CEREBROVASCULAR CARBON DIOXIDE REACTIVITY DURING EXPOSURE TO EQUIPOTENT ISOFLURANE AND ISOFLURANE IN NITROUS OXIDE ANAESTHESIA

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SUMMARY

We have studied the effects of hypocapnia on cerebrovascular changes in two MAC-equivalent anaesthetic regimens, using the transcranial Doppler technique as an index of cerebral blood flow (CBF) in 24 healthy ASA I patients undergoing spinal surgery. Eight of the patients were subjected to carbon dioxide reactivity challenges in the awake state. Before surgery, the other 16 patients received, in random order, either 1.15% isoflurane in oxygen or 0.5% isoflurane with 70% nitrous oxide. Carbon dioxide reactivity was calculated for each group as the increase in flow velocity per kPa change in PE'_{CO_2} (cm s^{-1} kPa^{-1}). It was significantly greater for the isoflurane group (14.09 (SD 2.44) cm s^{-1} kPa^{-1}) and significantly less for the isoflurane–nitrous oxide group (7.95 (1.32) cm s^{-1} kPa^{-1}) compared with the awake group (11.24 (0.95) cm s^{-1} kPa^{-1}). We conclude that cerebrovascular responsiveness to changes in arterial carbon dioxide concentration is influenced markedly by the anaesthetic procedure. Hyperventilation is more likely to affect CBF during isoflurane anaesthesia than during an MAC-equivalent isoflurane–nitrous oxide anaesthesia. (Br. J. Anaesth. 1993; 71: 272–276)

All volatile anaesthetics have cerebral vasodilator properties that produce a dose-dependent increase in cerebral blood flow (CBF) [1]. Administration may cause potentially dangerous increases in CBF, and hence intracranial pressure, in some neurosurgical patients. However, these changes in CBF may be attenuated effectively by controlled hyperventilation [2]. In addition to hypocapnia, many clinicians use volatile anaesthetics in combination with nitrous oxide, thereby reducing the concentration of volatile drug required.

Isoflurane is considered increasingly for neurosurgical anaesthesia because it has weaker cerebral vasodilator properties than other halogenated anaesthetic agents [3–5]. In neuroanaesthesia, nitrous oxide is used commonly in combination with isoflurane during moderate hypocapnia. Because hyper-

ventilation is an almost universal component of neurosurgical anaesthesia, with or without nitrous oxide, it is essential to understand the relationship between CBF and arterial carbon dioxide concentration during anaesthetic conditions. The present study was designed to compare carbon dioxide responsiveness during two anaesthetic regimens—either isoflurane alone or an MAC-equivalent isoflurane–nitrous oxide combination, with the awake state. The anaesthetic-induced CBF changes were assessed using a transcranial Doppler (TCD) technique.

PATIENTS AND METHODS

We studied 24 ASA I patients (mean age 36 yr (range 24–54 yr); 14 male) undergoing elective spinal surgery. No patient had signs or symptoms of neurological or cerebrovascular disease. Informed consent was obtained and the study was approved by the Committee for Ethics in Human Research of our institution. All patients had fasted for at least 8 h and were unpremedicated. Monitors were used to record ECG (Spacelabs), arterial pressure, non-invasive (Spacelabs) and percutaneous oxygen saturation (Sp_{O_2}) (Nellcor 2500). A carbon dioxide analyser and a multigas analyser (Nellcor 2500) were incorporated in the breathing system to monitor end-tidal carbon dioxide partial pressure (PE'_{CO_2}) and concentrations of nitrous oxide and isoflurane.

Cerebral blood flow velocity was measured for each subject both with and without carbon dioxide challenge; all measurements were made before surgery. Eight of the patients were subjected to carbon dioxide reactivity measurements in the awake state before induction of anaesthesia. The remaining 16 patients were allocated randomly to receive a 1-MAC anaesthetic gas concentration comprising isoflurane alone or isoflurane and nitrous oxide.

Anaesthesia was induced with a single dose of propofol 1 mg kg^{-1} and alfentanil 20 µg kg^{-1}; vecuronium 0.1 mg mg^{-1} was given for neuromuscular block. The lungs were ventilated for 4 min with isoflurane in oxygen, the trachea intubated and thereafter the lungs ventilated mechanically (Sulla

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TABLE I. *Patient characteristics (mean (SD) [range]). No significant differences*

	Awake (n = 8)	Isoflurane (n = 8)	Isoflurane–nitrous oxide (n = 8)
Age (yr)	36 [24–48]	34 [24–45]	38 [28–54]
Sex (M/F)	5/3	5/3	4/4
Weight (kg)	71.6 (10.9) [56–88]	74.6 (14.1) [52–88]	69.5 (12.8) [52–88]
Haemoglobin concn (g litre⁻¹)	142.1 (6.7)	142.0 (12.6)	141.3 (13.6)

808V) with a mixture of 30 % oxygen in air adjusted to achieve PE'_{CO_2} 5.2 kPa. Patients then received, in randomized order, either 1.15 % isoflurane or 0.50 % isoflurane and 70 % nitrous oxide to achieve a 1-MAC anaesthetic gas concentration [6]. Twenty minutes after steady-state exposure to one of the two gas mixtures, the first CBF velocity (CBFV) measurements were made. A second set of measurements was made during hyperventilation after PE'_{CO_2} had been stable at 4.2 kPa for about 10 min.

For measurements in the awake state, the eight subjects breathed through a suitable mouthpiece connected directly to a capnograph (Nellcor 2500). After baseline measurements, the patients were requested to hyperventilate to attain an approximately 20 % reduction in PE'_{CO_2}. Five minutes after a steady state was attained, TCD recordings were performed.

A 2-MHz pulsed Doppler instrumentation system (TC2-64B, tc–pc interface and its corresponding data acquisitions software, version 1.2; Eden Medical Electronics, Überlingen, Germany) was used for TCD examinations. The Doppler data were stored by a personal computer in digital form allowing post-processing possibilities to be carried out "off line" at a later time. We chose the middle cerebral artery (MCA) for examination because of its location and relatively large diameter which allows easy and reproducible accessibility for TCD measurements. The transducer (IMP2, Eden Medical Electronics) was positioned at the right temporal window using a circumferential apparatus fixed to the subject's head. The MCA Doppler signal was located at a depth of 4.5–5.5 cm. Collected Doppler data consisted of time-mean CBFV, each averaged during four to five heart beats in expiration.

A carbon dioxide response curve was generated for each patient. The mean of the two measurements at different values of PE'_{CO_2} was used to calculate CBF reactivity. Global carbon dioxide reactivity was calculated as an increase and decrease in CBFV per kPa change in PE'_{CO_2} (cm s⁻¹ kPa⁻¹).

Statistical analysis

All data are reported as mean, (SD) and [range] as appropriate. Physiological values and carbon dioxide reactivity slopes were compared between groups by one-way analysis of variance (GLM procedure of SAS, Release 6.03, SAS Inst. Inc., Cary, NC, U.S.A., 1988). If significant differences were found, the Newman–Keuls test was used for further analysis. $P < 0.05$ was considered statistically significant.

TABLE II. *Physiological values (mean (SD)) for normoventilated and hyperventilated patients. †PE'_{CO_2} maintained constant by mechanical ventilation. Normo. = Normocapnia; hypo = hypocapnia; PE_{CO_2} = end-tidal carbon dioxide partial pressure; Sp_{O_2} = percutaneous arterial oxygen saturation; MAP = mean arterial pressure; HR = heart rate*

	Awake (n = 8)	Isoflurane (n = 8)	Isoflurane–nitrous oxide (n = 8)
PE'_{CO_2} (kPa)			
Normo.	5.2 (0.1)	5.2 (—)†	5.2 (—)†
Hypo.	4.0 (0.3)	4.2 (—)†	4.2 (—)†
Sp_{O_2} (%)			
Normo.	98.9 (1.0)	99.7 (0.5)	99.8 (0.5)
Hypo.	99.8 (0.5)	99.9 (0.4)	99.9 (0.4)
MAP (mm Hg)			
Normo.	80 (6)	78 (10)	81 (8)
Hypo.	82 (5)	78 (10)	79 (7)
HR (beat min⁻¹)			
Normo.	73 (11)	77 (10)	75 (11)
Hypo.	78 (9)	78 (10)	73 (12)

RESULTS

Patient and clinical data were similar for all groups (table I). Physiological variables did not differ in the three study groups at baseline or during the study (table II). In the awake state, a CBFV decrease of 11.24 (1.00) [10.09–12.90] cm s⁻¹ kPa⁻¹ was calculated (fig. 1A). Carbon dioxide reactivities of the anaesthetized patients differed from those of the non-anaesthetized patients (fig. 1B, C). Compared with the awake group, reactivity to carbon dioxide was significantly ($P < 0.01$) greater for the isoflurane group (14.09 (2.44) [10.40–18.90] cm s⁻¹ kPa⁻¹) and significantly ($P < 0.01$) less for the isoflurane–nitrous oxide group (7.95 (1.32) [6.90–10.50] cm s⁻¹ kPa⁻¹). The difference in CBFV slopes produced by hyperventilation with the two anaesthetic regimens was highly significant ($P < 0.001$).

DISCUSSION

The purpose of this investigation was to assess hypocapnia-induced cerebrovascular effects in two MAC-equivalent anaesthetized groups of healthy patients. Both regimens, isoflurane alone or isoflurane in combination with nitrous oxide, are used commonly for neurosurgical procedures. Controlled hyperventilation, which decreases CBF, is routine during neurosurgery and non-neurological surgery in patients with reduced intracranial compliance. Although a linear relationship between arterial
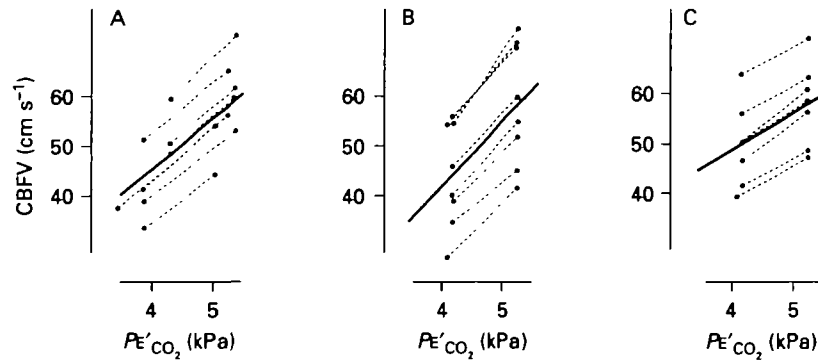
FIG. 1. Individual slopes (- - -) and their means (——) describing the relationship between end-tidal carbon dioxide partial pressure ($P_{E'CO_2}$) and cerebral blood flow velocity (CBFV) for awake patients (A) and for those anaesthetized with equipotent 1-MAC gas mixtures (isoflurane (B) and isoflurane with nitrous oxide (c)). A: mean of slope = 11.24 (0.95) [10.09–12.90] cm s^{-1} kPa^{-1} ($n = 8$); B: mean of slope = 14.09 (2.44) [10.40–18.90] cm s^{-1} kPa^{-1} ($n = 8$); c: mean of slope = 7.95 (1.32) [6.90–10.50] cm s^{-1} kPa^{-1} ($n = 8$) (mean (SD) [range]). Significant intergroup differences (ANOVA, Newman–Keuls test): isoflurane (B) *vs* awake (A), $P < 0.01$; isoflurane (B) *vs* isoflurane–nitrous oxide (c), $P < 0.001$; isoflurane–nitrous oxide (c) *vs* awake (A), $P < 0.01$.

carbon dioxide and CBF has been described [7], the influence of anaesthetic agents or combinations of anaesthetic agents on CBF sensitivity to carbon dioxide in humans is not well documented.

The effects of isoflurane on CBF and cerebral metabolism suggest that this agent may be more appropriate for use in neurosurgery than other volatile anaesthetics [5, 8]. Nitrous oxide is a common component of general anaesthesia; moreover, it has been used in neuroanaesthetic procedures for decades. Its use makes it possible to reduce the required concentration of volatile anaesthetic, and its potential cerebrovascular effects are believed to be blocked by some degree of hypocapnia. However, an increasing number of studies in animals and in humans suggest that nitrous oxide may have substantial effects on CBF [9, 10]. This is particularly true when the gas is added to a volatile anaesthetic. In several studies, using various methods and species, the interactive effect of nitrous oxide and volatile anaesthetics has been shown to be a substantial increase in CBF [11–15].

Reactivity of the cerebral vasculature to carbon dioxide is commonly used to evaluate cerebrovascular integrity. It is assumed that CBF varies almost linearly with arterial carbon dioxide concentration changes between 2.5 and 8.0 kPa [7, 16]. The present CBFV results following a carbon dioxide challenge in the awake state corroborate TCD results published elsewhere [17]. Our results are also in accord with carbon dioxide reactivity of CBF determined by a xenon-133 washout technique [18]. In the isoflurane-anaesthetized patients, TCD values demonstrated a significantly enhanced carbon dioxide reactivity compared with awake patients. However, this increase in reactivity was not found in patients who received the equi-MAC concentration of isoflurane in nitrous oxide; reactivity in the latter group was significantly less than in the awake group.

The mechanism by which volatile agents, including nitrous oxide, alter the slope of the CO_2–CBF relation is unknown. Cerebral reactivity to carbon dioxide is thought to be mediated by carbon dioxide-related changes in extracellular pH and it is not clear why volatile anaesthetics should alter this interaction. The reasons for the attenuation of the carbon dioxide response curve in the isoflurane–nitrous oxide group remain speculative. They may be related to the underlying mechanism by which nitrous oxide produces its effects: it may have a direct relaxant effect on vascular smooth muscle or may stimulate cerebral metabolism, with an associated increase in CBF. The effects of volatile anaesthetics on CBF are mediated to large extent by their effects on cerebral metabolism, and it may be postulated that perturbation of this relationship by nitrous oxide might increase CBF. It is important to note that nitrous oxide is not physiologically inert and, despite hyperventilation, may have striking effects on CBFV and CBF. Therefore it would seem prudent, upon encountering a "tight" brain during operation, to discontinue the use of nitrous oxide.

Several aspects of the methods used in the present study, particularly the validity of measuring MCA flow velocity as an index of CBF, deserve comment. This non-invasive technique of measuring CBF was first introduced in 1982 [19]. The main assumption is that the calibre of the MCA remains constant throughout the measurement. A change in vessel diameter could have a significant effect on flow velocity; however, angiographic evidence suggests that the calibres of the large basal arteries remain constant during changes in $P_{E'CO_2}$ [20]. Moreover, measurement of cerebrovascular reactivity to changes in $P_{E'CO_2}$ using TCD technology has yielded results similar to those obtained with direct measurements of CBF [21]. When the calibre of the MCA remains constant, changes in MCA flow velocity are proportional to the CBF. Nevertheless, it should be emphasized that there is considerable variation in the diameter of the MCA; this variability causes differences in blood flow velocity between individuals, thus precluding comparison of absolute flow values. Within a given individual, however, simultaneous measurements of CBF (determined with the xenon-133 technique) and MCA flow velocity have demonstrated a good correlation between proportional changes in these two variables in response to changing concentrations of carbon dioxide [17]. When the effects of anaesthesia on CBF are being

examined, the site of the measurement must be taken into consideration. The MCA carries about 80% of the flow volume received by the cerebral hemisphere [22]. Hence, changes in MCA flow velocity should be representative of general changes in brain perfusion. Comparative studies have demonstrated that individual changes in MCA CBFV reflect concomitant changes in internal carotid artery volume flow as determined by ipsilateral electromagnetic measurements [23].

Additional considerations when CBFV data are interpreted include arterial pressure and cerebral perfusion pressure, in addition to drug effects other than those related to anaesthetics. In the present study, arterial pressure was maintained at the same value during all experiments. In addition, autoregulation may be expected to be unaffected at a 1-MAC level of anaesthesia [24]. The pharmacokinetic profile of the short-acting i.v. anaesthetic propofol, used in this study, makes it unlikely that this drug exerted an appreciable effect on the cerebral vasculature. Alfentanil does not affect cerebral haemodynamics [25]. To our knowledge, there are no data on atracurium and cerebral circulation. However, as with the non-depolarizing neuromuscular blocker, tubocurarine [26], it is not likely that atracurium influences CBF. Thus it is unlikely that these factors might have contributed to our cerebrovascular findings and it seems reasonable to conclude that CBF was affected only by the anaesthetics and by Pe'_{CO_2}.

Arterial blood-gas estimation during CBF determination is a critical requirement for quantitative interpretation of the results. In this study, we used Pe'_{CO_2} as an estimate of arterial carbon dioxide tension. Recent data examining the correlation between arterial and Pe'_{CO_2} estimations and the relationship between the two methods to calculate cerebrovascular carbon dioxide reactivity demonstrated that the true slope of CBF response to changes in carbon dioxide tension can be estimated reliably from non-invasive measurement of Pe'_{CO_2} [27].

In conclusion, there are alterations in cerebrovascular responsiveness to changes in carbon dioxide concentrations that occur during anaesthetic procedures. The cerebrovascular reactivity to carbon dioxide is increased using 1 MAC isoflurane anaesthesia and attenuated using 1 MAC isoflurane in nitrous oxide anaesthesia. Thus hyperventilation is more likely to affect CBF during isoflurane than during MAC-equivalent isoflurane in nitrous oxide anaesthesia. The use of nitrous oxide, as opposed to an increased dose of a volatile anaesthetic, has no advantage with respect to minimizing anaestheticinduced increases in CBFV and CBF.

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