Neuroanesthesia and Intensive Care

Hypercapnia increases cerebral tissue oxygen tension in anesthetized rats

[L'hypercapnie augmente la tension en oxygène du tissu cérébral chez des rats anesthésiés]

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Purpose: To test the hypotheses that deliberate elevation of PaCO_2 increases cerebral tissue oxygen tension (PBrO_2) by augmenting PaO_2 and regional cerebral blood flow (rCBF).

Methods: Anesthetized rats were exposed to increasing levels of inspired oxygen (O_2) or carbon dioxide (CO_2 ; 5%, 10% and 15%, $n = 6$). Mean arterial blood pressure (MAP), PBrO_2 and rCBF were measured continuously. Blood gas analysis and hemoglobin concentrations were determined for each change in inspired gas concentration. Data are presented as mean $\pm$ standard deviation with $P < 0.05$ taken to be significant.

Results: The PBrO_2 increased in proportion to arterial oxygenation (PaO_2) when the percentage of inspired O_2 was increased. Proportional increases in PaCO_2 (48.7 ± 4.9 , 72.3 ± 6.0 and 95.3 ± 15.4 mmHg), PaO_2 (172.2 ± 33.1 , 191.7 ± 42.5 and 216.0 ± 41.8 mmHg), and PBrO_2 (29.1 ± 9.2 , 49.4 ± 19.5 and 60.5 ± 23.0 mmHg) were observed when inspired CO_2 concentrations were increased from 0% to 5%, 10% and 15%, respectively, while arterial pH decreased ($P < 0.05$ for each). Exposure to CO_2 increased rCBF from 1.04 ± 0.67 to a peak value of 1.49 ± 0.45 ($P < 0.05$). Following removal of exogenous CO_2 , arterial blood gas values returned to baseline while rCBF and PBrO_2 remained elevated for over 30 min. The hypercapnia induced increase in PBrO_2 was threefold higher than that resulting from a comparable increase in PaO_2 achieved by increasing the inspired O_2 concentration (34.9 ± 14.5 vs 11.4 ± 5.0 mmHg, $P < 0.05$).

Conclusion: These data support the hypothesis that the combined effect of increased CBF, PaO_2 and reduced pH collectively contribute to augmenting cerebral PBrO_2 during hypercapnia.

Objectif : Tester l'hypothèse voulant que l'élévation délibérée de la PaCO_2 augmente la tension en oxygène du tissu cérébral (TO_2TC) en haussant la PaO_2 et le débit sanguin cérébral régional (DSCr).

Méthode : Des rats anesthésiés ont été exposés à des niveaux croissants d'oxygène inspiré (O_2) ou de gaz carbonique (CO_2 ; 5 %, 10 % et 15 %, $n = 6$). La tension artérielle moyenne (TAM), la TO_2TC et le DSCr ont été mesurés en continu. L'analyse des gaz du sang et les concentrations d'hémoglobine ont été déterminées pour chaque changement de concentration des gaz inspirés. Les données comprennent la moyenne $\pm$ l'écart type où $P < 0,05$ est considéré significatif.

Résultats : La TO_2TC a augmenté en proportion de l'oxygénation artérielle (PaO_2) quand on augmentait le pourcentage de l' O_2 inspiré. Des hausses proportionnelles de la PaCO_2 ($48,7 \pm 4,9$, $72,3 \pm 6,0$ et $95,3 \pm 15,4$ mmHg), de la PaO_2 ($172,2 \pm 33,1$, $191,7 \pm 42,5$ et $216,0 \pm 41,8$ mmHg) et de la TO_2TC ($29,1 \pm 9,2$, $49,4 \pm 19,5$ et $60,5 \pm 23,0$ mmHg) ont été observées avec l'augmentation des concentrations de CO_2 inspiré de 0 % à 5 %, 10 % et 15 %, respectivement, tandis que le pH s'est abaissé ($P < 0,05$ pour chacune). L'exposition au CO_2 a fait monter la TO_2TC de $1,04 \pm 0,67$ à une valeur maximale de $1,49 \pm 0,45$ ($P < 0,05$). Après le retrait du CO_2 exogène, les gaz du sang artériel ont retrouvé leurs valeurs de base tandis que le DSCr et la TO_2TC sont demeurés élevés pendant plus de 30 min. L'hypercapnie qui a provoqué une hausse de la TO_2TC a été trois fois plus élevée que celle qui a provoqué une hausse comparable de la PaO_2 réalisée en augmentant la concentration d' O_2 inspiré ($34,9 \pm 14,5$ vs $11,4 \pm 5,0$ mmHg, $P < 0,05$).

Conclusion : Nos données confirment l'hypothèse voulant que l'effet combiné de l'augmentation du DSC, de la PaO_2 et de la réduction du pH contribue à l'augmentation de la TO_2TC pendant l'hypercapnie.

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OPTIMIZING cerebral tissue oxygen (O_2) delivery is a key concern in caring for the critically ill and in patients undergoing anesthesia.¹ Accepted strategies for augmenting tissue O_2 delivery include the use of supplemental O_2 , different modalities of mechanical ventilation, red blood cell transfusion and inotropic support. However, many of these techniques have not been demonstrated to be effective,²⁻⁴ and in some cases may have resulted in increased mortality.⁵

"Permissive hypercapnia", first implemented in neonatal practice by Wung *et al.*,⁶ was demonstrated to improve survival in patients with adult respiratory distress syndrome in studies by Hickling *et al.*^{7,8} The concept of 'therapeutic hypercapnia', whereby $PaCO_2$ is deliberately elevated in order to attenuate end-organ injury, has evolved from studies which have demonstrated reduced tissue injury in association with hypercapnia.^{9,10} Elevation of $PaCO_2$ attenuated injury resulting from myocardial ischemia,¹¹ stroke¹² and lung reperfusion¹³ and has been associated with improved neurological outcome following cardiopulmonary bypass.¹⁴ Although the mechanisms of protection have not been clearly delineated, improved balance between tissue O_2 supply and demand may play a significant role.^{9,10}

Experimental studies help to explain how hypercapnia may improve cerebral tissue oxygenation. Although not predicted by the alveolar gas equation, elevated $PaCO_2$ has been demonstrated to increase arterial PaO_2 , possibly by improved ventilation perfusion matching in the lung.¹⁵⁻¹⁸ In addition to augmenting PaO_2 , hypercapnia has been shown to increase arterial blood O_2 carrying capacity^{19,20} and increase cardiac output.^{15,21} Hypercapnia might also improve tissue O_2 delivery due to a right shift in the O_2 hemoglobin dissociation curve.²² Finally, elevated $PaCO_2$ causes a well described increase in cerebral blood flow (CBF),^{23,24} while reducing systemic and cerebral metabolic demands,²⁵⁻²⁷ thereby optimizing the balance between cerebral tissue O_2 supply and demand.

Although global O_2 delivery appears to be enhanced by hypercapnia, the specific effects on cerebral tissue oxygen tension ($PBrO_2$) are incompletely understood. Because of the potential vulnerability of cerebral function during critical illness the current study attempts to determine the contribution of increased PaO_2 and elevated CBF on cerebral $PBrO_2$ following hypercapnia. To achieve this goal we tested the hypotheses that deliberate elevation of $PaCO_2$ causes an increase in cerebral $PBrO_2$ as a result of elevated PaO_2 , and increased CBF in anesthetized rats.

Material and methods

Animal model

All animal protocols were approved by the Animal Care and Use Committee at St. Michael's Hospital in accordance with the requirements of the Canadian Animal Care Committee. Anesthesia was induced in male Sprague Dawley rats (Charles River, St. Constant, PQ, Canada) with ketamine/xylazine ($100/7.5 \text{ mg}\cdot\text{kg}^{-1} \text{ ip}$, Parke-Davis/Bayer, Toronto, ON, Canada) and maintained with 1 to 2% isoflurane (Abbott, St. Laurent, PQ, Canada) following tracheostomy and ventilation with a pressure controlled ventilator (Kent Scientific, Litchfield, CT, USA). Cannulation of the tail artery (PE 50) was performed for direct measurement of mean arterial blood pressure (MAP) and arterial blood gas determinations. Ventilation was adjusted to achieve normocapnia and normoxia as determined by blood gas analysis (Radiometer ALB 500, London Scientific, London, ON, Canada). Hemoglobin concentrations were determined using a co-oximeter (Radiometer OSM 3).

Animals were placed in a stereotaxic frame (ADI Instruments, Harvard Apparatus, Saint-Laurent, PQ, Canada) and the scalp incised sagittally. Bilateral 5-mm diameter burr holes were trephined at the level of the bregma, 2 to 3 mm lateral to the sagittal sinus, exposing the intact dura. Bilateral calibrated polarographic O_2 sensing electrodes, with a maximal diameter of 500 μm and a sensing aperture 1 mm in diameter (LICOX GMS, Harvard Apparatus, Saint-Laurent, PQ, Canada), were then inserted about 6 mm past the dura into the region of the right and left caudate nuclei.²⁸ Corresponding bilateral temperature probes were placed at similar coordinates. Bilateral caudate $PBrO_2$ measurements were averaged for each animal (mmHg). Bilateral laser Doppler flow probes (Oxyflo, Oxford Optronix, Oxford, UK) were positioned over the dura to measure regional cortical regional cerebral blood flow (rCBF). rCBF values were normalized to the baseline and then averaged for each animal. After a one-hour equilibration period, a steady baseline was measured for 20 min, while a heating pad and heating lamp were utilized to maintain the brain temperature near 37°C . Caudate $PBrO_2$, temperature, CBF and MAP, were recorded using a computerized data acquisition system (DASYLab, Kent Scientific, Litchfield, CT, USA).

Experimental procedures

CHANGES IN CAUDATE $PBrO_2$ INDUCED BY INCREASING THE PERCENTAGE OF INSPIRED O_2 OR HYPERVENTILATION

After probe equilibration, the baseline $PBrO_2$ was measured for 20 min. Animals were then exposed to

serial increases in the percentage of inspired O_2 from 30% to 50% and 100% ($n = 12$ rats). The percentage of inspired O_2 was confirmed using an O_2 analyzer (Ohmeda 5100, Datex-Ohmeda, Mississauga, ON, Canada) connected to the inspiratory limb of the ventilatory circuit. Arterial blood gas and hemoglobin measurements were taken at each different level of inspired O_2 . The effect of hyperventilation was determined in a different group of rats ($n = 7$). $PBrO_2$ measurements were performed once the $PaCO_2$ was measured near 40 mmHg with an inspired O_2 concentration of 100%. Hyperventilation was initiated by increasing the degree of pressure control to achieve a target $PaCO_2$ near 25 mmHg. $PBrO_2$, hemoglobin concentration, MAP and arterial blood gases were measured before and after hyperventilation.

EFFECT OF INCREASED INSPIRED CO_2 ON CAUDATE $PBrO_2$ AND RCBF

Anesthetized rats were initially ventilated with 50% O_2 in nitrogen (0% CO_2) and baseline measurement for arterial blood gases, brain temperature, MAP, cerebral oxygenation and CBF were determined over 20 min ($n = 6$). Rats were then ventilated with gas mixtures containing an increasing concentration of CO_2 , from 5% to 10% and then 15% mixed with 50% O_2 and nitrogen (Praxair Canada Inc., Mississauga, ON, Canada). Rats were exposed to each concentration of CO_2 for 20 min, prior to increasing the CO_2 concentration to the next level. After exposure to 15% CO_2 , the rats were then ventilated with 50% O_2 in nitrogen (0% CO_2) for an additional 30 min prior to terminating the experiment. Arterial blood gases were taken at baseline (0 and 20 min) and after ten minutes of exposure to each different CO_2 concentration (30, 50 and 70 min, respectively). Two subsequent blood gas determinations were performed after the inspired CO_2 concentration was reduced to 0% (90 and 110 min). Animals were then euthanized with ketamine (100 mg·kg⁻¹ *iv*, Parke-Davis, Toronto, ON, Canada) and the position of the bilateral O_2 sensing probes confirmed.

Data analysis

A sample size calculation, performed prior to initiating the experiments, indicated that six animals per group would be sufficient to detect a 50% change in $PBrO_2$ given a power of 80% and a type I error of 5%. Data were initially assessed for any time or group effect using a two-way analysis of variance (SAS Institute Inc., Cary, NC, USA). Comparisons between and within groups were performed using Wilcoxon rank sum and signed rank tests, respectively. Following exposure to inspired CO_2 , values for brain tempera-

FIGURE 1 Column A: Increased PaO_2 levels resulted in increased brain oxygenation. Column B: Hyperventilation resulted in a parallel reduction in $PaCO_2$ and $PBrO_2$.

ture, MAP, $PBrO_2$ and CBF were determined at 0%, 5%, 10%, 15% and 0% CO_2 , respectively, by averaging ten sequential values for each variable, obtained over a ten-minute period, ten minutes after each change in inspired gas concentration. Correlation between variables was assessed using a correlation coefficient. Statistical significance was assigned at a P value less than 0.05 in all cases. Data are presented as mean $\pm$ standard deviation (SD). For clarity of presentation, graphical data are presented as mean $\pm$ standard error of the mean (SEM).

Results

Effect of increasing the percentage of inspired O_2 or hyperventilation on caudate $PBrO_2$

At an inspired O_2 concentration of 30%, a PaO_2 of 109.5 ± 25.5 mmHg corresponded to a $PBrO_2$ of 17.8 ± 8.3 mmHg (Figure 1, column A, $n = 12$). Increasing the inspired O_2 concentration to 50% and 100% resulted in an increase in the PaO_2 to 180.6 ± 52.1 and 330.9 ± 83.6 mmHg, respectively. These values corresponded to $PBrO_2$ values of 29.2 ± 9.0 and 43.9 ± 14.3 mmHg, respectively (Figure 1, column A, $P < 0.05$). There were no significant changes in pH (7.38 ± 0.07 mmHg), $PaCO_2$ (40.1 ± 9.0 mmHg), hemoglobin concentration (118 ± 13.3 g·L⁻¹) or MAP (83.6 ± 24.2 mmHg), when compared to baseline values. For the hyperventilation experiments, the baseline values for PaO_2 , $PaCO_2$

FIGURE 2 Brain temperature, mean arterial pressure, brain oxygenation and normalized cerebral blood flow with exposure to increasing percentages of inspired CO_2 ($n = 6$ rats).

and PbO_2 were 250 ± 89.2 , 37.8 ± 3.7 and 40.7 ± 21.6 mmHg, respectively (Figure 1, column B, $n = 7$). Hyperventilation reduced the PaCO_2 to 25.5 ± 2.5 mmHg and the PbO_2 to 21.9 ± 15.9 mmHg, respectively (Figure 1, column B, $P < 0.05$), despite a tendency for the PaO_2 and pH to increase. The hemoglobin concentration ($125 \pm 9.8 \text{ g}\cdot\text{L}^{-1}$) and MAP (82.6 ± 21.1 mmHg) did not change significantly.

Effect of increasing inspired CO_2 on arterial blood gases, caudate PbO_2 and rCBF

Sequential increases in inspired CO_2 resulted in an increase in brain temperature from a baseline value of $35.3 \pm 1.3^\circ\text{C}$, to a maximum of $37.0 \pm 0.9^\circ\text{C}$. (Figure 2, $P < 0.05$). Brain temperature reduced to $36.2 \pm 0.9^\circ\text{C}$ after reduction of inspired CO_2 to 0%. At lower CO_2 concentrations, the MAP remained near baseline values of 81.7 ± 8.1 mmHg. At higher inspired CO_2 concen-

FIGURE 3 Blood gas analysis following exposure to serial increases in the percentage of inspired CO_2 from 0 to 5%, 10% and 15% ($n = 6$ rats).

trations, the MAP increased significantly, reaching a maximum of 101.3 ± 12.5 mmHg (Figure 2, $P < 0.05$). With removal of CO_2 , MAP returned to baseline.

Caudate PbO_2 increased from a baseline of 14.5 ± 5.6 mmHg to 29.1 ± 9.2 , 49.4 ± 19.5 and 60.5 ± 23.0 mmHg after exposure to 5%, 10% and 15% CO_2 , respectively (Figure 2, $P < 0.05$, for each increase). Removal of CO_2 from the inspiratory gas mixture resulted in a reduction of PbO_2 . However, 30 min after reduction of the CO_2 to 0%, the PbO_2 remained elevated at 25.1 ± 10.1 mmHg, despite the return of PaO_2 and PaCO_2 to baseline values (Figure 2, $P < 0.05$). CBF followed a similar pattern, increasing from a normalized baseline of 1.04 ± 0.07 to 1.20 ± 0.27 , 1.40 ± 0.47 and 1.49 ± 0.45 after exposure to 5%, 10% and 15% CO_2 , respectively (Figure 2, $P < 0.05$). The maximum CBF (1.59 ± 0.34) was achieved after exposure to 15% CO_2 . Thirty minutes after reduction of CO_2 to 0%, the CBF tended to remain elevated above control values (1.31 ± 0.34).

Increasing the inspired CO_2 from 0% to 5%, 10% and 15% resulted in a sequential reduction in the pH from 7.4 ± 0.09 to 7.27 ± 0.02 , 7.13 ± 0.02 , and 7.03 ± 0.22 , respectively (Figure 3, $P < 0.05$, for each increase). The pH returned to 7.39 ± 0.02 following reduction of the inspired CO_2 to 0%. Similarly, sequentially increasing the percentage of inspired CO_2 raised the PaCO_2 from a baseline value of 36.2 ± 19.8 mmHg to 48.7 ± 4.9 , 72.3 ± 6.0 and 95.3 ± 15.4 mmHg, respectively (Figure 2, $P < 0.05$, for each increase). The

FIGURE 4 Correlations between cerebral tissue oxygen tension (PBrO₂) and arterial blood gas PaCO₂ and pH ($n = 6$ rats).

increase in PaCO₂ was paralleled by an increase in PaO₂ from a baseline of 121.6 ± 36.0 to 172.2 ± 39.1 , 191.7 ± 42.5 and 216.0 ± 41.8 mmHg, respectively (Figure 3, $P < 0.05$). Both the PaCO₂ and PaO₂ returned to baseline values after reduction of inspired CO₂ to 0%. There were no statistically significant changes in hemo-

globin concentration or arterial blood O₂ content. Changes in PBrO₂ correlated with the observed increases in PaCO₂ and with the decrease in arterial pH (Figure 4, $P < 0.05$ for each correlation).

Comparison of changes in caudate PBrO₂ in response to increased inspired O₂ and CO₂

The relative effect of increasing inspired O₂ and CO₂ on PBrO₂ is compared in the Table. Increasing the inspired O₂ from 30 to 50% increased the mean PaO₂ by 71.1 ± 46.4 mmHg and resulted in a mean increase in PBrO₂ of 11.4 ± 5.0 mmHg, without changing pH or PaCO₂. By contrast, increasing the inspired CO₂ from 0 to 10% resulted in an increase in PaCO₂ of 36.1 ± 13.9 mmHg with a corresponding average decrease in pH of 0.27 ± 0.09 . Under these conditions, an increase in PaO₂ of 70.1 ± 41.4 mmHg resulted in a mean increase in PBrO₂ of 34.9 ± 14.5 mmHg (Table, $P < 0.05$).

Discussion

The current study demonstrates that hypercapnia augments cerebral PBrO₂ in proportion to increased PaCO₂, by mechanisms which include incremental increases in PaO₂ and rCBF and incremental reductions in arterial pH. Previous experimental studies have characterized hypercapnia induced elevation in PaO₂ which may result from improved ventilation-perfusion matching in the lung.¹⁵⁻¹⁸ The significant increase in PaO₂ observed during hypercapnia would be expected to enhance cerebral tissue oxygenation, as has been demonstrated in this and other studies.^{29,30} However, the relative magnitude of the increase in PBrO₂ achieved during hypercapnia was threefold higher than that obtained when a comparable increase in PaO₂ was achieved by increasing the percentage of inspired O₂. This suggests that other important factors contribute to augmenting cerebral PBrO₂.

The increase in CBF associated with hypercapnia is a

TABLE Comparison of increases in caudate tissue oxygen tension (PBrO₂) associated with increased levels of inspired oxygen or carbon dioxide

Maneuver (* $P < 0.05$)	pH	PaCO ₂ mmHg	PaO ₂ mmHg	PBrO ₂ mmHg
Baseline	7.38 ± 0.07	40.1 ± 9.0	109.5 ± 25.5	17.8 ± 8.3
Increase inspired oxygen from 30% to 50%	7.35 ± 0.03	41.0 ± 8.0	180.6 ± 52.1	29.2 ± 9.0
Mean change ($n = 12$)	-0.03 ± 0.07	0.9 ± 9.3	71.1 ± 46.4	11.4 ± 5.0
Baseline	7.40 ± 0.09	36.2 ± 9.8	121.6 ± 36.0	14.5 ± 5.6
Increase inspired carbon dioxide from 0% to 10%	7.13 ± 0.02	72.3 ± 6.0	191.7 ± 42.5	49.4 ± 19.5
Mean change ($n = 6$)	$-0.27 \pm 0.09^*$	$36.1 \pm 13.2^*$	70.1 ± 41.4	$34.9 \pm 14.5^*$

* Represents statistically significant differences between mean changes, $P < 0.05$.

well described phenomenon which is known to augment cerebral O_2 delivery.^{31,32} Increased rCBF measured in this study would significantly contribute to increased cerebral tissue O_2 delivery thereby enhancing $PBrO_2$. The transient increase in caudate temperature, which resolved after removal of CO_2 , provides further indirect evidence of increased blood flow to the caudate nucleus during hypercapnia. Persistent elevation of $PBrO_2$ and rCBF for over 30 min following removal of inspired CO_2 , despite normalization of arterial blood gas measurements, emphasizes the importance of CBF in contributing to cerebral oxygenation, in the absence of any significant contribution by arterial PaO_2 , $PaCO_2$ or pH. This persistent elevation of $PBrO_2$ may be due to residual acidification of cerebrospinal fluid,²⁴ however this was not established in the current study. Although previous studies have demonstrated increased cerebral $PBrO_2$ following hypercapnia,^{29,30} the relative contribution of increased PaO_2 and rCBF have not been determined. The results of this study demonstrate a stepwise increase in cerebral $PBrO_2$ following exposure to serial increases in the percentage of inspired CO_2 . Factors that contribute to this increase in $PBrO_2$ include an increase in arterial oxygenation and an increase in CBF. The reduction in arterial pH also correlated with the increase in $PBrO_2$, suggesting that a rightward shift of the O_2 -hemoglobin dissociation curve may have favoured O_2 delivery to cerebral tissue during hypercapnia.²²

In addition to influencing factors that result in increased cerebral tissue O_2 delivery, hypercapnia may also improve cerebral $PBrO_2$ by reducing the systemic and cerebral metabolic rate for O_2 . Forslid *et al.* have demonstrated a significant reduction in electroencephalographic activity and somatosensory evoked potential amplitude following exposure to 80% CO_2 while Sachdeva and Jennings have estimated that hypercapnia may reduce the systemic metabolic rate for O_2 by about 40% after exposure to 4% CO_2 .^{26,27} In addition to these effects on global and cerebral O_2 utilization, Ward describes potential alterations in cellular metabolism, which occur in response to hypercapnia induced cellular acidosis.²⁵ These include an inhibition of the glycolytic enzyme phosphofructokinase, preventing generation of adenosine triphosphate (ATP) by anaerobic metabolism. Compensation for this inhibition of glycolysis include a concurrent increase in oxidative deamination, with subsequent depletion of intracellular amino acids, which are utilized to generate ATP by oxidative processes.^{25,33} Thus, anaerobic generation of ATP is inhibited and cells become more dependent on aerobic metabolism. Under these circumstances the brain may be relatively protected from injury as long as adequate O_2 is available.³³

Therefore, the mechanisms by which cerebral tissue oxygenation is augmented during hypercapnia may have evolved teleologically as a defence against respiratory acidosis. These observations may help to explain why hypercapnia reduces tissue injury secondary to ischemia and reperfusion¹¹⁻¹³ possibly contributing to the observed increase in survival of critically ill patients treated with permissive hypercapnia.^{7,8} The ability to exploit the capacity of hypercapnia to augment cerebral tissue oxygenation, and defend tissue against ischemic injury, requires further characterization.

It is unknown whether the observed increase in cerebral $PBrO_2$ would improve aerobic metabolism at the cellular level in critically ill patients. Previous strategies to augment tissue O_2 delivery by increasing cardiac output, failed to demonstrate improved outcomes, in part because the tissue O_2 utilization can be severely impaired at the cellular level in the setting of multi-organ failure.^{2,3} However, in specific settings of myocardial ischemia, cerebral ischemia and lung reperfusion, hypercapnia was demonstrated to protect against ischemic end-organ damage.¹¹⁻¹³ Furthermore, hypercapnia induced increases in tissue oxygenation may also protect against surgical wound infections.²¹ Alternately, increased $PBrO_2$ may lead to an increase in reactive O_2 species which may promote free radical mediated tissue damage,^{34,35} demonstrating that excessive elevation of $PBrO_2$ may also have detrimental effects. Further research will be required to define the optimum balance between the potentially beneficial and harmful effects of hypercapnia on end-organ oxygenation and function.

Limitations of this study include creation of local tissue trauma by the invasive O_2 sensitive micro-electrodes, leading to inaccurate values of $PBrO_2$. This acknowledged disadvantage of all invasive tissue probes would be expected to influence measurements equally at all levels of CO_2 tested and should not interfere with assessment of relative changes following administration of CO_2 . Furthermore, our current and previously reported measurements of caudate $PBrO_2$ ²⁸ fall within the range of values reported by other experimental studies for rat cerebral cortex, thalamus and hippocampus utilizing invasive O_2 electrodes.³⁶⁻³⁹ Measurement of cortical CBF was not performed at the same site as the O_2 electrodes to minimize local tissue damage in the caudate nucleus. Other studies have demonstrated that the caudate nucleus has similar metabolic rate and blood flow as the cerebral cortex suggesting that changes in flow within the cerebral cortex reflect those that occur in the caudate nucleus.^{40,41}

In summary, this study demonstrates that the dramatic increase in caudate $PBrO_2$, associated with hypercapnia, results from a combined increase in PaO_2

and CBF. The correlation between changes in PBrO_2 and arterial pH suggests that a right shift of the O_2 hemoglobin dissociation curve may have also contributed to increasing cerebral tissue O_2 delivery. The hypercapnia induced increase in PBrO_2 was threefold higher than that achieved by a comparable increase in PaO_2 alone, suggesting that augmented CBF and reduced arterial pH contributed to increasing the cerebral PBrO_2 . These data suggest that the combined effect of elevated PaO_2 , CBF and reduced pH contribute collectively to augmenting PBrO_2 during hypercapnia. Further studies are required to determine if hypercapnia induced augmentation of cerebral tissue oxygenation may protect against hypoxic or ischemic organ injury.

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