The Influence of Inspired Oxygen Fraction and End-Tidal Carbon Dioxide on Post-Cross-Clamp Cerebral Oxygenation During Carotid Endarterectomy Under General Anesthesia

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BACKGROUND: Ten to fifteen percent of awake patients develop neurological deficits secondary to cerebral hypoperfusion after carotid artery cross-clamping. The reversal of such deficits by increasing the inspired oxygen fraction (FiO₂) has been demonstrated, and regional cerebral oxygenation (rSO₂) has been shown to improve during carotid cross-clamping in awake patients by increasing FiO₂. Paradoxical improvements in cerebral blood flow during carotid endarterectomy (CEA) at the time of cross-clamping and normalization of post-cross-clamp electroencephalographic abnormalities have been induced by hypocapnia. We performed this study to determine the influence of FiO₂ and end-tidal carbon dioxide (PetCO₂) on rSO₂ in patients undergoing CEA with general anesthesia during carotid cross-clamping.

METHODS: Twenty patients were recruited. Ten underwent elective shunting. Patients received standardized general anesthesia. rSO₂ was measured using the INVOS 5100B monitor (Somanetics Corporation, Troy, MI). After carotid cross-clamping, FiO₂ and minute ventilation were sequentially adjusted: 1) FiO₂ 30%, PetCO₂ 30–35 mm Hg; 2) FiO₂ 100%, PetCO₂ 30–35 mm Hg; and 3) FiO₂ 100%, PetCO₂ 40–45 mm Hg. At each point, rSO₂ was recorded from both operative and nonoperative sides, and arterial blood gas analysis was performed.

RESULTS: Results from shunted and unshunted patients were analyzed separately. Increasing FiO₂: Administration of 100% oxygen while maintaining PetCO₂ in the range 30–35 mm Hg in unshunted patients resulted in an 8% increase (P = 0.008) in rSO₂ on the operative side and a 6% increase (P = 0.011) on the nonoperative side compared with an FiO₂ of 30%. In shunted patients, administration of 100% oxygen while maintaining the PetCO₂ in the range 30–35 mm Hg resulted in a 4% increase in rSO₂ on both the operative side (P = 0.012) and the nonoperative side (P = 0.011) compared with an FiO₂ of 30%. Increasing PetCO₂: In unshunted patients, there was a 2% increase (P = 0.008) increase in rSO₂ on the operative side and a 5% increase (P = 0.024) on the nonoperative side at PetCO₂ 40–45 mm Hg compared with PetCO₂ 30–35 mm Hg maintaining FiO₂ at 100%. In shunted patients, there was a 3% increase (P = 0.018) in rSO₂ on the operative side and a 4% increase (P = 0.007) on the nonoperative side at PetCO₂ 40–45 mm Hg compared with PetCO₂ 30–35 mm Hg maintaining FiO₂ at 100%.

CONCLUSION: rSO₂ is reliably improved during carotid cross-clamping by increasing FiO₂ in patients undergoing CEA with general anesthesia. Additional improvement in rSO₂ may be gained by increasing PetCO₂.


The perioperative risk of stroke for patients undergoing carotid endarterectomy (CEA) ranges from 1.1% to 6%.1 The recently published GALA trial did not demonstrate a definite difference in outcome when regional anesthesia was compared with general anesthesia for CEA2 nor has the use of any monitoring device been consistently shown to reduce stroke.1 Perioperative stroke is multifactorial including emboli, hemorrhage, and hypoperfusion. Ten to fifteen percent of awake patients develop neurological deficits secondary to cerebral hypoperfusion after carotid cross-clamping.3 Although normally treated by shunt...

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2 The INVOS 5100B cerebral oxygenation monitor and cerebral oxygenation optics were provided at no cost by the manufacturer (Somanetics Corporation, Troy, MI).
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placment, the reversal of such deficits has been described by increasing the inspired oxygen fraction (FiO₂). It has also been demonstrated that regional cerebral oxygenation (rSO₂) can be reliably improved during carotid cross-clamping in awake patients by the administration of 100% oxygen (O₂) compared with 28% O₂.

In healthy subjects, both middle cerebral artery flow velocity and rSO₂ increase with increasing partial pressure of carbon dioxide in arterial blood (Paco₂). Middle cerebral flow velocity increases with Paco₂ in patients with carotid stenosis, without a carotid cross-clamp in situ. During carotid cross-clamping, many clinicians avoid hypocapnia because increasing cerebral vascular resistance in collateral vessels as well as the leftward shift in the O₂ dissociation curve may be detrimental. Studies from the 1970s, however, demonstrated paradoxical improvements in cerebral blood flow on the ipsilateral side at the time of cross-clamping, with hypocapnia during CEA, presumably by provoking vasosconstriction in normally perfused brain, thereby creating conditions for preferential flow to ischemic brain. Normalization of post-cross-clamp electroencephalographic abnormalities has been achieved by applying this theory. Hypocapnia also restores cerebral autoregulation during isoflurane anesthesia.

The use of cerebral near-infrared spectroscopy (NIRS) allows for the continuous noninvasive monitoring of rSO₂. It measures the relative concentrations of oxyhemoglobin and deoxyhemoglobin within the field of view. Under most circumstances, the contribution from the cerebral venous saturation predominates, and therefore, NIRS provides an estimate of the balance between cerebral O₂ supply and demand. It has been validated as a measurement tool for monitoring rSO₂ in patients undergoing CEA.

Our review of the literature has revealed a paucity of published data on changes in cerebral oxygenation seen with increases in the FiO₂ or changes in end-tidal carbon dioxide (PETCO₂) in patients undergoing CEA with general anesthesia.

We sought to determine whether increases in the FiO₂ or PETCO₂ correlate to a significant change in rSO₂ in patients undergoing CEA under general anesthesia with and without shunts during the period of the carotid cross-clamp.

METHODS

This was a prospective, controlled study, approved by our ethics committee, to determine whether increasing the FiO₂ or changing the PETCO₂ improved cerebral O₂ saturation during carotid cross-clamping. Twenty patients were recruited. Ten patients were to undergo elective shunting, and 10 were planned to undergo surgery without shunting. Written informed consent was obtained from all patients, on the day of surgery, who were scheduled for elective CEA under general anesthesia. Patients were excluded if they refused to give consent, had respiratory failure, or did not speak English.

Patients were premedicated with midazolam (0.5–2 mg). After administration of O₂, anesthesia was induced using fentanyl (25–100 µg) and propofol (0.5–2 mg/kg). Vecuronium or cisatracurium were used for initiation and maintenance of muscle relaxation. The patients’ tracheas were intubated, and their lungs were ventilated. Anesthesia was maintained with isoflurane, O₂, nitrous oxide (N₂O) or air, and remifentanil via infusion (0.5–1.5 µg/kg·min⁻¹). Phenylephrine (200 µg/ml) was titrated by infusion to maintain a stable arterial blood pressure that was increased no more than 25% above normal during cross-clamping. Routine perioperative monitoring, including invasive arterial blood pressure, was used for all patients. rSO₂ was measured using the INVOS 5100B monitor (Somanetics Corporation, Troy, MI). Optodes were placed by a single researcher on both sides of the patient’s forehead immediately above the eyebrow before induction of anesthesia.

After carotid cross-clamping, FiO₂ and minute ventilation were sequentially adjusted to achieve: 1) FiO₂ 30%, PETCO₂ 30–35 mm Hg; 2) FiO₂ 100%, PETCO₂ 30–35 mm Hg; and 3) FiO₂ 100%, PETCO₂ 40–45 mm Hg. Minute ventilation was adjusted by changing the respiratory rate and maintaining tidal volume. After at least 5 min at each set point, once rSO₂ had stabilized, rSO₂ was recorded from both the operative and nonoperative sides, and arterial blood gas analysis was performed. It has been shown that rSO₂ values are stable after an intervention after 5 min has elapsed. These data were recorded as a snapshot at the time of blood gas analysis. Data from shunted patients were recorded after shunts were in situ and open. Demographic, intraoperative, and outcome data were retrieved from the patient’s electronic anesthetic and medical records.

There are scant published data to allow for a robust power analysis in this patient group undergoing general anesthesia. This is a pilot study. Each patient acted as their own control. A paired samples t-test was used to evaluate the change in rSO₂ resultant upon each intervention. P values <0.05 were considered statistically significant.

RESULTS

Data from shunted and unshunted patients were analyzed separately. Complete analysis was conducted for the results of all shunted patients and 9 patients in the unshunted group: 1 patient developed hypotension, which proved difficult to correct. The anesthesia provider for this particular patient elected to maintain the patient on 100% O₂ for the entire duration of the cross-clamp, and this patient was therefore excluded from the first intervention. Data from this patient after an increase in PETCO₂ while ventilated with 100% O₂ were, however, included. All patients for whom an elective shunt was
Table 1. Demographic Information and Baseline Regional Cerebral Oxygenation (rSO₂)

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Sex</th>
<th>Age</th>
<th>ASA physical status</th>
<th>Shunt</th>
<th>Stenosis (%) (operative side)</th>
<th>Stenosis (%) (nonoperative side)</th>
<th>Baseline rSO₂ (operative side)</th>
<th>Baseline rSO₂ (nonoperative side)</th>
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<td>Yes</td>
<td>83</td>
<td>50-69</td>
<td>58</td>
<td>44</td>
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</table>

TIA = transient ischemic attack.

Table 2. Regional Cerebral Oxygenation (rSO₂) Values (Mean ± SD) at the Set Ventilatory Points of the Study

<table>
<thead>
<tr>
<th>Shunt</th>
<th>Side</th>
<th>FIO₂ 0.3, PETCO₂ 30-35</th>
<th>FIO₂ 1.0, PETCO₂ 30-35</th>
<th>FIO₂ 1.0, PETCO₂ 40-45</th>
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</thead>
<tbody>
<tr>
<td>No</td>
<td>Operative</td>
<td>47 ± 15</td>
<td>55 ± 16 (P = 0.008)</td>
<td>61 ± 18 (P = 0.008)</td>
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<tr>
<td></td>
<td>Nonoperative</td>
<td>62 ± 13</td>
<td>68 ± 13 (P = 0.011)</td>
<td>73 ± 13 (P = 0.024)</td>
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<tr>
<td>Yes</td>
<td>Operative</td>
<td>57 ± 13</td>
<td>61 ± 13 (P = 0.008)</td>
<td>64 ± 11 (P = 0.016)</td>
</tr>
<tr>
<td></td>
<td>Nonoperative</td>
<td>57 ± 11</td>
<td>61 ± 11 (P = 0.011)</td>
<td>65 ± 11 (P = 0.007)</td>
</tr>
</tbody>
</table>

FIO₂ = fraction of inspired oxygen; PETCO₂ = end-tidal carbon dioxide.

No patients were shunted, and no patients for whom shunting was planned were shunted. All patients received phenylephrine. N₂O was used in 2 unsutured patients and 1 shunted patient.

Demographic information and baseline rSO₂ from operative and nonoperative sides are presented in Table 1. The mean percentage stenosis in the nonoperative side was significantly higher in the shunted patient group: 56.4 ± 26.8 compared with 26.7 ± 28.9 (P = 0.026). The baseline rSO₂ (measured with patients awake and breathing room air) varied between 36%-71% on the operative side and 38%-71% on the nonoperative side. Table 2 demonstrates the rSO₂ during the trial interventions on both the operative and nonoperative sides. Figures 1 and 2 present these data in a graphical form and also display the temporal relationship of the trial measurement points.

Increasing FIO₂

Administration of 100% O₂ while maintaining PETCO₂ in the range 30-35 mm Hg in cross-clamped, unsutured patients resulted in an 8% increase (P = 0.008) in rSO₂ on the operative side (mean 47%, SD 15% to mean 55%, SD 16%) and a 6% increase in rSO₂ (P = 0.011) on the nonoperative side compared with an FIO₂ of 30%. In cross-clamped, shunted patients, administration of 100% O₂ while maintaining the PETCO₂ in the range 30-35 mm Hg resulted in a 4% increase in rSO₂ on both the operative side (P = 0.008) (mean 57%, SD 13% to mean 61%, SD 13%) and the nonoperative side (P = 0.011) compared with an FIO₂ of 30%.

Increasing PETCO₂

In cross-clamped, unsutured patients, there was a 6% increase (P = 0.008) in rSO₂ on the operative side (mean 55%, SD 16% to mean 61%, SD 18%) and a 5% increase (P = 0.024) on the nonoperative side at PETCO₂ 40-45 mm Hg compared with PETCO₂ 30-35 mm Hg maintaining FIO₂ at 100%. In cross-clamped, shunted patients, there was a 3% increase (P = 0.018) in rSO₂ on the operative side (mean 61%, SD 13% to mean 64%, SD 11%) and a 4% increase (P = 0.007) on the nonoperative side at PETCO₂ 40-45 mm Hg compared with PETCO₂ 30-35 mm Hg maintaining FIO₂ at 100%.

Outliers

After an increase in FIO₂, all patients responded consistently and demonstrated a bilateral increase in...
Figure 1. The percentage change of rSO₂ from baseline on the operative side.

Figure 2. The percentage change of rSO₂ from baseline on the nonoperative side.

rSO₂. Two patients did not respond consistently after the increase in PETCO₂. In 1 patient without shunt placement, a small bilateral decrease in rSO₂ was observed (operative 46%–44% and nonoperative 76%–72%) while ventilated in the PETCO₂ 40–45 mm Hg range. This patient failed to display an increase in Paco₂ and the Paco₂ decreased from 354 to 272 mm Hg, which explained the decrease in rSO₂. One shunted patient had a decrease in rSO₂ (74%–72%) on the operative side and an increase on the nonoperative side (73%–76%) after an increase in PETCO₂. This was the only patient in the study who experienced a decrease on the operative side and an increase on the nonoperative side during any intervention. This patient was asymptomatic and had an 81% stenosis on the operative side and a 59% stenosis on the...
nonoperative side. There were no easily identifiable unique features to indicate why this patient responded differently. All data from outliers were included for analysis.

There were no significant changes in heart rate, arterial blood pressure, end-tidal isoflurane, hematocrit, or patient position at the measurement points. All patients recovered well without complication.

**DISCUSSION**

The results of this study demonstrate that rSO₂ increases bilaterally in patients undergoing CEA with general anesthesia, during carotid cross-clamping, by increasing FiO₂ and PerCO₂ in both shunted and unshunted patients. These changes were highly statistically significant. The improvements seen with increasing FiO₂ are similar to those found in awake, unshunted patients.

Unshunted patients seemed to display a greater decrease at cross-clamp and greater increase at each study intervention point in rSO₂ on the operative side than shunted patients. However, statistical significance was not obtained. Because the post–cross-clamp measurements were taken after shunt insertion, it is not surprising that an ipsilateral decrease in rSO₂ would be of greater magnitude in unshunted patients. On the nonoperative side, the values of rSO₂ were higher at each measurement point in unshunted patients. These differences did not reach statistical significance. The greater degree of contralateral stenosis encountered in shunted patients helps to explain this observation.

Carotid artery stenosis causes complex changes in cerebral blood flow and oxygenation with considerable interindividual variation. The circle of Willis is not always complete, and the presence of an anterior communicating artery does not always provide for sufficient blood flow to prevent severe ischemia of the ipsilateral cerebral hemisphere. In some individuals, the external carotid artery may provide cerebral blood flow if the circle of Willis is incomplete.

Changes in rSO₂ detected by both the NlRO series of instruments and the INVOS series of devices are predominantly related to internal carotid artery flow rather than external carotid artery flow. The INVOS system, used in this study, uses "depth resolution." Detectors are placed at different distances from the light source, allowing for superficial signal subtraction from the deep signal, thereby reducing interference from surface tissue. The NlRO series of instruments uses spatially resolved spectroscopy and determines tissue oxygen index—the ratio of oxygenated to total tissue hemoglobin.

Cerebral oximetry has a low positive predictive value in detecting cerebral ischemia and predicting reliably which patients would benefit from shunt insertion. Near-infrared light penetrates the cortex by no more than 3 mm, and therefore, samples change in light absorbance only in the gray matter. There is inherent intrapatient and interpatient variability in rSO₂ as measured by NlRO. The patient population in this study displayed a baseline (awake and breathing room air) range of 36%–71% on the operative side.

It seems that changes from baseline are of greater significance. A decrease of 10 points below baseline or a reduction below an absolute value of 50% has been consistently associated with evidence of cerebral ischemia. Patients who experience deterioration in somatosensory evoked potentials (SEPs) after carotid cross-clamping display significantly lower absolute rSO₂ values and a significantly greater reduction in rSO₂ compared with patients with unaffected SEPs. However, cortical SEPs can be lost with no or minimal change in rSO₂. There is the possibility that subtle neurological deterioration may be related to changes in cerebral oximetry during CEA. After carotid cross-clamping, rSO₂ decreases by 7%–17% and increases toward normal after shunt insertion. Shunting, however, is not without risk.

Values for rSO₂ do not vary with height, weight, head size, or sex, whereas the negative variation in baseline levels seen with age may well reflect increasing pathologic change. Changes in cerebral blood volume and hence patient position, sensor location, hematocrit, and systemic blood pressure can affect rSO₂ values. All were constant throughout the study period. Additionally, cerebral metabolic rate and arterio/venous ratio also affect rSO₂ values. These were not measured during the study and may have acted as confounding factors.

Table 3: Hemodynamic, Blood Gas, and Anesthetic Data

<table>
<thead>
<tr>
<th>Patients without shunt</th>
<th>HR</th>
<th>SBP</th>
<th>DBP</th>
<th>Pao₂</th>
<th>Paco₂</th>
<th>EtSO</th>
<th>Hct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postclamp FiO₂ 0.5, PerCO₂ 30–35</td>
<td>64 ± 7</td>
<td>145 ± 20</td>
<td>69 ± 12</td>
<td>113 ± 41</td>
<td>39 ± 4</td>
<td>0.7 ± 0.1</td>
<td>34 ± 5</td>
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<tr>
<td>Postclamp FiO₂ 1.0, PerCO₂ 30–35</td>
<td>63 ± 8</td>
<td>149 ± 22</td>
<td>69 ± 10</td>
<td>377 ± 95 (P &lt; 0.001)</td>
<td>37 ± 5</td>
<td>0.8 ± 0.1</td>
<td>35 ± 5</td>
</tr>
<tr>
<td>Postclamp FiO₂ 1.0, PerCO₂ 40–45</td>
<td>61 ± 7</td>
<td>130 ± 23</td>
<td>63 ± 9</td>
<td>395 ± 79</td>
<td>44 ± 3 (P &lt; 0.001)</td>
<td>0.9 ± 0.4</td>
<td>34 ± 5</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. When a statistically significant change exists between that and the preceding study point the level of significance is included.

Pao₂ = PaO₂, Paco₂ = PaCO₂, HR = Heart rate measured in bpm; SBP = Systolic blood pressure measured in mm Hg; EtSO = EtSO₂; Hct = hematocrit %.
use of $\text{N}_2\text{O}$ for CEA is controversial. $\text{N}_2\text{O}$ causes an increase in plasma homocysteine and has been associated with an increased incidence of cardiac ischemia. $\text{N}_2\text{O}$ was used in 3 patients during this study. It may have acted as a confounder in those patients who received it and would be better avoided in future investigations.

The increase in r$\text{SO}_2$ seen with $\text{PETCO}_2$ 40–45 mm Hg as compared with $\text{PETCO}_2$ 30–35 mm Hg may seem surprising. We must be cautious with interpretation. We investigated only 2 $\text{PETCO}_2$ ranges and did not seek to fully investigate the relationship between cerebral oxygenation and $\text{PETCO}_2$ in this patient population. Additionally, it may have been more appropriate to target $\text{Paco}_2$ rather than $\text{PETCO}_2$. More precise interpretation of results may have been possible. However, the $\text{Paco}_2$ did increase when $\text{PETCO}_2$ increased, allowing interpretation of the results to be made. It is possible that $\text{Paco}_2$ affects the measured r$\text{SO}_2$ without changing cerebral oxygenation measured using other methodologies. For example, $\text{Paco}_2$ can directly affect cerebral arterio-venous ratio and, hence, act as a confounder. The sample size was small, and r$\text{SO}_2$ reflects oxygenation only in the superficial hemisphere. There may be areas of undetected ischemic brain that may benefit from relative hypocapnia to improve local blood flow and oxygenation. There are probably critical thresholds and optimal $\text{CO}_2$ for cerebral oxygenation on a regional level that are patient specific.

Our results achieved statistical significance, but the clinical significance is not clear. Published data on patients undergoing CEA under regional anesthesia and our work in patients undergoing general anesthesia demonstrate convincingly that r$\text{SO}_2$ is improved during cross-clamping by increasing $\text{FiO}_2$. Furthermore, case reports suggest that temporary neurological deficits occurring at cross-clamping can be reversed by increasing $\text{FiO}_2$ in awake patients. It would seem that a strategy of increasing the $\text{FiO}_2$ to 100% during carotid cross-clamping is justified and can be recommended. The risk of providing patients with 100% inspired $\text{O}_2$ for the brief period of carotid cross-clamping is likely to be low.

r$\text{SO}_2$ improves by increasing $\text{FiO}_2$ and improves further by allowing a high-normal $\text{PETCO}_2$. In unshunted patients, a total improvement of 14% was gained on the operative side. Whether this level of improvement would prevent poor neurological outcome or negate the need for shunt insertion is not known. The additional increase in r$\text{SO}_2$ at $\text{PETCO}_2$ 40–45 mm Hg might not occur in all patients, and one cannot infer from the results of this study a best management strategy or recommend a target $\text{Paco}_2$ that would optimize r$\text{SO}_2$ during the period of the cross-clamp. Patients probably react differently depending on the degree of carotid and cerebral artery disease. It would be particularly interesting to examine the effects of increasing $\text{Paco}_2$ using different measures of cerebral oxygenation in a larger group of patients. Further work is warranted.

In conclusion, bilateral cerebral oxygenation is consistently increased in both shunted and unshunted patients by ventilating their lungs with $\text{CO}_2$ for the duration of the carotid cross-clamp. It is possible to gain additional improvements in r$\text{SO}_2$ by manipulating $\text{Paco}_2$.

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