Neuroanesthesia and intensive care

Ophthalmic artery blood flow velocity increases during hypocapnia

[La vitesse circulatoire de l'artère ophtalmique augmente pendant l'hypocapnie]

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Purpose: The effects of anesthetic management on blood flow to the optic nerve have not been well-studied. The ophthalmic artery provides the majority of the blood supply to the optic nerve via several smaller branches. Retinal blood flow has been shown to react to carbon dioxide (CO_2) similar to intracranial vessels, but insufficient data exist for the ophthalmic artery. The purpose of this study is to examine the CO_2-reactivity of the ophthalmic artery.

Methods: Eight healthy awake subjects aged 28 to 50 yr were tested for CO_2-reactivity in the ophthalmic artery using transcranial Doppler (TCD) insonation of blood flow velocity (V_{op}), while simultaneously recording the V_{op} of the middle cerebral artery (V_{mca}) as an internal control. V_{op} and V_{mca} recordings were made under hypocapnic, normocapnic and hypercapnic conditions.

Results: The CO_2-reactivity slope of V_{mca} was 3.27% per mmHg $PaCO_2$. From normocapnia to hypercapnia, V_{op} did not change significantly (mean ± SD, 18 ± 4 cm·sec^{-1} to 18 ± 6 cm·sec^{-1}), (end-tidal CO_2, $etCO_2$, = 43 ± 5 mmHg to 53 ± 4 mmHg, respectively). In contrast, V_{op} increased significantly under hypocapnic conditions ($etCO_2$ = 26 ± 4 mmHg) to 25 ± 5 cm·sec^{-1} ($P < 0.05$). The CO_2-reactivity slope of V_{op} from normocapnia to hypocapnia was 2.57% per mmHg.

Conclusions: This study demonstrates that V_{op} increases with hypocapnia, but is unaffected by hypercapnia. The anastomoses of the ophthalmic artery with the external carotid artery, which displays a relatively fixed resistance, may account for these findings.

Objectif : *Les effets de la démarche anesthésique sur le débit sanguin vers le nerf optique ne sont pas bien connus. L'artère ophtalmique nourrit en grande partie le nerf optique par quelques ramifications plus petites. On a montré que le débit sanguin de la rétine réagit au gaz carbonique (CO_2) de façon similaire aux vaisseaux intracrâniens, mais les données manquent sur l'artère ophtalmique. Notre objectif était de vérifier la réactivité au CO_2 de l'artère ophtalmique.*

Méthode : *Huit sujets sains, éveillés, de 28 à 50 ans, ont été testés pour connaître la réactivité au CO_2 de l'artère ophtalmique en utilisant l'enregistrement de la vitesse circulatoire (V_{op}) avec le Doppler transcrânien (DTC) et, simultanément, la V_{op} de l'artère cérébrale moyenne. (V_{acm}) comme témoin interne. Les enregistrements de la V_{op} et la V_{acm} ont été faits sous hypocapnie, normocapnie et hypercapnie.*

Résultats : *La pente de réactivité au CO_2 de la V_{acm} était de 3,27 % par mmHg de $PaCO_2$. De la normocapnie à l'hypercapnie, la V_{op} n'a pas significativement changé (moyenne ± écart type, 18 ± 4 cm·sec^{-1} à 18 ± 6 cm·sec^{-1}), (CO_2 télé-expiratoire, $etCO_2$, = 43 ± 5 mmHg à 53 ± 4 mmHg, respectivement). Toutefois, la V_{op} a augmenté de façon significative en hypocapnie ($etCO_2$ = 26 ± 4 mmHg) à 25 ± 5 cm·sec^{-1} ($P < 0,05$). La pente de la réactivité au CO_2 de la normocapnie à l'hypocapnie est de 2,57 % par mmHg.*

Conclusion : *L'étude démontre que la V_{op} augmente sous hypocapnie, mais n'est pas affectée par l'hypercapnie. Les anastomoses de l'artère ophtalmique avec l'artère carotide externe, qui affiche une résistance relativement fixe, peuvent rendre compte de ces résultats.*

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THERE is a paucity of published information on the effects of anesthetic agents, and hemodynamic and ventilatory changes on the blood flow to the eye in humans. The ophthalmic artery provides the majority of the blood supply to the optic nerve and retina via branches which include the central retinal artery, the short and long posterior ciliary arteries, and the pial arteries.[1,2]

Because of its proximity to the brain and the origin of its blood supply, it might be expected that blood flow to the eye would respond in a similar fashion to other intracranial vasculature in terms of autoregulation and carbon dioxide (CO_2) vasoreactivity. Indeed retinal blood flow has been shown to increase with increasing CO_2 tensions.[3–6] However, perfusion to the eye as a whole appears to be more complex, as other investigations have revealed that ophthalmic artery blood flow velocity (V_{op}) does not increase with hypercapnia.[4,5,7] Conversely, hypocapnia has been shown to cause a reduction in retinal artery blood flow,[3,6] but the effects of hypocapnia on ophthalmic artery blood flow have not been studied.

Since the ophthalmic artery is the origin for the blood supply to the optic nerve, as well as the retina, the vasoreactivity of this vessel to CO_2 may have important clinical implications. The purpose of this study is to determine the effects of hypocapnia and hypercapnia on the V_{op} in humans. Simultaneous measurement of flow velocity in the middle cerebral artery (V_{mca}) was undertaken to confirm the normal cerebral vascular response control.

Materials and methods

After obtaining approval from the Institutional Review Board and informed consent, eight volunteer subjects (ages 28–50 yr, two males/six females) were studied. Subjects were free of significant disease and were classified as ASA I or ASA II physical status.

Experimental protocol

Subjects were placed in a semi-reclined position and the following variables were recorded: continuous non-invasive blood pressure, end-tidal CO_2 ($etCO_2$), V_{op} and V_{mca}. V_{op} and V_{mca} were measured simultaneously on the right side. With a nose clip in place, measurements were first made during normocapnia under stable conditions. The subjects then inhaled 5% CO_2 in 40% oxygen for three minutes via a non-rebreathing valve. Following return to normocapnia with stable conditions for three minutes, subjects were instructed to voluntarily hyperventilate to maintain an $etCO_2$ of approximately 25 mmHg for three minutes.

Blood flow velocity measurements

V_{op} and V_{mca} were measured simultaneously using a transcranial Doppler (TCD; DWL, Neuroscan, Sterling, VA, USA) with 2 MHz probes. Both vessels were identified using standard criteria. The MCA was insonated transtemporally with the TCD probe and measured at a depth between 45 to 50 mm. The probe was anchored using the Lam Rack™ (DWL, Sterling, VA, USA) to maintain a constant angle of insonation.

The handheld probe for the ophthalmic artery was positioned over the closed eyelid angled posteriorly and slightly medially, as previously described.[8] The depth was set at 50 mm with the power set at the lowest level consistent with satisfactory recordings. The probe for the ophthalmic artery cannot be anchored and was handheld during the study. To minimize error, all measurements were performed by only two individuals, and results were only accepted if optimal audio signals were obtained consistently. Because the ophthalmic artery runs directly outward horizontally from its origin, the error introduced by probe movement would be small.

$etCO_2$ measurements

Calibration of the $etCO_2$ monitor (Datex, Puritan Bennett Corp., Tewksberry, MA, USA) was performed at the start of each experiment. A plastic mouthpiece connected to a one-way valve was placed into the subject's mouth. The one-way valve allowed separation of inflow gases from exhaled breath, without mixing and re-breathing. The $etCO_2$ sampling line was on the outflow limb of the one-way valve. A clip was placed on the subject's nose to prevent contamination from nasal breathing.

Blood pressure measurements

Continuous non-invasive blood pressure measurements (Colin Model 7000, Colin Medical Instruments Corp., San Antonio, TX, USA) were based on the radial arterial pulse. The continuous measurements of the arterial pulse displacement was calibrated against a conventional cuff placed on the ipsilateral arm. Automatic re-calibration occurred at 2.5-minute intervals throughout each study session.

CO_2-reactivity calculations

Linear regression analysis was used to determine the relationship between $etCO_2$ *vs* V_{op}, and $etCO_2$ *vs* V_{mca}, and corrected to baseline velocity. Since V_{op} exhibited a non-linear relationship from hypocapnia to hypercapnia, CO_2-reactivity was calculated for V_{op} as the percent change in blood flow velocity (V) per mmHg change in $etCO_2$ from baseline to either hypercapnia or hypocapnia:

CO_2-reactivity =

$$\frac{[(\text{Vbaseline} - \text{Vhypercapnia or hypocapnia}) / \text{Vbaseline}] \times 100}{(\text{etCO}_2 \text{ baseline} - \text{etCO}_2 \text{ hypercapnia or hypocapnia})}$$

Statistical analysis

$etCO_2$ measurements were expressed as mean ± SD. Analysis of variance for repeated measures and Student's two-tailed paired t test with Bonferonni's correction for multiple comparisons were used to compare measurements obtained during normocapnia, hypocapnia and hypercapnia. A P value < 0.05 was considered statistically significant.

Results

Mean values ± SD for the mean arterial pressure (MAP), $etCO_2$, V_{mca} and V_{op} are shown in the Table. MAP ± SD during hypocapnia, normocapnia and hypercapnia were 74 ± 14, 80 ± 11, and 79 ± 13 mmHg, respectively. There were no significant differences in MAP between groups (P = 0.74). Mean $etCO_2$ ± SD during hypocapnia, normocapnia and hypercapnia were 26 ± 4, 43 ± 5, and 53 ± 4 mmHg, respectively. V_{mca} increased linearly with $etCO_2$ (r = 0.97). The hypocapnic, normocapnic, and hypercapnic values for V_{mca} ± SD were 36 ± 9, 62 ± 18, and 92 ± 22 $cm \cdot sec^{-1}$, respectively. The CO_2-reactivity slope for V_{mca} was 3.27% change in flow velocity per mmHg CO_2. The V_{op} ± SD for the hypocapnic, normocapnic, and hypercapnic conditions were 25 ± 5, 18 ± 4, and 18 ± 6 $cm \cdot sec^{-1}$, respectively. V_{op} demonstrated a nonlinear relationship with $etCO_2$ (r = -0.75). The V_{op} during normocapnia were significantly different from those during hypocapnia ($P < 0.05$) with all subjects demonstrating a consistent increase in V_{op} with hypocapnia (mean increase = 42.6 ± 16.4%; Figure). The CO_2-reactivity slope for V_{op} was 2.57% change in flow velocity per mmHg CO_2 from normocapnia to hypocapnia. The V_{op} did not differ between normocapnia and hypercapnia (P = 0.31).

TABLE Blood flow velocity changes of the middle cerebral artery and ophthalmic artery during hypocapnia and hypercapnia

	Hypocapnia	*Normocapnia*	*Hypercapnia*
MAP (mmHg)	74 ± 14	80 ± 11	79 ± 13
$etCO_2$ (mmHg)	26 ± 4	43 ± 5	53 ± 4
V_{mca} ($cm \cdot sec^{-1}$)	36 ± 9*	62 ± 18	92 ± 22*
V_{op} ($cm \cdot sec^{-1}$)	25 ± 5*	18 ± 4	18 ± 6

All values are mean ± SD. MAP = mean arterial pressure; $etCO_2$ = end-tidal carbon dioxide; V_{mca} = middle cerebral artery blood flow velocity; V_{op} = ophthalmic artery blood flow velocity. *$P < 0.05$ compared to normocapnic baseline.

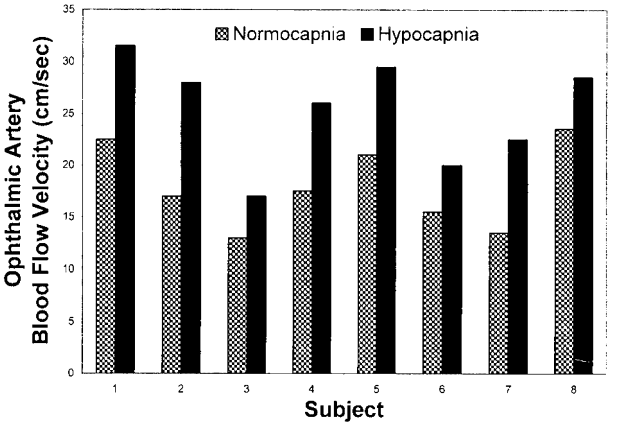

FIGURE Ophthalmic artery blood flow velocity response to hypocapnia. Compared to normocapnia [end-tidal ($etCO_2$ = 43 mmHg), hypocapnia (26 mmHg)] increased ophthalmic artery blood flow velocity (V_{op}) in every subject ($P < 0.05$).

Discussion

Prior studies using colour Doppler imaging and Doppler ultrasound have demonstrated that hypercapnia does not affect V_{op},[4,5,7] but have not examined the effects of hypocapnia. This study evaluated the effects of hypocapnia and hypercapnia on V_{op}, while simultaneously comparing it to V_{mca} as an internal control.[9] As anticipated, V_{mca} increased linearly with CO_2, and the slope recorded was consistent with previously reported values.[10] In contrast, hypercapnia had no effect on V_{op}, whereas hypocapnia caused a significant increase (42.6 ± 16.4% SD) in V_{op}. These data suggest that the ophthalmic artery behaves differently from intracranial vessels in response to changing CO_2 partial pressure in awake subjects.

Although there has been a significant amount of research on retinal artery blood flow, little work has been done on ophthalmic artery blood flow which supplies the optic nerve. The blood vessels to the optic nerve are small and originate in a retrobulbar location, making them difficult to study. Retinal blood flow is more accessible to study and has been shown to increase with hypercapnia.[3–6]

Tsacopoulos and David showed that retinal artery blood flow in monkeys decreases with hypocapnia and increases with hypercapnia.[6] Their study was confirmed in humans by Harris *et al.* who demonstrated

decreased retinal artery blood flow velocity with hypocapnia[3] and increased retinal blood flow velocity with hypercapnia.[3–5] They also found that the blood flow velocity in the short posterior ciliary arteries, a branch of the ophthalmic artery, increased with hypercapnia.[5] The results of these studies indicate that the retinal artery and the short posterior ciliary artery behave similarly to the intracranial blood vessels in response to CO_2.

The ophthalmic artery may behave differently than the intracranial vessels in response to CO_2 because of its many anatomic connections with branches of the external carotid artery, which displays a relatively fixed resistance with significantly less CO_2-reactivity.[11,12] Other extracranial vessels, such as the brachial artery, demonstrate no CO_2-reactivity.[13] The ophthalmic artery usually originates from the internal carotid artery, but occasionally originates from aberrant locations such as the middle meningeal artery.[14,15] It maintains an anastomosis to the external carotid artery via the lacrimal artery and other extracranial vessels. Therefore, the central retinal artery and short posterior ciliary arteries, which supply only structures originating from neuroectoderm, may respond to CO_2 like the intracranial vessels. On the other hand, the ophthalmic artery has anastomoses with the external carotid artery, which has little CO_2-reactivity.[12] Thus, a plausible explanation for the present findings is that hypocapnia causes increased V_{op} due to a diversion of blood flow ("inverse steal") away from the vasoconstricted intracranial vessels and toward the ophthalmic artery.

Although the effects of hypocapnia have not been previously studied, consistent with our present findings, other studies have demonstrated a lack of change in V_{op} with mild to moderate hypercapnia in the ophthalmic artery.[4,5,7] If "inverse steal" occurs with hypocapnia resulting in increased flow in the ophthalmic artery, it is not clear why hypercapnia does not result in decreased flow in the ophthalmic artery. It is possible that the collateral blood supply from the external carotid is sufficient to prevent a decrease in flow. Adequacy of this collateral circulation is supported by the frequent observation of "retrograde" flow in the ophthalmic artery to maintain normal MCA flow in the presence of ipsilateral internal carotid occlusion.[16]

Since vasoconstriction of retinal and optic nerve head capillary blood vessels with hyperoxemia has been demonstrated previously,[17] it is possible that the admixture of 40% oxygen (hyperoxemia) with the inhaled CO_2 in this study caused some vasoconstriction of the ophthalmic artery and counteracted the vasodilatory effects of CO_2. However, Roff and colleagues previously demonstrated a similar lack of change in V_{op} under normoxemic hypercapnic conditions.[5] Therefore, it is unlikely that the addition of 40% oxygen in our study which was used to simulate intraoperative conditions, significantly altered the CO_2 response.

An alternative explanation for the present findings is that the ophthalmic artery diameter changes in response to changing CO_2 partial pressure, which would invalidate the use of TCD to determine blood flow through this vessel. TCD flow studies are based upon the assumption that the caliber of the vessel being insonated is relatively constant, so that changes in V reflect corresponding changes in blood flow. Agreement between studies utilizing direct blood flow measurements *vs* blood flow velocity measurements of the effects of CO_2 on the retinal artery suggests that velocity measurements accurately reflect changes in blood flow.[3–6]

However, if the ophthalmic artery dilates in response to hypercapnia, then an unchanged V_{op} might actually represent an increase in blood flow. Conversely, if the ophthalmic artery is constricting in response to hypocapnia, then an increase in V_{op} may represent no change, or even a decrease, in blood flow. CO_2 has been shown to have little influence on the MCA diameter, but its effect on the ophthalmic artery has never been studied.[18,19]

It is not feasible to measure the diameter of the ophthalmic artery with current technology. Using the brachial artery as a representative peripheral artery, and as a surrogate for the ophthalmic artery, we examined the influence of CO_2 on its diameter and flow velocity using colour Doppler imaging. Preliminary data on five healthy volunteer subjects demonstrated no significant change in diameter or blood flow velocity with either hypocapnia ($etCO_2$ 25 mmHg, diameter 3.6 mm ± 0.04 SD, velocity 74.3 cm·sec^{-1} ± 21 SD) or hypercapnia ($etCO_2$ 53 mmHg, diameter 3.8 mm ± 0.05 SD, velocity 72 cm·sec^{-1} ± 22 SD) compared to baseline ($etCO_2$ 46 mmHg, diameter 4.0 mm ± 0.06 SD, 74.6 cm·sec^{-1} ± 19 SD, $P > 0.05$ for both diameter and velocity). Therefore, if the ophthalmic artery behaves in a similar fashion to the extracranial vessels because of its anastomoses with the external carotid artery, then the diameter should be unaffected by CO_2, and TCD flow velocities should correlate with blood flow.

We have demonstrated in this study that hypocapnia increases flow velocity in the ophthalmic artery, whereas hypercapnia has no effect. Further research will need to be done to determine how blood flow in the short posterior ciliary arteries, which also supply the optic nerve, is affected by hypocapnia.

Determination of the optimal conditions for maximizing perfusion to the eye and the optic nerve may help us to understand the pathophysiology of ischemic conditions of the optic nerve in the future. The present study suggests that mild hypocapnia may increase blood flow to the ophthalmic artery, but it is unclear whether or not this would result in increased blood flow to the optic nerve.

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