral energy metabolism using microdialysis (MD), in both a healthy and a compromised state in a pig model.

Materials and Methods

Animals

In this experimental study, ten pigs (Sus scrofa domesticus, three-breed cross; Norwegian Landrace [1/4], Yorkshire [1/4], and Hampshire [1/2]) aged 2–3 months with mixed gender were included (Supplementary Table S1).

Anesthesia and mechanical ventilation

Sedation was initiated with tiletamine/zolazepam (6 mg/kg, Zoletil Forte, Virbac, Denmark) and xylazine (2.2 mg/kg, Rompun, Elanco, Denmark), followed by a fentanyl bolus (5 μg/kg, Braun, Sweden) after intravenous access. Anesthesia was maintained throughout the experiment using ketamine (30 mg/kg/h; Abcur, Helsingborg, Sweden), fentanyl (4 μg/kg/h; Braun, Danderyd, Sweden), and midazolam (0.12 mg/kg/h; Accord-Healthcarre, Solna, Sweden). After confirming adequate anesthesia through lack of nociceptive reflexes, rocuronium (2.5 mg/kg/h, Braun, Sweden) was administered for muscle relaxation. Ringer acetate (Baxter, Kista, Sweden) was infused at 10 mL/kg/h for the first hour, then 5 mL/kg/h. After induction, the animals were intubated via tracheostomy and mechanically ventilated (Flow I, Maquet, Sweden). They were canulated in supine position, then repositioned to prone for intracranial catheters placement, and stayed prone for the duration of the session.

Study design

All animals underwent a standardized protocol for placement of multimodal monitoring, including ICP, CPP, CBF, $pbtO_2$, and brain energy metabolism, alongside systemic monitoring of ABP, arterial blood gas (ABG), and cardiac output (Supplementary Fig. S1). A balloon catheter was inserted epidurally in the contralateral frontotemporal region to allow induction of a compromised brain state with high ICP and low CPP.[30,31]

The effects of different ventilatory pCO_2 targets on brain physiology were explored under both healthy and compromised cerebral conditions (Fig. 1) by adjusting ventilatory settings while aiming to maintain stable arterial oxygenation (pO_2). Four distinct ventilatory pCO_2 targets were studied: normoventilation (4.5–6.0 kPa), moderate hyperventilation (4.0–4.5 kPa), severe hyperventilation (2.5–3.5 kPa), and hypoventilation (7.0–8.0 kPa). Normoventilation served as the baseline and reference. Moderate hyperventilation (target pCO_2 4.0–4.5 kPa) was included to reflect commonly employed ranges in clinical NIC settings for ICP reduction,[13,18] and is largely consistent with the control group in Muizelaar's trial.[17] Severe hyperventilation and hypoventilation represented extreme physiological perturbations for comparison.[10–12] Systemic and cerebral physiological variables were collected over 30 min for each pCO_2 interval. Normoxia (pO_2 12–18 kPa) was targeted throughout the experiment. The respiratory settings for each pCO_2 target interval were standardized as described below, but they were individually adjusted as needed to achieve comparable pCO_2 and pO_2 targets across phases based on end-tidal capnography and ABG analyses.

First, in the healthy state, baseline data were collected during normoventilation (*phase A*), achieved with a respiratory rate of 20–25 breaths/min, tidal volume of 260–300 mL (8.9–10.0 mL/kg), and fraction of inspired oxygen (FiO_2) of 25%. Subsequently, moderate hyperventilation (*phase B*) was induced by increasing the respiratory rate by $\sim$10 breaths/min, while maintaining tidal volume unchanged and reducing FiO_2 by 1%. This

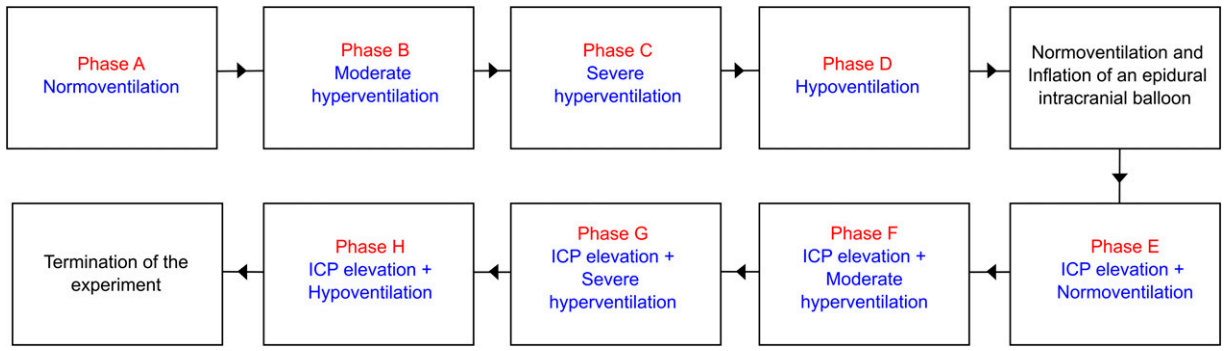


FIG. 1. Flowchart of the experimental design. The figure illustrates the experimental design of this pig study. Each phase included 30 min of monitoring. ICP, intracranial pressure.

was followed by severe hyperventilation (*phase C*), achieved by increasing the respiratory rate to 55 breaths/min and raising tidal volume by 20 mL (≈ 0.7 mL/kg), with a further 1% reduction in FiO_2. Thereafter, hypoventilation (*phase D*) was induced by lowering the respiratory rate to 10–15 breaths/min, decreasing tidal volume by 40 mL (≈ 1.4 mL/kg) relative to baseline, and increasing FiO_2 by approximately 10%. Second, to induce a compromised brain state, the epidurally placed balloon catheter was inflated with approximately 3–7 mL of water to induce intracranial hypertension (ICP ≈ 30–40 mmHg) and a CPP of ≈ 30 mmHg, thresholds that have previously been associated with cerebral hypoxia and cerebral energy metabolic decompensation using this model.[32] Balloon adjustments were individualized based on downstream multimodal monitoring to ensure significant, but not critically irreversible ischemia, accounting for variations in baseline ABP and intracranial compliance across animals. After stabilization of ICP, the same ventilatory manipulations were repeated: baseline normoventilation (*phase E*), moderate hyperventilation (*phase F*), severe hyperventilation (*phase G*), and hypoventilation (*phase H*), following the same respiratory settings as mentioned above.

Monitoring, data acquisition, and analysis

Systemic (ABP, ABG, SpO_2, and CO) and cerebral variables (ICP, CPP, CBF, $pbtO_2$, and cerebral energy metabolism) were continuously or intermittently monitored. ABP was continuously measured via an arterial line (Careflow™, Merit Medical, Singapore Pte. Ltd., Singapore) in the right carotid artery. Blood samples were taken every 15 min through a separate femoral arterial line for ABG analysis (ABL800 Flex, Version 6.20 Build 1068; TRIOLAB AB, Mölndal, Sweden). The estimated plasma osmolality was calculated as "2[Na] + [Glucose]",[33] i.e., using the traditional formula without urea [Urea] in blood since it was not available. Cardiac output was measured every 15 min using intermittent bolus thermodilution method via a pulmonary artery catheter (Merit Medical Systems, USA). Systemic vascular resistance (SVR) was approximated as mean arterial blood pressure (MAP)/cardiac output*80,[34] i.e., using the traditional formula but without central venous pressure which was not recorded. ICP and $pbtO_2$ were measured using a Neurovent PTO probe (Raumedic, Germany), inserted together with the MD catheter into the brain parenchyma in separate directions via a burr hole. Regional CBF and brain temperature were assessed with a thermal diffusion probe (Bowman Perfusion Monitor, Hemedex, USA) inserted through a separate burr hole using a bolt for stabilization of the probe. Signals were collected using the Moberg CNS Monitor (USA), with artifacts removed manually and automatically. CPP was calculated as the difference between MAP and ICP. Three CA metrics were also calculated. PRx, a global CA metric, was calculated as the Pearson correlation coefficient between 10-sec averages of ABP and ICP over 5 min.[35] High PRx indicates impaired CA, e.g., when an increase in ABP leads to increased ICP due to pressure passive vessels, whereas a low PRx indicates preserved CA.[35] The oxygen reactivity index (ORx), a focal $pbtO_2$-based CA-metric, was calculated as the Pearson correlation coefficient of $pbtO_2$ and CPP based on 30 sec values over 30 min, i.e., shorter than the traditional 60-min calculations to match the length of each study phase.[36] High ORx values, i.e., positive correlations between CPP and $pbtO_2$, suggest impaired CA, as changes in perfusion pressure directly influence oxygenation. In contrast, near-zero ORx values indicate preserved autoregulation, where oxygen delivery remains stable despite CPP fluctuations. The physiological significance of negative ORx values remains unclear.[37] We also calculated a similar index (CBFx) based on the Pearson correlation coefficient of CBF and CPP using 30 sec values over each 30-min phase.[31,38] Positive CBFx values indicate impaired CA, where CBF varies passively with changes in CPP. Near-zero values suggest intact CA, with stable CBF despite CPP fluctuations. The

physiological interpretation of negative CBFx values remains uncertain.[31] MD was performed using 71 High Cut-Off catheters (M Dialysis AB, Sweden; 100 kDa membrane, 10 mm length) perfused at 2 μL/min with artificial cerebrospinal fluid. Samples were collected every 15 min and stored at −20°C until analysis. Metabolites (glucose, lactate, pyruvate, and urea) were quantified using ISCUSflex (M Dialysis AB), and the lactate/pyruvate ratio (LPR) was calculated. Brain tissue urea was assumed to remain stable throughout the experiment and used as an internal quality control for the MD measurements.[39]

Statistical analysis

Statistical analyses were performed in RStudio (version 2022.12.0). For each physiological variable, median values were calculated per 30-min phase. Comparisons between normoventilation and the subsequent hyper- and hypoventilation phases were performed separately for the healthy and compromised brain states, using the normoventilation period preceding each condition as the respective baseline. Statistical analysis was conducted using the Wilcoxon signed-rank test. Additionally, the Mann–Whitney *U* test was used to compare physiological variables within phases G and H between animals that showed improvement versus deterioration in CBF following hypoventilation in the compromised brain state. A p value <0.05 was considered statistically significant.

Ethics

The study was approved by the Animal Ethics Committee in Uppsala, Sweden (Dnr 5.8.18–21799/2022) and conducted in accordance with the European Communities Council Directive (2010/63/EU) at the Hedenstierna Laboratory, Uppsala University. All institutional and national guidelines for animal care and use were followed. The study complies with the ARRIVE 2.0 guidelines for the reporting of animal experiments.

Results

The effects of hyper- and hypoventilation on brain physiology in a healthy brain state

The pCO_2 levels were maintained within the targeted ranges during each phase (Table 1 and Fig. 2), with median values of 5.4 (IQR 5.3–5.6) kPa in *phase A*

Table 1. Physiological Changes in Relation to pCO_2 in the Healthy Brain State

	Healthy state			
Variable	*Normoventilation (phase A)*	*Moderate hyperventilation (phase B)*	*Severe hyperventilation (phase C)*	*Hypoventilation (phase D)*
ABG				
pH (scale)	7.46 (7.43–7.48)	***7.55 (7.53–7.57)***[b]	***7.69 (7.65–7.70)***[b]	***7.31 (7.30–7.33)***[b]
pCO_2 (kPa)	5.4 (5.3–5.6)	***4.2 (4.1–4.3)***[b]	***2.8 (2.7–2.9)***[b]	***7.7 (7.7–8.1)***[b]
pO_2 (kPa)	15.2 (14.4–15.6)	15.1 (14.8–15.4)	15 (14.4–15.3)	***15.6 (15.3–16.8)***[a]
Hb (g/L)	89 (82–91)	89 (81–90)	90 (84–92)	***86 (79–89)***[b]
Sodium (mM)	134 (134–136)	***134 (133–135)***[a]	***132 (132–134)***[b]	***134 (133–134)***[a]
Glucose (mM)	6.6 (5.9–7.3)	***6.2 (5.8–7.2)***[b]	***5.9 (5.3–6.6)***[b]	***6.0 (5.3–7.1)***[a]
Lactate (mM)	1.2 (0.8–1.7)	***1.5 (1.3–1.8)***[a]	***2.1 (1.8–2.3)***[b]	***1.7 (1.6–2.2)***[a]
Estimated osmolality (mmol/kg)	276 (274–278)	***276 (272–276)***[b]	***271 (270–274)***[b]	***273 (273–275)***[a]
Systemic physiology				
HR (bpm)	81 (76–85)	83 (69–86)	***88 (81–92)***[b]	77 (73–81)
MAP (mmHg)	81 (74–87)	80 (74–85)	***73 (71–84)***[a]	79 (66–89)
Cardiac output (L/min)	3.2 (3.1–3.5)	3.6 (3.1–3.7)	***3.7 (3.4–4.3)***[a]	3.0 (2.7–3.5)
SVR (dyn*s/cm^5)	2132 (1899–2239)	1969 (1599–2162)	***1639 (1255–1855)***[b]	2044 (1863–2337)
Cerebral physiology				
Brain temperature (°C)	38.6 (38.1–38.8)	38.4 (38.2–38.5)	38.3 (38.2–38.4)	38.6 (38.3–38.8)
ICP (mmHg)	9 (7–12)	***10 (8–13)***[a]	***11 (8–15)***[a]	***17 (11–21)***[b]
CPP (mmHg)	73 (66–80)	68 (66–80)	***65 (57–76)***[a]	***58 (52–70)***[a]
PRx (coefficient)	−0.14 (−0.31–0.07)	−0.24 (−0.37–0.13)	−0.14 (−0.48–0.06)	−0.18 (−0.39–0.04)
ORx (coefficient)	−0.19 (−0.38–0.25)	0.00 (−0.09–0.21)	0.16 (−0.19–0.35)	−0.33 (−0.66–0.31)
CBFx (coefficient)	−0.02 (−0.11–0.39)	0.23 (−0.06–0.47)	0.32 (0.07–0.66)	−0.17 (−0.50–0.49)
CBF (mL/100 g/minute)	30 (25–37)	25 (20–33)	28 (14–32)	***66 (58–73)***[b]
$PbtO_2$ (mmHg)	12 (10–15)	11 (9–15)	11 (8–14)	18 (13–22)
Relative $pbtO_2$ (%)	100 (100–100)	100 (94–108)	96 (88–105)	***148 (143–170)***[a]
MD-glucose (mM)	0.41 (0.29–0.51)	0.45 (0.28–0.66)	0.36 (0.24–0.62)	0.35 (0.26–0.72)
MD-pyruvate(μM)	26 (15–48)	27 (15–40)	31 (19–47)	25 (19–38)
MD-lactate (mM)	0.55 (0.44–0.89)	0.52 (0.44–0.67)	0.64 (0.59–0.87)	0.68 (0.59–0.72)
MD-LPR (ratio)	27 (20–34)	21 (15–30)	24 (16–35)	24 (17–37)

The table shows median values (interquartile ranges) and compares *phase A* (normoventilation) with *phase B* (moderate hyperventilation), *phase C* (severe hyperventilation), and *phase D* (hypoventilation), respectively, using the Wilcoxon signed-rank test. Bold and italics indicate statistical significance.

[a]p value <0.05. [b]p value <0.01. Relative $pbtO_2$ (%) indicates the $pbtO_2$ value at each phase in relation to the baseline value at normoventilation (*phase A*).

ABG, arterial blood gas; CBF, cerebral blood flow; CBFx, CBF index; CPP, cerebral perfusion pressure; Hb, hemoglobin; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial blood pressure; LPR, lactate-pyruvate ratio; MD, microdialysis; ORx, oxygen reactivity index; $PbtO_2$, partial pressure of brain tissue oxygenation. pCO_2, partial pressure of carbon dioxide; PRx, pressure reactivity index; SVR, systemic vascular resistance.

(normoventilation), 4.2 (IQR 4.1–4.3) kPa in *phase B* (moderate hyperventilation), 2.8 (IQR 2.7–2.9) kPa in *phase C* (severe hyperventilation), and 7.7 (IQR 7.7–8.1) kPa in *phase D* (hypoventilation). Moderate and severe hyperventilation (*phases B and C*) induced alkalosis, while hypoventilation (*phase D*) resulted in acidosis (all $p < 0.01$). Sodium levels and estimated plasma osmolality decreased significantly during the hyperventilation phases ($p < 0.05$). Arterial glucose levels decreased while lactate levels increased in response to hyperventilation, with partial normalization during hypoventilation. Severe hyperventilation also led to significant reductions in MAP ($p < 0.05$) and SVR ($p < 0.01$), accompanied by increases in heart rate and cardiac output ($p < 0.05$).

Regarding cerebral physiology, ICP increased modestly during hyperventilation from 9 (*phase A*) to 10 and 11 mmHg (in *phases B and C*, respectively), and more markedly during hypoventilation (*phase D*) to 17 mmHg. This was associated with a reduction in CPP during both severe hyperventilation and hypoventilation ($p < 0.05$). The autoregulatory metrics, PRx, ORx, and CBFx, showed variable changes, but no consistent or significant alterations across the phases. CBF showed a non-significant numerical decrease during both moderate and severe hyperventilation ($p > 0.05$), whereas it increased more than twofold during hypoventilation compared to normoventilation ($p < 0.01$). There was a significant increase in relative (%) $pbtO_2$ (the $pbtO_2$ in the corresponding phase divided by the baseline value during normoventilation) but not when assessed as absolute $pbtO_2$ values (mmHg), during hypoventilation. The MD variables of cerebral energy metabolism remained largely stable across all phases.

The effects of hyper- and hypoventilation on brain physiology in a compromised brain state

In the compromised brain state (elevated ICP), the targeted arterial pCO_2 levels were also achieved (Table 2 and Fig. 3), with median values of 5.1 (IQR 5.0–5.3) kPa in *phase E* (normoventilation), 4.0 (IQR 3.9–4.2) kPa during *phase F* (moderate hyperventilation), 2.7 (IQR 2.6–2.8) kPa during *phase G* (severe hyperventilation), and 7.7 (IQR 7.6–8.1) kPa during *phase H* (hypoventilation). Similar to the healthy state, hyperventilation led to alkalosis ($p < 0.01$) and hypoventilation to acidosis, although without reaching statistical significance ($p = 0.103$). Sodium, estimated osmolality, glucose, and lactate in blood also showed similar dynamics for ventilatory phases as in the healthy state. Regarding systemic physiology, MAP and SVR decreased during both severe hyperventilation and hypoventilation ($p < 0.05$), whereas heart rate and cardiac output remained relatively stable.

For the cerebral physiological variables, median ICP was 31 (IQR 28–42) mmHg during *phase E* (normoventilation), did not change significantly during *phases F and G* (hyperventilation), but increased to 42 (IQR 40–48) mmHg following hypoventilation in *phase H* ($p < 0.01$). The latter phase was also accompanied by a significant drop in CPP to a median value of 19 (IQR 16–24) mmHg ($p < 0.01$). PRx improved during *phase F* (moderate hyperventilation, $p < 0.05$) and deteriorated during *phase H* (hypoventilation, $p < 0.01$), while the other CA metrics did not change significantly across the phases. Notably, CBF decreased progressively, but non-significantly, from normo-, to hyper-, and hypoventilation. $PbtO_2$ decreased during both *phase G* (both in mmHg and % in relation to baseline following severe hyperventilation, $p < 0.05$) and during *phase H* (only in % in relation to baseline, $p < 0.05$). MD-glucose levels dropped during both (moderate and severe) hyperventilation and hypoventilation ($p < 0.05$), while MD-LPR increased significantly during hypoventilation ($p < 0.05$). The other MD-metabolites remained largely unchanged. Notably, the response to hypoventilation was heterogeneous: Four pigs exhibited improved CBF, whereas the remaining animals showed deterioration (Fig. 4). The former group had slightly higher CPP and maintained MAP during the transition from *phase G to H*, in contrast to the subgroup with reduced CBF (Supplementary Table S2 and Supplementary Fig. S2).

Discussion

This experimental pig study with state-of-the-art neuromonitoring demonstrates that arterial pCO_2 has a strong and complex impact on systemic and cerebral physiology. In the healthy brain, hyperventilation caused modest reductions in CBF, whereas hypoventilation elicited marked increases; however, CA, $pbtO_2$, and cerebral energy metabolism remained stable. In the compromised brain with elevated ICP, moderate hyperventilation improved CA, with a slight decline in cerebral glucose levels, but preserved $pbtO_2$ and LPR, while severe hyperventilation lowered $pbtO_2$. Hypoventilation in the compromised brain state

FIG. 2. Dynamic changes in systemic and cerebral physiology in relation to pCO_2 in a healthy brain state—a multimodality monitoring analyses. Each phase corresponds to a certain pCO_2 ventilatory target; *A* (normoventilation; 4.5–6.0 kPa), *B* (moderate hyperventilation; 4.0–4.5 kPa), *C* (severe hyperventilation; 2.5–3.5 kPa), and *D* (hypoventilation; 7.0–8.0 kPa). The subfigures **A** to **J** represent each of the physiological variables of interest. ABG, Arterial blood gas; CBF, Cerebral blood flow; CBFx, CBF index; CPP, Cerebral perfusion pressure; ICP, Intracranial pressure; LPR, Lactate-pyruvate ratio; MD, Microdialysis; ORx, Oxygen reactivity index; $PbtO_2$, Partial pressure of brain tissue oxygenation; pCO_2, Partial pressure of carbon dioxide; PRx, Pressure reactivity index.

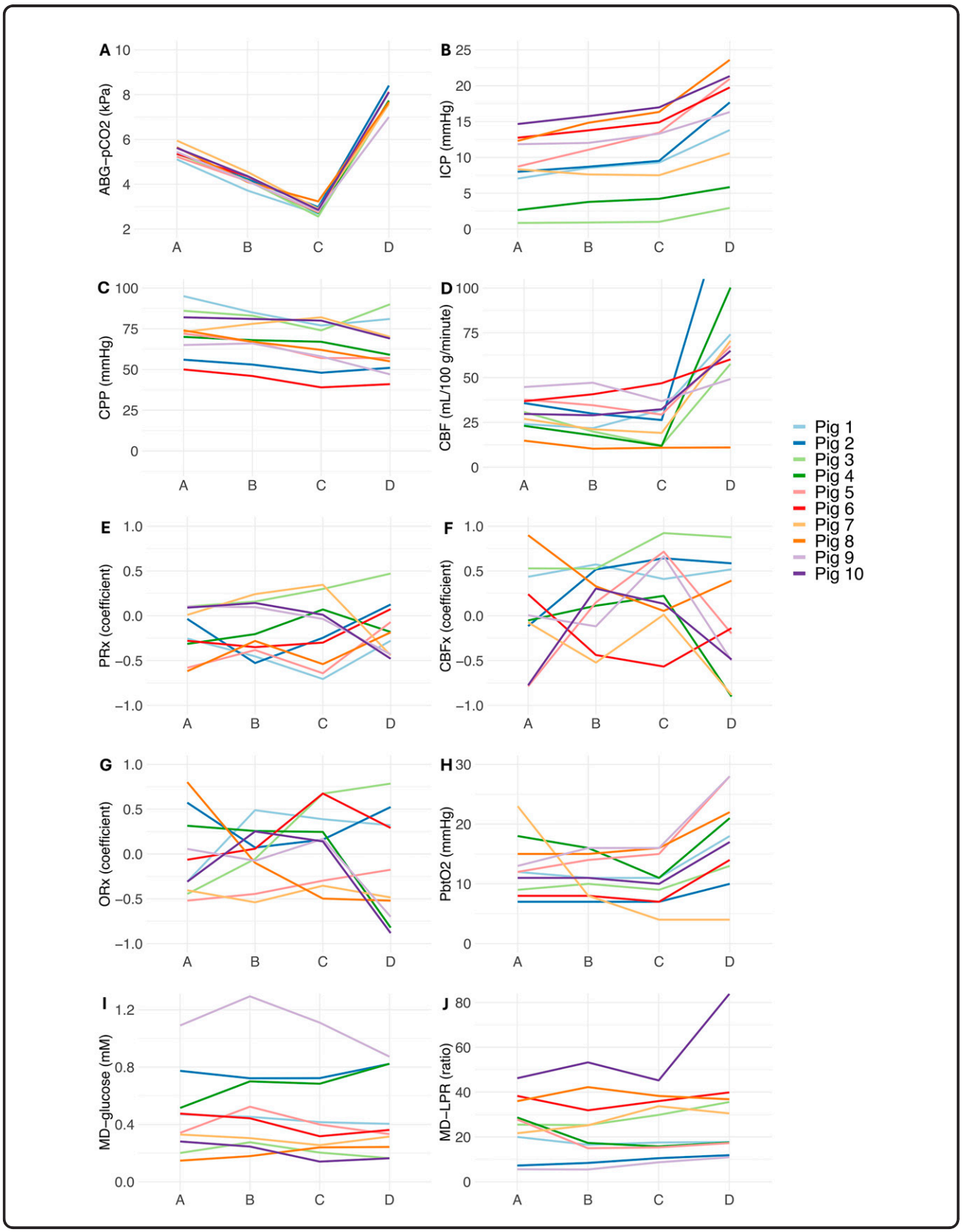


Table 2. Physiological Changes during Hypo/Hypercapnia in the Compromised Brain State

	Compromised brain state			
Variable	*Normoventilation (phase E)*	*Moderate hyperventilation (phase F)*	*Severe hyperventilation (phase G)*	*Hypoventilation (phase H)*
Arterial blood gas				
pH (scale)	7.49 (7.46–7.49)	***7.57 (7.55–7.58)***[b]	***7.71 (7.70–7.71)***[b]	7.33 (7.30–7.35)
pCO_2 (kPa)	5.1 (5.0–5.3)	***4.0 (3.9–4.2)***[b]	***2.7 (2.6–2.8)***[b]	***7.7 (7.6–8.1)***[b]
pO_2 (kPa)	15.0 (14.7–15.4)	15.1 (14.4–15.4)	14.8 (13.9–15.1)	15.6 (14.8–16.8)
Hb (g/L)	85 (77–86)	84 (76–88)	85 (77–91)	84 (76–87)
Sodium (mM)	132 (130–134)	***132 (131–133)***[a]	***131 (130–133)***[a]	132 (131–134)
Glucose (mM)	6.3 (5.3–6.7)	***6.0 (5.0–6.3)***[a]	***5.7 (4.8–5.8)***[b]	***5.7 (4.9–6.1)***[b]
Lactate (mM)	1.3 (1.2–1.7)	1.5 (1.2–1.8)	***1.9 (1.6–2.6)***[b]	1.5 (1.2–2.1)
Estimated osmolality (mmol/kg)	270 (268–274)	***268 (267–272)***[a]	***268 (265–271)***[b]	269 (267–273)
Systemic physiology				
HR (bpm)	79 (71–83)	79 (73–82)	80 (77–84)	75 (69–81)
MAP (mmHg)	75 (62–94)	77 (62–94)	***72 (59–77)***[a]	***66 (58–73)***[a]
Cardiac output (L/min)	3.3 (2.9–4.0)	3.4 (2.8–3.8)	3.5 (2.9–3.9)	3.2 (3.1–3.8)
SVR ($dyn*s/cm^5$)	1965 (1532–2274)	1967 (1602–2177)	***1683 (1271–1914)***[b]	***1501 (1324–1884)***[a]
Cerebral physiology				
Temperature (°C)	38.4 (38.2–38.8)	38.4 (38.2–38.7)	38.3 (38.2–38.5)	38.3 (38.1–38.7)
ICP (mmHg)	31 (28–42)	30 (28–37)	32 (29–37)	***42 (40–48)***[b]
CPP (mmHg)	48 (28–54)	50 (32–60)	40 (24–48)	***19 (16–24)***[b]
PRx (coefficient)	−0.19 (−0.40–0.05)	***−0.49 (−0.55–−0.29)***[a]	−0.60 (−0.65–−0.52)	***0.57 (0.35–0.81)***[b]
ORx (coefficient)	0.53 (0.41–0.76)	0.15 (0.08–0.70)	0.54 (0.14–0.77)	0.80 (0.69–0.84)
CBFx (coefficient)	0.66 (0.31–0.73)	0.39 (0.20–0.75)	0.62 (0.40–0.78)	0.73 (–0.24–0.89)
CBF (mL/100 g/minute)	27 (22–29)	25 (22–30)	20 (12–25)	12 (2–34)
$PbtO_2$ (mmHg)	8 (6–13)	9 (7–12)	***6 (5–9)***[a]	4 (3–5)
Relative $pbtO_2$ (%)	100 (100–100)	100 (94–106)	***76 (60–92)***[a]	***63 (40–70)***[a]
MD-glucose (mM)	0.14 (0.09–0.29)	***0.13 (0.06–0.19)***[a]	***0.08 (0.05–0.14)***[b]	***0.06 (0.03–0.16)***[a]
MD-pyruvate(μM)	23 (11–39)	24 (15–42)	26 (15–47)	18 (7–30)
MD-lactate (mM)	1.02 (0.86–1.23)	1.11 (0.91–1.32)	1.27 (1.05–1.65)	1.17 (0.97–1.79)
MD-LPR (ratio)	53 (23–85)	44 (22–76)	58 (22–81)	***111 (28–188)***[a]

The table shows median values (interquartile ranges) and compares *phase E* (normoventilation) with *phase F* (moderate hyperventilation, *phase G* (severe hyperventilation), and *phase H* (hypoventilation), respectively, using the Wilcoxon signed-rank test.

[a]*p* value <0.05. [b]*p* value <0.01. Relative $pbtO_2$ (%) indicates the $pbtO_2$ value at each phase in relation to the baseline value at normoventilation (*phase E*).

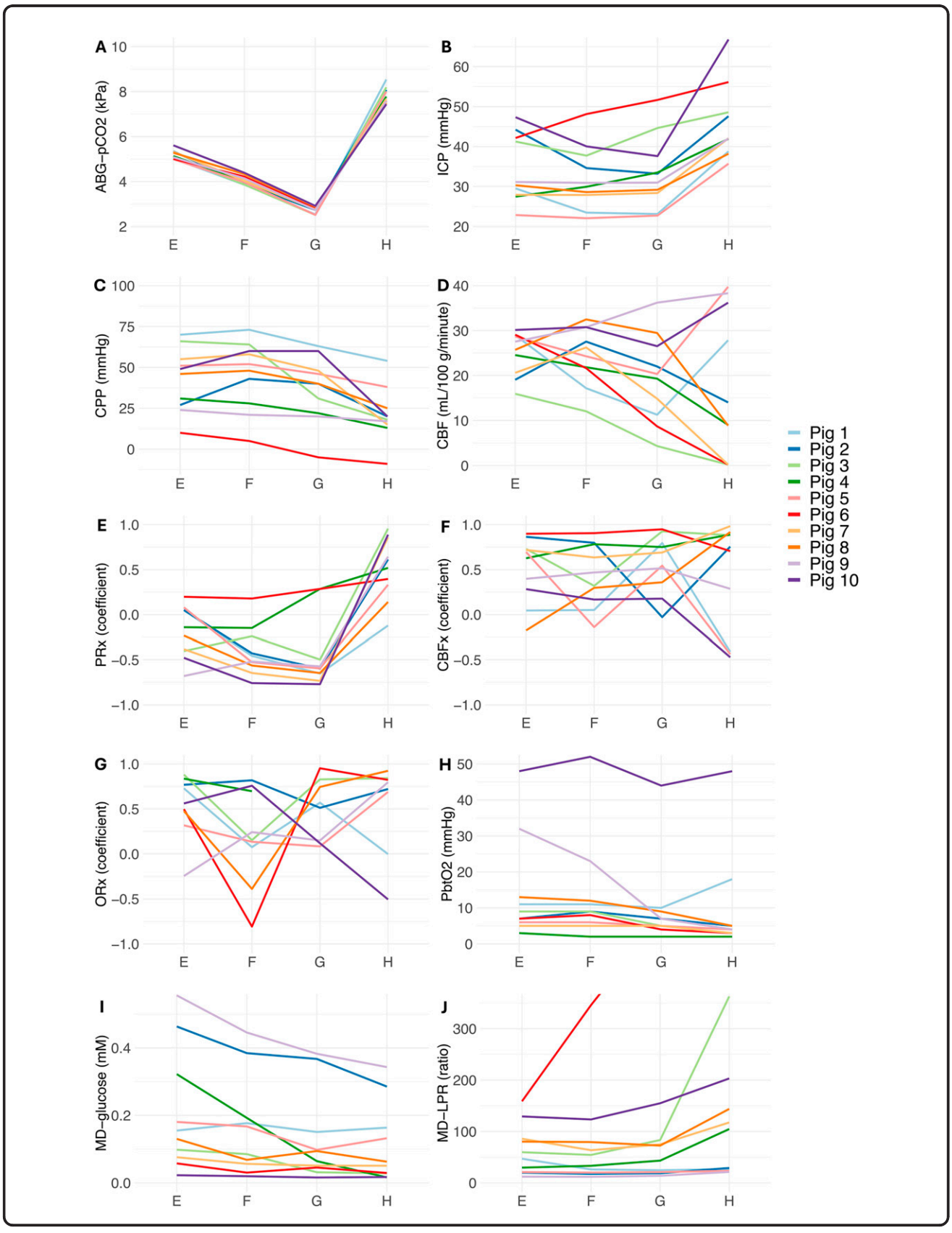
ABG, arterial blood gas; CBF, cerebral blood flow; CBFx, CBF index; CPP, cerebral perfusion pressure; Hb, hemoglobin; HR, heart rate; ICP, intracranial pressure; MAP, mean arterial blood pressure; LPR, lactate-pyruvate ratio; MD, microdialysis; ORx, oxygen reactivity index; $PbtO_2$, partial pressure of brain tissue oxygenation; pCO_2, partial pressure of carbon dioxide; PRx, pressure reactivity index; SVR, systemic vascular resistance.

led to diverging physiological responses depending on the balance between ICP and CPP. These findings highlight the importance of individualized ventilation strategies in NIC and the role of multimodal monitoring to assess the net cerebral impact of pCO_2 modulation on the different aspects of brain physiology.

pCO_2 levels in relation to systemic physiology

Before discussing the cerebral effects, the systemic consequences of altered pCO_2 must be acknowledged. Hyperventilation resulted in decreased MAP and SVR, while heart rate and cardiac output typically increased. Mechanical hyperventilation is expected to decrease MAP due to a reduction in right and left ventricle preloads due to increased intrathoracic pressure.[40] Interestingly, cardiac output increased by 10–15% during hyperventilation despite a decrease in MAP in the healthy state. This may be due to measurement inaccuracies related to the high ventilation settings affecting thermodilution via the pulmonary artery catheter,[41] or a

FIG. 3. Dynamic changes in systemic and cerebral physiology in relation to pCO_2 in a compromised brain state—a multimodality monitoring analyses. Each phase corresponds to a certain pCO_2 ventilatory target; *E* (normoventilation; 4.5–6.0 kPa), *F* (moderate hyperventilation; 4.0–4.5 kPa), *G* (severe hyperventilation; 2.5–3.5 kPa), and *H* (hypoventilation; 7.0–8.0 kPa). Extreme LPR values from Pig 6 in *phases G and H* were excluded from the graph to preserve visual clarity. In pig 9 and 10, the $pbtO_2$ probe was manipulated after the completion of the healthy brain state phases and before the start of the compromised brain state phase, due to technical concerns (dislocation or extreme values during epidural balloon inflation). ABG, Arterial blood gas; CBF, Cerebral blood flow; CBFx, CBF index; CPP, Cerebral perfusion pressure; ICP, Intracranial pressure; LPR, Lactate-pyruvate ratio; MD, Microdialysis; ORx, Oxygen reactivity index; $PbtO_2$, Partial pressure of brain tissue oxygenation; pCO_2, Partial pressure of carbon dioxide; PRx, Pressure reactivity index.



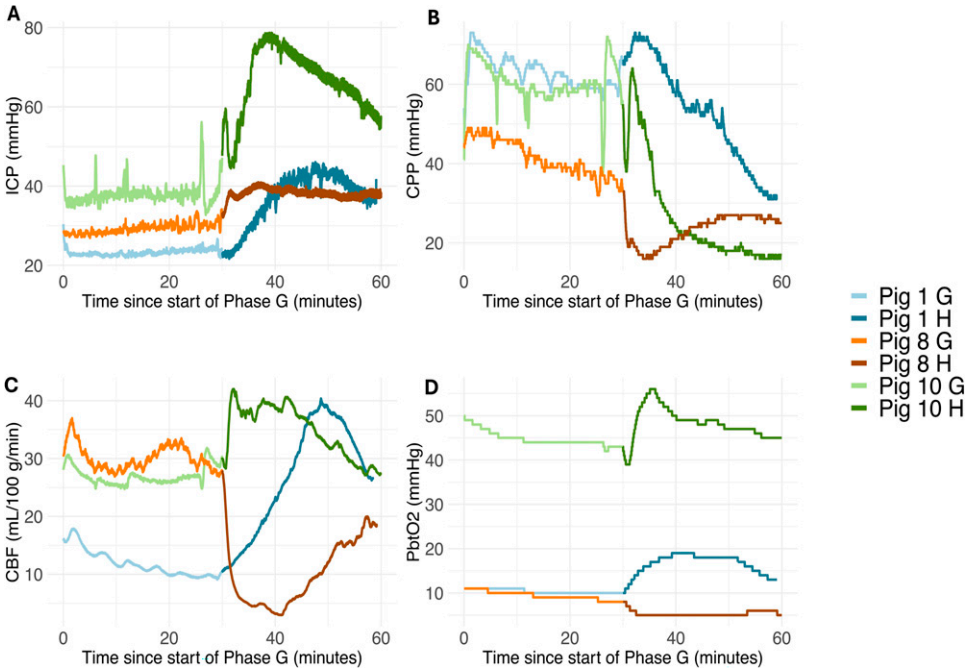


FIG. 4. Heterogeneous response in relation to hypoventilation in a compromised brain state. The figure illustrates the individual physiological responses during the transition from *phase G* (severe hyperventilation) to *phase H* (hypoventilation). In all pigs, ICP increased and CPP decreased during hypoventilation. However, for pig 1 CPP remained above 30 mmHg in *phase H* and both CBF and $pbtO_2$ improved during this phase. In contrast, pig 8 started with a lower CPP, which dropped below 30 mmHg during *phase H*, resulting in a marked, but partially reversible, decline in CBF and $pbtO_2$. Pig 10 showed dynamic changes in ICP and CPP, with CPP probably just around the lower limit of autoregulation, accompanied by highly variable changes in CBF and $pbtO_2$. CPP, Cerebral perfusion pressure; ICP, Intracranial pressure; $PbtO_2$, Partial pressure of brain tissue oxygenation.

complex hemodynamic response involving changes in pre-/afterload (with peripheral vasodilation) and autonomic regulation.[42,43] Notably, in contrast to the healthy condition, while SVR still decreased, there was no increase in cardiac output observed during severe hyperventilation in the compromised brain state. Although the exact mechanisms remain unclear, we speculate that impaired autonomic compensation may contribute to this blunted cardiac response. Also, in the compromised brain state, hypoventilation was associated with a significant decrease in SVR, in contrast to the healthy state when SVR remained unchanged. Again, while we lack definitive explanations, it is possible that brain injury induced a stress response and impacted on autonomic function, which modulated the complex systemic vascular response to hypercapnia.[44]

The hyperventilation phases also led to decreased arterial glucose and increased lactate levels, likely due to alkalosis-induced stimulation of phosphofructokinase activity leading to increased glycolysis.[45] Furthermore, both sodium and the estimated plasma osmolality decreased during hypocapnia, which may be explained by an alkalosis-induced intracellular sodium shift and antidiuretic hormone-mediated water retention.[46,47] Furthermore, pCO_2 critically regulates acid–base balance, which in turn alters hemoglobin—oxygen affinity via the hemoglobin—oxygen dissociation curve. Hypocapnia with alkalosis shifts the curve leftward, impairing oxygen release, while hypercapnia shifts it rightward, enhancing tissue oxygen delivery.[48] Taken together, these systemic changes provide essential context for interpreting the cerebral effects of different ventilatory settings and pCO_2 levels.

pCO_2 levels and ICP dynamics

Hyperventilation is expected to induce cerebral vasoconstriction,[11] leading to reduced CBV[49] and lower ICP.[8,21] However, in the healthy brain state, both moderate and severe hyperventilation were paradoxically associated with modest, but significant, ICP elevations. One plausible explanation is that the pigs maintained intact CA, as

indicated by low PRx, CBFx, and ORx, while experiencing a slight drop in MAP. In such a scenario, the vasoconstrictive effects of hyperventilation-induced hypocapnia may have been offset by autoregulatory vasodilation triggered by reduced perfusion pressure, leading to a net increase or preservation rather than reduction of CBV. In the compromised brain state, ICP remained unchanged during moderate and severe hyperventilation. In this setting, the smaller MAP reduction compared to the healthy state, combined with impaired autoregulation, likely reduced the MAP-driven impact on ICP, thereby allowing the vasoconstrictive effects of hypocapnia to play a more dominant role. However, hypoventilation consistently resulted in marked ICP elevations in both the healthy and compromised brain, with the most pronounced increase observed in the injured state, i.e., when the intracranial compliance was low. Notably, despite high ICP and low CPP indicative of conditions near the lower limit of autoregulation, hypoventilation still induced an ICP rise, suggesting that some vasodilatory reserve remained despite approaching exhaustion. Altogether, these findings underscore that while hyperventilation is often used at the bedside,[18] its efficacy to reduce ICP may be limited or even counteracted under certain physiological conditions, either due to insufficient vasoconstrictive effect or autoregulatory compensation in response to concurrent reduction in MAP. However, hypoventilation triggered a detrimental vasodilatory cascade that often resulted in critical cerebral hypoperfusion in the compromised brain state, underscoring the potential danger of hypercapnia in patients with impaired intracranial compliance, elevated ICP, and low MAP.

pCO_2 levels in relation to cerebral autoregulation

Neither hyper- nor hypoventilation significantly altered any of the autoregulatory indices, PRx, CBFx, and ORx, in the healthy brain state, indicating preserved vascular reactivity across a wide pCO_2 range. Although pCO_2 can shift both the limits and position of the autoregulatory plateau,[12,22,50] it is not surprising that CA remained intact under these optimized, healthy conditions with adequate MAP and CPP. However, in the injured state with compromised ICP and CPP, PRx decreased during moderate hyperventilation, suggesting improved CA. A similar trend was observed during severe hyperventilation, although statistical significance was not reached, likely due to hyperventilation-induced systemic hypotension in a subset of the pigs. These findings are consistent with clinical TBI studies reporting improved PRx during hyperventilation.[13,24] Notably, CBFx and ORx remained unchanged across all ventilatory phases. To understand these discrepancies, it is important to note that these three indices are surrogates of dynamic CA and are based on different signal inputs of cerebral physiology.[7,51] PRx, which reflects the correlation between MAP and ICP, is closely influenced by changes in cerebrovascular tone and CBV, which probably makes it particularly sensitive to the direct effects of pCO_2 on the vessels of the brain. Hyperventilation likely induced vasoconstriction in previously dilated vessels close to the lower limit of autoregulation in the compromised brain state, potentially restoring vasodilatory reserve and improving dynamic pressure reactivity. However, while this led to lower PRx values, CBF decreased slightly numerically although not significantly, likely due to a down-shift of the autoregulatory plateau.[12,22] As such, downstream variables like CBF may still decline despite apparent autoregulatory improvement. Otherwise, CBFx, reflecting the correlation between CPP and CBF, may be a less reliable surrogate of dynamic CA function during these acute pCO_2 changes, as CBF during ventilatory manipulation was likely more influenced by pCO_2 mediated changes in vascular tone rather than changes in perfusion pressure. Similarly, ORx, reflecting the correlation between CPP and $pbtO_2$, was likely only minimally affected, as $pbtO_2$ changed relatively little during these phases. Such $pbtO_2$ changes were probably also more driven by pCO_2 mediated effects on CBF. Lastly, hypoventilation significantly worsened PRx in the injured brain, most likely due to elevated ICP and critically low CPP, leading to pressure-passive cerebral perfusion. This deterioration highlights the vulnerability of cerebrovascular control in states of compromised intracranial compliance.

pCO_2 in relation to CBF, $pbtO_2$, and cerebral energy metabolism

Moderate hyperventilation resulted in a slight numerical, but non-significant, reduction in CBF in the healthy brain, while $pbtO_2$ and cerebral energy metabolism remained largely stable. In the injured brain, a similar, non-significant trend with lower CBF was seen during moderate hyperventilation, while downstream physiological variables were generally preserved, except for a slight, but significant decrease in cerebral glucose. Severe hyperventilation led to further, but non-significant, reductions in CBF in both states, but only in the injured brain did this translate into significantly lower $pbtO_2$ and lower cerebral glucose. Despite these changes, cerebral energy metabolism (LPR levels) remained largely unchanged. These findings suggest that the CBF reductions were modest in magnitude and did not reach a threshold of ischemic compromise, at least not at the group level, consistent with several clinical TBI studies.[13,19–21] It is worth noting that technical limitations, such as transient instability in CBF monitoring, may have influenced measurement accuracy and reduced statistical power in some comparisons. Nevertheless, the stability of $pbtO_2$ and LPR across most conditions supports the interpretation that cerebral oxygen

delivery and metabolic function were not critically impaired during short-term hyperventilation, except for severe hyperventilation in the compromised brain.

The effects of hypoventilation were more complex. In the healthy brain, it consistently increased CBF and tended to improve $pbtO_2$ (in %change, but not mmHg, in relation to baseline), while cerebral metabolism remained unchanged. This suggests intact CO_2-reactivity, with $pbtO_2$ (to some extent) and cerebral glucose stability possibly reflecting already saturated oxygen and glucose gradients, a balanced increase in metabolic demand, or an early stage of "luxury perfusion". In contrast, the compromised brain exhibited highly heterogeneous responses to hypoventilation. On group level, hypercapnia was associated with reductions in CBF (numerical, but nonsignificant) and $pbtO_2$ ($p < 0.05$), as well as decreased cerebral glucose and elevated LPR, suggesting impaired oxygen and substrate delivery due to low CPP. However, subgroup analysis revealed two distinct response patterns. In pigs with lower baseline MAP and CPP or where MAP dropped markedly due to hypoventilation, CBF, $pbtO_2$, and metabolic markers deteriorated substantially. Conversely, in animals with elevated ICP but more preserved MAP and CPP, hypercapnia was associated with increased CBF, improved oxygenation, and more favorable metabolic profiles. These findings suggest that hypoventilation in the compromised brain can exert diametrically opposing physiological effects depending on the ICP dynamics and hemodynamic conditions.

Implications

In acute brain injuries, normocapnia remains the standard target for ventilatory management.[52] However, hyperventilation is commonly employed as a temporizing measure to lower ICP.[13,18,21,52] While this therapy usually reduces ICP in a clinical setting,[21] our data also highlight that systemic hypotension may counteract any ICP-lowering benefit. This may be particularly relevant in pre- or interhospital settings, where continuous ABP monitoring and management may be more limited. Notably, moderate hyperventilation appeared to improve CA function, consistent with previous clinical findings in TBI[13,23,24] and may therefore offer physiological benefits beyond ICP control. The preservation of CBF, $pbtO_2$, and LPR further suggests that this strategy is likely safe, particularly when accompanied by careful MAP management. However, severe hyperventilation led to more severe downstream effects on CBF, $pbtO_2$, and energy metabolism, consistent with previous clinical studies[19,53] and is likely detrimental.

Hypoventilation, on the other hand, exhibited highly variable effects that were strongly dependent on the underlying systemic and cerebral physiological state. In the compromised brain state, characterized by reduced intracranial compliance and impaired autoregulation, elevated pCO_2 exacerbated ICP, reduced CPP, and was associated with impaired CA function, lower $pbtO_2$, and metabolic distress. These results reinforce the clinical caution against hypoventilation in conditions such as TBI, especially in the early phases of care when the risk of ICP compromise is greatest. Early airway protection and avoidance of hypoventilation are therefore crucial to prevent secondary cerebral injury in these patients. Conversely, in acute brain injuries not primarily dominated by raised ICP, such as aSAH, the situation may be different. In these cases, relatively preserved intracranial compliance may allow for a safe increase in CBV without critical ICP elevations. Thus, the net effect of hypoventilation may shift toward improved CBF and oxygenation, as previously suggested by small, preliminary clinical studies.[5,27,28] While speculative, our findings lend support to further investigation of targeted hypercapnia as a therapeutic strategy in selected patient populations characterized by hypoperfusion without major ICP problems.

Lastly, controlled hyperventilation is frequently used during elective neurosurgical procedures to reduce CBV, relax the brain, and facilitate safer craniotomy, dural opening, and brain dissection.[54] In this study, brief periods of moderate hypocapnia in the healthy brain were not associated with deleterious effects on CA, CBF, $pbtO_2$, or cerebral energy metabolism, suggesting that this strategy is physiologically well-tolerated. These findings support the safety of short-term moderate hyperventilation during elective neurosurgery under controlled conditions.

Methodological considerations

This study has several methodological strengths. The controlled experimental design enabled clearer causal inference compared with observational clinical studies. The use of juvenile pigs enhances the translational relevance of our findings, as their gyrencephalic brains and cerebrovascular anatomy more closely resemble those of humans compared to small, lissencephalic species.[55,56] Moreover, pigs share key features of human cardiorespiratory physiology, brain growth, and developmental trajectories, and their size allows for advanced multimodal monitoring, making them well suited for NIC research.[55,57] Furthermore, the use of a state-of-the-art multimodal neuromonitoring platform, encompassing ICP, CPP, CBF, $pbtO_2$, and cerebral MD, allowed for comprehensive evaluation of the cerebral physiological cascade under different pCO_2 conditions. This mirrors the setup of modern NIC units and strengthens the applicability of our results to clinical practice. Nevertheless, the study has some limitations. The number of pigs was limited, increasing the risk of both type I and type II errors. However, the high degree of physiological control in the experimental setup

likely minimized variability and reduced noise. Additionally, we used median values and non-parametric statistics to mitigate the influence of outliers, thereby enhancing the robustness of observed significant differences. Furthermore, limited reliability of intracranial monitors represented a potential source of measurement error. In particular, the thermal diffusion probe used for CBF monitoring required intermittent re-calibration, which occasionally introduced baseline shifts. These fluctuations may have influenced some of the CBF comparisons. Moreover, while all monitoring devices were allowed to stabilize for approximately one hour prior to the start of the protocol, certain probes, such as the Neurovent PTO, may require up to 8 h to reach full equilibration, potentially affecting the reliability of absolute $pbtO_2$ readings. Furthermore, in a few cases (pig 9 and 10), minor adjustments were made to the $pbtO_2$ probe between *phase D* and *E*, i.e., after completion of the healthy brain state and before the start of the compromised brain state phases, due to technical concerns about the probe (dislocation or extreme values). This may have influenced absolute $pbtO_2$ values at the start of the compromised brain phase. However, the same probe was consistently used within each experimental period (healthy and compromised brain state, respectively), and all analyses were performed relative to the respective normoventilation baseline. Additionally, in the compromised brain state, a fully standardized level of compromise could not be achieved due to interindividual differences among the pigs, particularly in baseline MAP. Small changes in balloon volume caused large, variable shifts in ICP, reflecting reduced intracranial compliance and making it difficult to match ICP dynamics and CPP across pigs. This variability was most evident during hypoventilation, where physiological responses differed markedly with small changes in pressure. Although this reduced the overall homogeneity of results, it closely reflects the clinical reality and highlights how subtle physiological differences can lead to divergent responses to the same intervention. While we considered actively adjusting MAP to reduce variability, doing so would have masked the full systemic effects of the ventilatory manipulations and introduced confounding through the use of vasopressors, making it more difficult to isolate the specific impact of pCO_2 on cerebral physiology. Instead, our study design prioritized capturing the integrated physiological response to pCO_2 modulation, encompassing both systemic and cerebral effects. Moreover, each ventilatory phase was maintained for 30 min, allowing assessment of acute physiological responses. This time frame reflects clinically relevant decision-making windows but may not fully capture the effects of sustained pCO_2 alterations, particularly regarding cerebral metabolism. On one hand, longer durations might be necessary to elicit measurable changes in energy metabolic markers. On the other, the physiological impact of altered ventilation may diminish over time, as the acid-base effects of pCO_2 typically attenuate within a few hours due to compensatory mechanisms. Also, the analgosedation protocol used in this study, including ketamine, midazolam, and fentanyl, was optimized for experimental conditions and hemodynamic stability. However, we acknowledge that other sedatives such as propofol are more commonly used in clinical NIC. The choice of sedative may therefore influence the generalizability of the findings. Finally, while both male and female pigs were included, the animals were prepubescent (2–3 months old), and no systematic sex differences were observed. Nonetheless, we cannot exclude the possibility of subtle sex-dependent physiological differences that might become more apparent in sexually mature subjects.

Conclusions

This experimental pig study with state-of-the-art neuromonitoring illustrates that arterial pCO_2 exerts a strong and complex influence on both systemic and cerebral physiology. In the healthy brain, pCO_2 alterations induced predictable changes in CBF, with preserved CA, oxygenation, and energy metabolism. In contrast, the injured brain showed a more complex pattern; moderate hyperventilation improved CA while maintaining stable CBF, $pbtO_2$, and LPR, whereas severe hyperventilation and hypoventilation were associated with impaired oxygenation and signs of metabolic stress, particularly under conditions of reduced CPP. However, hypoventilation elicited divergent responses depending on the balance between ICP and MAP in the compromised brain state. These findings emphasize the need for individualized, physiology-based ventilation strategies in NIC and support the use of multimodal monitoring to guide safe and effective pCO_2 management. Future research should explore whether individual multimodal physiological characteristics, such as ABP, ICP, intracranial compliance, and CA function, could help guide pCO_2-targeted interventions.

Transparency, Rigor, and Reproducibility Statement

This experimental study was conducted in accordance with international guidelines for animal research and approved by the appropriate institutional ethics committee. To ensure transparency, detailed descriptions of animal preparation, anesthesia protocols, ventilatory settings, and multimodal neuromonitoring methods are provided in the Materials and Methods section. All data were collected prospectively according to a pre-defined protocol. Cerebral physiological parameters were continuously recorded using validated equipment with synchronized

time-stamping, enabling precise temporal alignment with changes in arterial pCO_2. Rigor was maintained by standardizing experimental procedures across all animals. Data preprocessing and statistical methods are clearly outlined to facilitate reproducibility. Raw data are available upon reasonable request.

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Authors' Contributions

Conceptualization: T.S.W. Methodology: All authors. Formal analysis: M.A. Resources: T.S.W. Data curation: All authors. Writing—original draft preparation: T.S.W. Writing—review and editing: All authors.

Author Disclosure Statement

No competing financial interests exist.

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Supplementary Material

Supplementary Data

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