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Effects of Inspired Hypoxic and Hypercapnic Gas Mixtures on Cerebral Oxygen Saturation in Neonates with Univentricular Heart Defects

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Background: **Neonates with functional single ventricle often require hypoxic or hypercapnic inspired gas mixtures to reduce pulmonary overcirculation and improve systemic perfusion. Although the impact of these treatments on arterial oxygen saturation has been described, the effects on cerebral oxygenation remain uncertain. This study examined the effect of these treatments on cerebral oxygen saturation and systemic hemodynamics.**

Methods: **Neonates with single ventricle mechanically ventilated with room air were enrolled in a randomized crossover trial of 17% inspired oxygen or 3% inspired carbon dioxide. Each treatment lasted 10 min, followed by a 10–20-min washout period. Cerebral and arterial oxygen saturation were measured by cerebral and pulse oximetry, respectively. Cerebral oxygen saturation, arterial oxygen saturation, and other physiologic data were continuously recorded.**

Results: **Three percent inspired carbon dioxide increased cerebral oxygen saturation (56 ± 13 to 68 ± 13%; $P < 0.01$), whereas 17% inspired oxygen had no effect (53 ± 13 to 53 ± 14%; $P = 0.8$). Three percent inspired carbon dioxide increased the mean arterial pressure (45 ± 8 to 50 ± 9 mmHg; $P < 0.01$), whereas 17% inspired oxygen had no effect. And 3% inspired carbon dioxide decreased arterial *p*H and increased arterial carbon dioxide and oxygen tensions.**

Conclusions: **Inspired 3% carbon dioxide improved cerebral oxygenation and mean arterial pressure. Treatment with 17% inspired oxygen had no effect on either.**

NEONATES with hypoplastic left heart syndrome and other single ventricle (SV) cardiac malformations depend on a patent ductus arteriosus for survival. The proportion of blood flow into the pulmonary ($\dot{Q}p$) and systemic ($\dot{Q}s$) circulation depends on the resistance of each of these circuits. Systemic arterial oxygen saturation (Sa_{O_2}) is often used to gauge relative blood flows between these circuits. Sa_{O_2} greater than 85% suggests excessive pulmonary blood flow at the expense of systemic blood flow, often resulting in insufficient vital organ perfusion and metabolic acidosis.[1] Two strategies are used to counter excessive pulmonary blood flow, namely, inspiration of hypoxic or hypercapnic gas mixtures.[2] Both strategies increase pulmonary vascular resistance and redirect blood flow to the systemic circulation.

Neonates born with SV disease sometimes experience neurologic complications in the form of seizures, impaired cognition, developmental delay, and cerebral palsy.[3,4] Although these neurologic complications are clearly multifactorial in origin, a growing body of evidence indicates that many neonates with SV experience cerebral hypoxia–ischemia before surgery.[5,6] Thus, the use of hypoxic gas mixtures raises the concern of contributing to this preoperative hypoxic–ischemic injury.

Near-infrared spectroscopy is a noninvasive optical technique used to monitor brain tissue oxygenation by measuring concentrations of oxyhemoglobin and deoxyhemoglobin, cerebral oxygen saturation (Sc_{O_2}), or cytochrome aa_3 redox state.[7] This technology has been used to examine cerebral oxygenation before and during congenital heart surgery[8,9] and may also be used to examine cerebral oxygenation in response to medical therapies before and after surgery.

In this prospective, randomized, crossover trial, we examined the effect of 17% fraction of inspired oxygen (F_{IO_2}) and 3% fraction of inspired carbon dioxide (F_{ICO_2}) on cerebral oxygenation and systemic hemodynamics in neonates with SV before the Norwood operation. We hypothesized that, although both treatments would improve systemic hemodynamics, 3% F_{ICO_2} would increase Sc_{O_2}, whereas 17% F_{IO_2} would decrease Sc_{O_2}.

Materials and Methods

After obtaining institutional review board approval (Children's Hospital of Philadelphia, Philadelphia, PA), informed parental consent was obtained. This study was conducted between June and October 1999 at the Children's Hospital of Philadelphia. Eligibility criteria included a diagnosis of univentricular heart defect with Sa_{O_2} greater than 80% (evidence of $\dot{Q}p/\dot{Q}s > 1.0$). Exclusion criteria were postnatal age greater than 1 month,

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preoperative seizures, associated craniofacial anomalies that precluded near-infrared spectroscopy monitoring, and participation in an investigational drug study. The study was conducted in the operating room after induction of anesthesia and before start of stage 1 Norwood surgery.

Per institutional practice, prostaglandin infusion was discontinued immediately before transport to the operating room. No premedication was administered. After placement of electrocardiogram, pulse oximeter, and arterial pressure monitors, the subjects received fentanyl citrate (20 μg/kg bolus, then 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and pancuronium bromide (0.2 mg/kg), were nasally intubated, and mechanically ventilated to normocapnia with 21% F_{IO_2} using a Servo SV 300 ventilator (Siemens-Elema, Solna, Sweden) without positive end-expiratory pressure. Heart rate, systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure (MAP), Sa_{O_2} and nasopharyngeal temperature were continuously monitored during the study.

To deliver 17% F_{IO_2} and 3% F_{ICO_2}, nitrogen and carbon dioxide, respectively, were added to the inspiratory limb of the ventilator circuit. Nitrogen (size H tank) flow was adjusted to obtain 17% F_{IO_2} as measured in the inspired limb ($MaxO_2$ oxygen analyzer; Ceramatec, Salt Lake City, UT). Carbon dioxide (size E tank) was adjusted to achieve a partial pressure of 20 mmHg in the inspired limb (equivalent to 2.8% CO_2, with a water vapor pressure of 47 mmHg at 37°C; measured using Nellcor Ultracap; Nellcor Inc., Pleasanton, CA). No changes were made to the minute ventilation during the study period.

Near-infrared Spectroscopy Methodology

The near-infrared cerebral oximeter used in this study (NIM Incorporated, Philadelphia, PA) was a prototype 3 wavelength frequency-domain device.[10] This device uses laser diodes at measuring wavelengths of 754, 785, and 816 nm with an internal reference wavelength at 780 nm. The emitted light is sinusoidally oscillated at 200 MHz, and the phase-shift and intensity of the detected light relative to the emitted light were monitored by heterodyne frequency domain technology. Fiberoptic bundles mounted in soft rubber housing (optical probe) delivered the light to and from the head, and emitter and detector were separated by 3 or 4 cm. The probe, placed on the forehead below the hairline, monitors Sc_{O_2} located in the frontal cerebrum; the scalp and skull do not contribute to the optical signal.[7,10] The main unit housing the electronic hardware sends data to a computer for storage and analysis. Sc_{O_2} is calculated from the phase shift signals.[10] Instrument precision relative to cooximetry is 6% from 0 to 100%. Near-infrared spectroscopy Sc_{O_2} represents predominantly oxygen saturation in the venous blood.[11]

Study Protocol

The protocol consisted of two treatment periods with three baseline periods (before and after each treatment). Treatments were 17% F_{IO_2} and 3% F_{ICO_2}. Arterial blood gases, arterial pressure, saturation, and cerebral saturation were obtained at the end of each period. Arterial blood gases were drawn from an indwelling umbilical arterial catheter in all subjects. The sequence of treatment was assigned randomly from a previously generated chart. Each treatment was maintained for 10 min, followed by a 10–20-min baseline period.

Statistical Analysis

Sample size calculation (n = 16) was based on a power of 0.8 and $\alpha = 0.01$ to detect a 20% change in Sc_{O_2} from baseline with treatment (3% F_{ICO_2} or 17% F_{IO_2}). Data are presented as mean ± SD. Significance was set at 0.01 after Bonferroni correction for multiple comparisons.

The primary outcome measure was Sc_{O_2}. Secondary outcome measures included heart rate, MAP, Sa_{O_2}, *p*H, arterial carbon dioxide tension, arterial oxygen tension, and base excess. To examine the effect of period (time effect) and the order of treatment (carryover effects), independent two-sample *t* tests were conducted (SPSS Inc., Chicago, IL). In the absence of time and carryover effects, and differences between baseline and the two treatments were then examined by paired *t* tests for parametric data (data were normally distributed). Sc_{O_2} values during the last 1-min of each period (baseline, 3% F_{ICO_2}, 17% F_{IO_2}) were averaged by the computer to obtain the representative Sc_{O_2} value for that period. Change in Sc_{O_2} was the difference between treatment and the average of the baselines before and after the treatment.

Results

Of the 16 patients enrolled, data from 15 were included in the analysis. One neonate was excluded for protocol violation (error in administering 3% F_{ICO_2}). Table 1 shows the demographic data of 15 subjects. Before the study, in the intensive care unit, all neonates had received prostaglandin infusion (0.025–0. 05 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 10 had received dopamine (3–5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 13 had received digoxin and lasix, and 4 had inspired a hypoxic gas mixture (17–19% F_{IO_2}) by spontaneous ventilation in a hood. There were 12 full-term birth infants and 3 prematurely (< 37 weeks) born infants. None of the infants had neurologic abnormalities by history or physical examination.

During the study, 8 of 15 subjects received hypoxic mixture first followed by 3% F_{ICO_2}. Because neither the order of treatments (crossover effect, $P = 0.16$) or time (period effect, $P = 0.45$) was statistically significant, data are presented by condition (*i.e.*, F_{ICO_2}, F_{IO_2}, baseline)

Table 1. Subject Demographics

	Age at Study (d)	Gest Age (wk)	Weight (kg)	Gender	Dig and Lasix	Dopa	N_2 Use	Diagnosis
1	5	40	2.8	M	Y	N	N	HLHS; PAPVR
2	2	40	3.4	M	Y	Y	Y	HLHS
3	5	40	3.7	F	Y	N	Y	HLHS
4	3	40	3.0	M	N	Y	N	HLHS
5	3	40	3.5	F	N	Y	N	HLHS
6	4	40	3.5	M	Y	N	N	DILV, Hypoplastic RV
7	3	41	3.9	M	Y	Y	N	HLHS
8	7	39	2.4	F	Y	Y	N	HLHS
9	2	40	3.0	M	N	Y	N	HLHS
10	4	40	3.7	M	Y	Y	N	HLHS
11	5	38	2.7	M	Y	N	Y	HLHS
12	10	40	2.8	M	Y	Y	N	TGV; TA; Hypoplastic Ao Arch
13	14	36	1.9	M	Y	Y	Y	HLHS
14	5	35	3.7	F	Y	N	N	HLHS
15	5	36	2.6	M	Y	N	N	Unbalanced AV canal, Sub AS; Ao Coarct
Mean ± SD	5 ± 3	39 ± 2	3 ± 0.6					

Gest age = gestational age; Dopa = dopamine; dig = digoxin; N_2 use = use of 17–19% FiO_2 preoperatively in the intensive care unit; HLHS = hypoplastic left heart syndrome; PAPVR = partial anomalous pulmonary venous return; DORV = double outlet right ventricle; Ao Coarct = coarctation of aorta; DILV = double inlet left ventricle; RV = right ventricle; TGV = transposition of great vessels; TA = triscuspid atresia; AV = atrioventricular; AS = aortic stenosis.

rather than by treatment order (baseline, 3% $FICO_2$, baseline, 17% FIO_2, baseline; or baseline, 17% FIO_2, baseline, 3% $FICO_2$, baseline). Mean data from the 15 subjects are shown in table 2, and the change from baseline (δ) in the MAP and SCO_2 for each subject is shown in table 3.

Hemodynamics

Heart rate, systolic arterial pressure, and SaO_2 did not change significantly with either $FICO_2$ or FIO_2 (table 2). With 3% $FICO_2$, diastolic arterial pressure and MAP increased significantly by 12 and 10%, respectively. During 17% FIO_2, diastolic arterial pressure and MAP did not change significantly ($P = 0.02$ and 0.11, respectively). With 3% $FICO_2$, *p*H decreased and arterial carbon dioxide tension increased as intended, and arterial oxygen tension increased ($P < 0.01$); although the base excess increased, it was not significant ($P = 0.09$). With 17% FIO_2, *p*H increased and arterial oxygen and carbon dioxide tensions decreased (although no alterations were made to the minute ventilation, adding nitrogen increased the minute ventilation; $P < 0.01$); the decrease in base excess was not significant ($P = 0.3$). Nasopharyngeal temperature remained unchanged during the study (36 ± 0.4 *vs.* 35.98 ± 0.4°C, start *vs.* end), as did hematocrit (42 ± 6 *vs.* 42.6 ± 6%, start *vs.* end).

Table 2. Hemodynamic and Arterial Blood Gas Data (n = 15)

	Base	17% FIO_2	Base	3% $FICO_2$
HR (bpm)	156 ± 17	152 ± 17	156 ± 22	150 ± 20
SAP (mmHg)	63 ± 11	61 ± 10	64 ± 13	69 ± 11
DAP (mmHg)	34 ± 8	32 ± 8	33 ± 7	37 ± 8*
MAP (mmHg)	45 ± 9	44 ± 8	45 ± 8	50 ± 9*
pH	7.43 ± 0.08	7.46 ± 0.07*	7.45 ± 0.06	7.34 ± 0.06*
$Paco_2$	37 ± 4	33 ± 5*	35 ± 5	49 ± 6*
Pao_2	51 ± 7	47 ± 5*	53 ± 6	56 ± 6*
Base excess	0.3 ± 4	0.1 ± 4	0.6 ± 4	1.3 ± 5

* $P < 0.01$ treatment compared with base.

HR = heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure; MAP = mean arterial pressure.

Cerebral Oxygen Saturation

Figure 1 shows a typical tracing of SCO_2 during the study in one subject, and table 4 shows the results of the 15 subjects. SCO_2 increased significantly with 3% $FICO_2$ ($P < 0.01$), whereas it did not change with 17% FIO_2 ($P = 0.85$). In 8 of 15 subjects, 17% FIO_2 decreased SCO_2, the largest decrease being 6.5%. By comparison, 3% $FICO_2$ increased SCO_2 in all subjects, the largest increase being 26%. At baseline, in two subjects SCO_2 was less than 40% (37 and 38.5%, respectively). In one of

Table 3. Changes in Mean Arterial Pressure and Cerebral Oxygen Saturation in Each Subject

Patient #	Delta MAP with 17% o_2 (mm Hg)	Delta SCO_2 with 17% o_2	Delta MAP with 3% $FICO_2$ (mmHg)	Delta SCO_2 with 3% $FICO_2$
1	2	−2.5	5	26
2	6	−2.5	0	12.5
3	−7	−2.5	1	7
4	−3	−4	12	20
5	−3	4.5	1	16.5
6	−9	0	2	10.5
7	−1	−0.5	4	16
8	−4	1.5	1	7
9	1	6	12	16.5
10	1	−1	6	1.5
11	−1	−2.5	17	18.5
12	−1	1.5	−1	3.5
13	−2	2	−1	7.5
14	−2	7	4	8.5
15	−1	−6.5	4	13.5

In each instance delta was calculated as the difference of posttreatment value from the pretreatment value.

MAP = mean arterial pressure; SCO_2 = cerebral oxygen saturation.

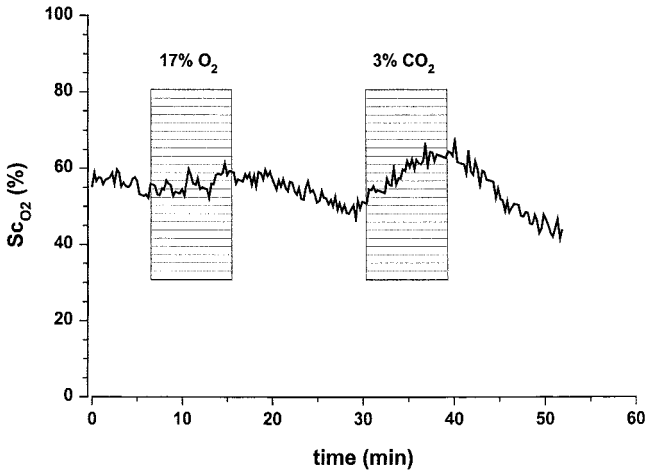

Fig. 1. A typical cerbral oxygen saturation (Sco_2) recording in a subject during the study protocol. At baseline the subject was ventilated to normocapnia with 21% fraction of inspired oxygen (Fio_2). This subject then received 17% Fio_2 as the first treatment condition for 10 min, after which the subject was returned to baseline (21% Fio_2) for 10 min. This was followed by 3% fraction of inspired carbon dioxide ($Fico_2$) for 10 min and then back to baseline (21% Fio_2). Sco_2 values during the last 1 min of each period were averaged by the computer to obtain representative Sco_2 value for that period. Baseline Sco_2 value was obtained by averaging the Sco_2 value before a treatment and that obtained immediately before the next treatment (allowing maximum time for a return to baseline conditions). Delta was calculated as the difference of treatment value and the averaged baseline.

these subjects, Sco_2 decreased to 32% with 17% Fio_2, whereas Sco_2 increased to 48% with 3% $Fico_2$. In the other subject, Sco_2 did not change with 17% Fio_2, but increased 10% during 3% $Fico_2$ administration.

Increase in Sco_2 began 2 ± 0.8 min after administration of 3% $Fico_2$, and the increase was linear at a rate of $0.075 \pm 0.05\% \cdot mmHg\ CO_2^{-1} \cdot min^{-1}$ ($r^2 = 0.68$). With the discontinuation of $Fico_2$, Sco_2 returned to baseline by 8 ± 1.5 min. The relation between change in Sco_2 and MAP during $Fico_2$ was not significant ($r^2 = 0.27$, $P = 0.048$). The Sco_2 response to 3% $Fico_2$ in the premature (10 ± 3%) and full-term birth (13 ± 6) infants was similar.

There were no complications from the study.

Discussion

In this group of neonates with SV heart defects, we found that Sco_2 and arterial pressure increased with 3% $Fico_2$, whereas these parameters did not change significantly with 17% Fio_2. These observations suggest that 3% $Fico_2$ provides better preoperative hemodynamics and cerebral oxygenation than 17% Fio_2 in this patient population.

Table 4. Peripheral Arterial and Cerebral Oxygen Saturation Data (n = 15)

	Base	17% Fio_2	Base	3% $Fico_2$
Sao_2 (%)	95 ± 4	94 ± 4	95 ± 3	95 ± 3
Sco_2 (%)	53 ± 13	53 ± 14	56 ± 13	68 ± 13*

* $P < 0.01$ treatment compared with base.

Sco_2 = cerebral oxygen saturation.

Previous studies conducted in immature animal models of SV heart defects reported increases in pulmonary vascular resistance and a decrease in pulmonary to systemic blood flow ratios ($\dot{Q}p:\dot{Q}s$) with 10% Fio_2 and 5% $Fico_2$.[12] However, no cerebral oxygenation or vital organ blood flow data exist in either animal model or human neonates. In anesthetized, mechanically ventilated human neonates with SV heart defects, Tabbutt *et al.*[13] compared the impact of 17% Fio_2 and 3% $Fico_2$ on systemic oxygen delivery after the same protocol as our study.[13] They found that both treatments decreased Sao_2 and $\dot{Q}p:\dot{Q}s$ similarly, although 3% $Fico_2$ increased systemic oxygen delivery, whereas 17% Fio_2 had no significant impact. These data suggest that 3% $Fico_2$ provides better systemic hemodynamics and oxygenation than 17% Fio_2. Our observations support these conclusions. However, lower inspired oxygen concentrations, as in the animal models, might provide a similar hemodynamic result as 3% $Fico_2$, with or without changes in cerebral oximetry.

Cerebral oximetry is an emerging technology to noninvasively monitor brain tissue oxygenation at the bedside. It is particularly applicable to the critically ill neonate and infant population, where the thin extra-cranial tissues do not interfere with brain monitoring, and in whom diagnosis of cerebral hypoxia–ischemia is otherwise problematic. At present, the instrumentation is based on continuous-wave or frequency-domain technologies. Continuous-wave devices have been commercially available for several years. They can monitor changes in Sco_2 over time but cannot determine baseline levels accurately. Frequency-domain devices (used in this study), a new technology using cellular phone technology, can accurately determine baseline Sco_2 as well as changes over time. It should be commercially available in the near future. However, the clinical utility of cerebral oximetry remains to be determined. Our study serves as an example of how the technology might be used clinically.

Cerebral oximetry and pulse oximetry differ in several respects. Although both use near-infrared light intensity signals, pulse oximetry monitors the pulsatile signal component reflecting the arterial circulation. Cerebral oximetry monitors the nonpulsatile signal component reflecting the gas-exchanging tissue circulation (capillaries, venules, arterioles), of which approximately 85% of the signal appears to originate from small venules.[11] Pulse oximetry often fails with poor perfusion as the pulsatile signal diminishes. Cerebral oximetry is not susceptible to this failure, although it is subject to motion artifact like pulse oximetry. The critical cerebral oxygen

saturation that results in brain damage remains uncertain. Studies in animal models suggest that the risk of brain damage increases as Sco_2 decreases to less than 40%, because electroencephalogram activity begins to slow, adenosine triphosphate decreases, and cytochrome aa_3 becomes reduced; these physiologic changes inevitably lead to neuronal necrosis.[14] In our study, Sco_2 was less than this 40% threshold in two subjects at baseline (incidence, 2 of 15 [13%]), which decreased further with 17% FIO_2 in one subject, whereas Sco_2 increased above the threshold in both subjects with 3% $FICO_2$. Based on this limited experience, 17% FIO_2 might increase the risk of cerebral hypoxia–ischemia before surgery in this patient population.

Cerebral oxygen saturation reflects a balance between cerebral oxygen delivery and cerebral oxygen consumption. Cerebral oxygen delivery is a product of cerebral blood flow (CBF) and arterial oxygen content. The latter depends on Sao_2 and hemoglobin. We did not measure hemoglobin, but during the study period there were no volume shifts; hence, use of hematocrit should be appropriate. During the study, Sao_2 and hematocrit remained constant; thus, a change Sco_2 resulted from changes in CBF or cerebral oxygen consumption. Hypercapnia and hypoxia in the magnitude used in our study do not alter cerebral oxygen consumption,[15] nor do they alter the proportion of arterial to venous blood in the brain.[11] Thus, changes in Sco_2 most likely reflect changes in CBF.

Treatment with 3% $FICO_2$ increased Sco_2. The decrease in *p*H with hypercapnia would lead to a right shift in the oxygen dissociation curve (Bohr effect), which would lead to a decrease in Sco_2 and not an increase. There was a small (3 mmHg) but significant increase in arterial oxygen tension with 3% $FICO_2$ treatment; however, this cannot explain the 12% increase in Sco_2 we observed. Hence, it is most likely that hypercapnic cerebral vasodilatation led to an increase in CBF with an increase in Sco_2.

Healthy adult volunteers breathing hypoxic mixtures (7–11% FIO_2) during isocapnic conditions showed decreases in Sco_2.[16] We had therefore expected treatment with 17% FIO_2 to lead to a decrease in Sco_2. However, the lack of change in Sco_2 reflects the fact that cerebral oxygen delivery was unchanged. Hypoxia can lead to cerebral vasodilatation, but 17% FIO_2 was an insufficient stimulus to evoke this. For example, in adult volunteers, CBF did not change with 18% FIO_2, and it increased only 5% in response to 16% FIO_2.[17]

Cerebral blood flow may also increase if the MAP increases above the limits of autoregulation. The upper lower limit of autoregulation is uncertain in human neonates but is approximately 90 mmHg in neonatal animals.[18,19] In our study, mean arterial pressure increased 10% in response to 3% $FICO_2$ but was still within the limits of autoregulation. Hence, an increase in CBF, and hence Sco_2, on this basis was unlikely.

There are several limitations in our study that might not allow generalization of our findings to care of neonates with SV in the intensive care unit. Our subjects were anesthetized and mechanically ventilated. Their baseline and posttreatment Sao_2 and Sco_2 were greater than that of nonanesthetized, spontaneously breathing subjects. It is possible that the response to hypoxic or hypercapnic gas mixtures differs in nonanesthetized, spontaneously breathing subjects with lower Sao_2 and Sco_2. Despite treatment with 3% $FICO_2$ and 17% FIO_2, the Sao_2 remained greater than 90% in our subjects, indicating continued excessive pulmonary blood flow. Use of higher $FICO_2$ or lower FIO_2 might have reduced Sao_2 further. Time constraints did not permit us to test this hypothesis. Time constraints also limited each baseline and treatment period to 10–20 min. Previous work has shown the CBF response to hypercapnia and hypoxia to be completed by 5 and 6 min, respectively, with return to baseline by 1–2 min.[17,20] Hence, treatment duration in our study should have been adequate to observe a response. However, chronic exposure (hours) might desensitize the cerebral response to hypoxia and hypercapnia.

In conclusion, we demonstrated that controlled ventilation with 3% $FICO_2$ increased the cerebral oxygen saturation as well as arterial pressure, whereas controlled ventilation with 17% FIO_2 maintained arterial pressure but did not change Sco_2 in most subjects, suggesting these treatments provide hemodynamic stability but affect cerebral oxygenation differently. The impact of 17% FIO_2 on cerebral oxygen saturation during spontaneous ventilation, prolonged administration of 17% FIO_2 and 3% $FICO_2$, as well as higher $FICO_2$ remain to be studied.

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