Cerebrovascular response to carbon dioxide during sodium nitroprusside- and isoflurane-induced hypotension

B. F. Matta, A. M. Lam, T. S. Mayberg, C. C. Eng and S. Strebel

Summary

We have examined the cerebrovascular response to carbon dioxide during normotension, sodium nitroprusside (SNP)-induced hypotension and high dose isoflurane-induced hypotension in 10 patients who received a standardized general anaesthetic. Carbon dioxide reactivity was determined by varying PaCO₂ between 3.0 and 8.0 kPa and recording simultaneously blood flow velocity from the middle cerebral artery (vmca). The paired vmca-PaCO₂ data were analysed using linear regression to determine carbon dioxide reactivity. During hypotension, both high-dose isoflurane and SNP reduced significantly mean absolute (from 17.4 (SEM 2.3) to 13.0 (1.7) and 8.8 (1.3) cm s⁻¹ kPa⁻¹, respectively; P < 0.05) and relative (from 32.5 (3.8) to 23.6 (2.0) and 15.5 (1.3) % kPa⁻¹, respectively; P < 0.05) cerebrovascular reactivity to carbon dioxide. This reduction was greater during SNP-induced hypotension (P < 0.05). We conclude that cerebrovascular reactivity to carbon dioxide was attenuated during isoflurane and SNP-induced hypotension, and that it was better preserved during isoflurane-induced hypotension. (Br. J. Anaesth. 1995; 74: 296-300)

Key words

Hyperventilation and induced hypotension are useful techniques used during anaesthesia for neurosurgical procedures. Hyperventilation reduces cerebral blood flow (CBF) and volume while induced hypotension decreases blood loss, the risk of aneurysm rupture, or both. The interaction between these two techniques, however, is far from clear. The cerebrovascular response to both changes in arterial pressure and carbon dioxide is dependent on the ability of the vasculature to constrict or dilate, which in turn is dependent on the presence of vascular tone. When the cerebral vessels are maximally dilated, the ability to constrict or dilate may be lost. Thus it is well known that during hypercapnia, autoregulatory capacity is impaired because of vasodilatation and loss of vascular tone [1]. Conversely, as most hypotensive agents are cerebral vasodilators, the carbon dioxide reactivity of the cerebral vasculature may be abolished during induced hypotension. Experimental studies in animals indicated that this interaction may be agent-dependent [2-4]. The purpose of this study was to clarify the influence of isoflurane- and SNP-induced hypotension on cerebral vasoreactivity to carbon dioxide.

Patients and methods

The study was approved by the University of Washington Human Subjects Review Committee and informed consent was obtained from each patient. We studied 10 patients, mean age 36 (range 23-50) yr, mean weight 81 (sd 10) kg, ASA status I or II, undergoing open reduction and internal fixation of a fractured pelvis. Patients who had cardiovascular, respiratory or neurological disease, and those receiving psychotropic drugs were excluded. All patients received a standardized anaesthetic comprising midazolam 1-2 mg i.v., thiopentone 3-5 mg kg⁻¹ i.v., fentanyl infusion 3 μg kg⁻¹ h⁻¹ and vecuronium 0.1 mg kg⁻¹ i.v. After tracheal intubation, the lungs were ventilated mechanically to normocapnia with an air-oxygen mixture and anaesthesia was maintained with isoflurane (0.5-1.0 % end-tidal). In addition to routine monitoring (ECG, pulse oximeter, end-tidal carbon dioxide and oesophageal temperature), a radial arterial cannula was inserted for monitoring mean arterial pressure (MAP) and repeated sampling for blood-gas tensions. Under stable anaesthetic conditions, cerebral vasoreactivity to carbon dioxide was determined by varying PaCO₂ between 3.0 and 8.0 kPa and recording simultaneously cerebral blood flow velocity by insonating the right middle cerebral artery (vmca) through the temporal window using a 2-MHz pulsed transcranial Doppler (CDS, Medasonics, Fremont, CA, USA). The probe was anchored using a head harness so that the angle of insonation remained constant throughout the study. Doppler signals were identified and measured at a depth of 45-50 mm. The shift in frequency spectra of the Doppler signals converted into peak systolic...
and time-mean flow velocity were displayed on a video monitor. To eliminate respiratory influence, 
\( \text{vmca} \) was recorded during end-expiration. The time-mean flow velocity (\( \text{vmca} \)) is considered to be the most physiological measurement of flow velocity [5]. Arterial \( P_{\text{aCO}_2} \) was varied by altering minute ventilation. A minimum of 5 min of stabilization (unchanged end-tidal carbon dioxide) was allowed at each \( P_{\text{aCO}_2} \), before measurements were made. At least five paired data were obtained in each carbon dioxide reactivity test.

All subjects were studied during the initial phase of normotension (MAP 70–90 mm Hg), during high-dose isoflurane-induced hypotension and during SNP-induced hypotension. Hypotension was defined as MAP 60 mm Hg, and the study sequence of hypotensive agent was randomized. Normotension was re-established between the two hypotensive conditions. When isoflurane was used first to induce hypotension, the end-tidal isoflurane concentration was allowed to return to the level during normotension before SNP-induced hypotension was started.

**DATA ANALYSIS**

Haemodynamic data and patient characteristics were analysed using descriptive statistics and analysis of variance as appropriate. \( \text{vmca} \) data were analysed using two approaches, absolute \( \text{vmca} \) and relative \( \text{vmca} \) values.

**Absolute \( \text{vmca} \) values**

Paired \( \text{vmca}-P_{\text{aCO}_2} \) data were fitted to both exponential and linear analysis to determine the best fit for the relationship. Because both methods yielded almost identical correlation coefficients, linear regression analysis was used for subsequent comparisons. The derived slopes were treated as a variable and comparisons were made between the three experimental conditions using analysis of variance for repeated measures. When significance was found (\( P < 0.05 \)), a post hoc multiple comparison procedure (Fisher’s protected least significant difference) was used to delineate where the differences lay. This method allowed comparison of slope (change in flow velocity per kPa change in \( P_{\text{aCO}_2} \)) between the experimental conditions. Because the \( P_{\text{aCO}_2} \) values at the time of \( \text{vmca} \) determinations varied among patients and between experimental conditions, it was difficult to make direct comparisons at any specific level of \( P_{\text{aCO}_2} \). Therefore, to allow comparative analysis of both slope and intercept between the three study conditions, we calculated also \( \text{vmca} \) at \( P_{\text{aCO}_2} \) 3.3, 5.3 and 7.3 kPa from each individual linear regression equation.

**Relative \( \text{vmca} \) values**

All individual measurements of \( \text{vmca} \) were expressed as a percentage of \( \text{vmca} \) at \( P_{\text{aCO}_2} \) 5.3 kPa, as derived from the individual regression line for the normotensive condition. All relative flow values were compared using analysis of covariance [6], with the experimental condition as the independent variable, individual \( P_{\text{aCO}_2} \) measurements as the covariant and the individual relative \( \text{vmca} \) as the dependent variable. This method allows pooling of all \( \text{vmca} \) data for each study condition to determine the slope, instead of treating the individual regression slope as an outcome variable. (The agreement between the two methods of analysis also serves as an independent means of verifying the validity of the data). When significance was found (\( P < 0.05 \)), Fisher’s protected least significant difference was used for individual comparisons.

**Results**

There was no significant change in body temperature for any patient during the course of the study. MAP, heart rate, haemoglobin concentration and \( P_{\text{aCO}_2} \) values are shown in table 1. There was no significant difference in MAP or haemoglobin concentration between the two hypotensive states. Heart rate was significantly higher during the two hypotensive states than during normotension.

<table>
<thead>
<tr>
<th></th>
<th>Normotension</th>
<th>Isoflurane hypotension</th>
<th>SNP hypotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>89 (2)</td>
<td>63 (1)*</td>
<td>63 (1)*</td>
</tr>
<tr>
<td>Heart rate (beat min(^{-1}))</td>
<td>81 (2)</td>
<td>87 (2)*</td>
<td>100 (2)*</td>
</tr>
<tr>
<td>Haemoglobin (g dl(^{-1}))</td>
<td>9.5 (0.2)</td>
<td>9.2 (0.2)</td>
<td>9.4 (0.2)</td>
</tr>
<tr>
<td>( P_{\text{aCO}_2} ) (kPa)</td>
<td>31 (2)</td>
<td>36 (2)*</td>
<td>27 (2)*</td>
</tr>
<tr>
<td>End-tidal isoflurane</td>
<td>0.7 (0.2)</td>
<td>2.3 (0.3)*</td>
<td>0.7 (0.2)</td>
</tr>
</tbody>
</table>

Linear regression analysis demonstrated a close relationship between \( \text{vmca} \) and \( P_{\text{aCO}_2} \), with correlation coefficients greater than 0.90 in all cases. Both mean absolute and relative cerebral vasoreactivity to carbon dioxide derived by linear regression analysis were within normal limits in all patients during normotension (17.4 (SEM 2.3) cm s\(^{-1}\) kPa\(^{-1}\) and 32.5 (3.8)% kPa\(^{-1}\), respectively). During hypotension, both high-dose isoflurane-induced and SNP-induced hypotension significantly reduced absolute and relative slope (table 2).

**Absolute \( \text{vmca} \) vs \( P_{\text{aCO}_2} \)**

For all paired data in terms of their respective linear regression lines (slopes) are shown in figures 1–3. Figure 4 shows relative cerebral vasoreactivity (relative \( \text{vmca} \) vs \( P_{\text{aCO}_2} \)) during the normotensive and the two induced hypotensive states. The actual data points were omitted for clarity. During normocapnia (\( P_{\text{aCO}_2} \) 5.3 kPa) \( \text{vmca} \)
Table 2  Relative and absolute slopes during normotension, isoflurane-induced hypotension and SNP-induced hypotension (mean (SEM)). *P < 0.05 compared with normotension. (n = 10 each group)

<table>
<thead>
<tr>
<th></th>
<th>Absolute slope (cm s(^{-1}) kPa(^{-1}))</th>
<th>Relative slope (% kPa(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>17.4 (2.3)</td>
<td>32.5 (3.8)</td>
</tr>
<tr>
<td>Isoflurane hypotension</td>
<td>13.0 (1.7)*</td>
<td>23.6 (2.0)*</td>
</tr>
<tr>
<td>SNP hypotension</td>
<td>8.8 (1.3)*</td>
<td>15.5 (1.3)*</td>
</tr>
</tbody>
</table>

Figure 1  Carbon dioxide reactivity (vmca vs corresponding \(P_{\text{CO}_2}\)) during normotension. Dashed lines = individual carbon dioxide reactivity; solid line = mean (SEM) carbon dioxide reactivity.

Figure 2  Carbon dioxide reactivity (vmca vs corresponding \(P_{\text{CO}_2}\)) during isoflurane-induced hypotension. Dashed lines = individual carbon dioxide reactivity; solid line = mean (SEM) carbon dioxide reactivity.

Figure 3  Carbon dioxide reactivity (vmca vs corresponding \(P_{\text{CO}_2}\)) during SNP-induced hypotension. Dashed lines = individual carbon dioxide reactivity; solid line = mean (SEM) carbon dioxide reactivity.

Figure 4  Composite plot of relative carbon dioxide reactivity (relative vmca vs \(P_{\text{CO}_2}\)) during normotension (—), isoflurane-induced hypotension (-----), and SNP-induced hypotension (———). Relative vmca was calculated by expressing all flow velocities as a percentage of individual vmca values at \(P_{\text{CO}_2}\) 5.3 kPa during normotension. (Data points were removed for clarity.)

was similar under all three study conditions. However, during hypocapnia (\(P_{\text{CO}_2}\) 3.3 kPa) vmca during SNP-induced hypotension was significantly higher than during high-dose isoflurane-induced hypotension and normotension (\(P < 0.05\)). During hypercapnia (\(P_{\text{CO}_2}\) 7.3 kPa) vmca was significantly lower during high-dose isoflurane-induced and SNP-induced hypotension than during normotension (\(P < 0.05\)) (table 3).

Discussion

In this study we have shown that, when used as hypotensive agents, both isoflurane and SNP attenuated cerebral vascular reactivity to carbon dioxide, but the reactivity was preserved better during isoflurane-induced hypotension.

There was no significant difference in the patients' body temperatures or haemoglobin concentrations

<table>
<thead>
<tr>
<th></th>
<th>vmca at 3.3 kPa (cm s(^{-1}))</th>
<th>vmca at 5.3 kPa (cm s(^{-1}))</th>
<th>vmca at 7.3 kPa (cm s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotension</td>
<td>20 (5)</td>
<td>54 (7)</td>
<td>89 (10)</td>
</tr>
<tr>
<td>Isoflurane hypotension</td>
<td>20 (5)</td>
<td>46 (7)</td>
<td>70 (10)†</td>
</tr>
<tr>
<td>SNP hypotension</td>
<td>31 (4)*</td>
<td>49 (7)</td>
<td>66 (9)†</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with normotension and isoflurane-induced hypotension; †P < 0.05 compared with normotension.
during normotension or hypotension. Haemoglobin can affect flow velocity as haemodilution decreases viscosity and increases CBF and flow velocity [7]. We chose a MAP of 60 mm Hg, as this is the normal level of hypotension used but is still within the limits of cerebral pressure autoregulation. There was no significant difference in MAP between the two hypotensive states. As expected, heart rate during the hypotensive states was higher than during normotension. $P_{A_{CO_2}}$ was significantly lower during SNP-induced hypotension than during normotension. This has been reported previously and is caused probably by increased ventilation–perfusion mismatch [8, 9]. In contrast, there was no decrease in $P_{A_{CO_2}}$ during isoflurane-induced hypotension. Although hypoxaemia and hyperoxaemia can affect CBF, it is unlikely that the small differences in $P_{A_{CO_2}}$ between the three study conditions affected CBF or CBF velocity.

The experimental design of this study allowed us to compare the influence of the two most commonly used agents for induced hypotension on carbon dioxide reactivity using each subject as his own control. With transcranial Doppler ultrasonography (TCD) it is possible to measure CBF velocity in a non-invasive and continuous manner. Because CBF velocity is not a direct measure of CBF, interpretation of our data and comparison with previously reported studies are dependent on the assertion that $\text{vmca}$ is a good estimate of the corresponding CBF and that the anaesthetic conditions imposed do not change the relationship appreciably. Although the correlation between absolute flow velocity and CBF in any given population may be poor, largely because of variation in the resting diameter of the MCA, there is good correlation between relative changes in flow velocity and CBF [10, 11]. Moreover, TCD is a particularly suitable tool for studies of carbon dioxide reactivity, as multiple paired measurements are taken and linear regression lines can be constructed more accurately than with a limited number of conventional blood flow measurements [12, 13]. The validity of TCD rests on the assumption that the MCA is a conductance and not a resistance vessel, and its diameter does not change appreciably with changes in $P_{A_{CO_2}}$ or arterial pressure [14]. Changes in cerebral vascular resistance occur primarily via dilatation of resistance arterioles and not the arteries of the circle of Willis [5]. Consequently the MCA is unlikely to be affected by vasoactive agents. If we accept the assumption that the MCA region that is insonated by TCD does not change in diameter, the change in blood flow velocity is proportional to changes in CBF. Indeed, Kirkham and colleagues have shown that carbon dioxide reactivity determined using TCD correlates well with carbon dioxide reactivity determined using direct methods of measuring CBF [13].

The normal $\text{vmca}$ varies from 35 to 90 cm s$^{-1}$ with an average of about 60 cm s$^{-1}$ during the awake and resting states [14]. This range of $\text{vmca}$ probably reflects individual differences in MCA diameter, baseline CBF and the angle of insonation. Because of this variation, we performed the analysis using two methods. The absolute $\text{vmca}-P_{A_{CO_2}}$ relationship for each patient during each study condition was analysed by linear regression and the derived slope was treated as a variable for comparison between experimental conditions. This assumes that carbon dioxide reactivity slope is a variable that follows a normal distribution pattern. This is a reasonable assumption because the variation in flow velocity and MCA diameter are probably distributed normally. To allow comparison with studies previously published, we normalized all $\text{vmca}$ values by expressing them as a percentage of $\text{vmca}$ during normotension at $P_{A_{CO_2}}$ 5.3 kPa. This allowed us to use analysis of covariance to compare the reactivity during the three conditions without using multiple regression analysis. The results of the two methods of analysis showed good concordance, verifying indirectly the validity of the data.

The differences in $\text{vmca}$ between the three study conditions during hypocapnia and hypercapnia provided indirect evidence that the diameter of the MCA was unchanged during the study. During hypocapnia, despite the vasodilation effect of SNP, $\text{vmca}$ was higher during SNP-induced hypotension than during normotension. It is highly improbable that a vasodilator such as SNP would vasoconstrict the MCA resulting in higher flow velocity at a lower MAP. The lack of significant change in MCA diameter with SNP has been documented recently [15].

We have shown that SNP-induced hypotension attenuated but did not abolish the cerebral vaso-reactivity to carbon dioxide. This is in contrast with the finding of Artru and Colley who reported no carbon dioxide reactivity during SNP-induced hypotension in dogs [2]; they induced hypotension to MAP 40 mm Hg, which may be below the level of cerebral pressure autoregulation. In this situation the reactive vessels in the cerebral circulation become maximally vasodilated to maintain perfusion and cannot dilate further with hypercapnia. At the same time, the need to maintain cerebral perfusion "over-rides" any vasoconstrictive effect of hypercapnia. CBF thus becomes pressure passive and carbon dioxide reactivity is lost [1]. We maintained MAP during the hypotensive states above the low limit of autoregulation at 60 mm Hg, and this may explain the difference in findings. On the other hand, consistent with other findings in their study, we observed that carbon dioxide reactivity was preserved better during isoflurane-induced hypotension, although it was still reduced from that during normotension.

$\text{vmca}$ at normocapnia was similar during the three study conditions. During hypocapnia, $\text{vmca}$ was significantly higher during SNP-induced hypotension than during normotension or isoflurane-induced hypotension. This was probably the result of vasodilatation of the cerebral vessels by SNP. Although isoflurane can cause cerebral vasodilatation, this effect is less than during SNP-induced hypotension and has been shown to reverse with hyperventilation [16, 17]. This is consistent with the low $\text{vmca}$-observed with isoflurane-induced hypotension during hypocapnia. In contrast, as $P_{A_{CO_2}}$ is increased, the cerebral vessels dilate. The combined vasodilator
effect of hypercapnia and hypotensive agents results in maximum dilatation of the cerebral vessels at a lower $\text{PaCO}_2$ than during normotension. CBF then becomes pressure passive at a lower level of $\text{PaCO}_2$ and decreases with the reduction in MAP. Consequently, flow velocity under hypercapnic conditions was lower during hypotension than during normotension.

These observations have important clinical implications. Should induced hypotension be required in a patient at risk of developing cerebral ischaemia and whose lungs are hyperventilated, SNP would be a more suitable agent as the risk of cerebral ischaemia is reduced. On the other hand, when cerebral vasoconstriction is required during induced hypotension, isoflurane is the more suitable agent.

Acknowledgement

We thank Medasonics (Fremont, CA, USA) for supplying the transcranial Doppler monitor.

References

16. Scheller MS, Todd MM, Drummond JC. Isoflurane, halothane, and regional cerebral blood flow at various levels of $\text{PaCO}_2$ in rabbits. *Anesthesiology* 1986; 64: 598-604.