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Cerebrovascular Carbon Dioxide Reactivity in Sheep: Effect of Propofol or Isoflurane Anaesthesia

J. A. MYBURGH*, R. N. UPTON†, G. L. LUDBROOK‡, A. MARTINEZ§, C. GRANT**
Department of Anaesthesia and Intensive Care, University of Adelaide, Adelaide, South Australia

SUMMARY
Propofol and isoflurane are commonly used in neuroanaesthesia. Some published data suggest that the use of these agents is associated with impaired cerebral blood flow/carbon dioxide (CO_2) reactivity. Cerebrovascular CO_2 reactivity was therefore measured in three cohorts of adult merino sheep: awake (n=6), anaesthetized with steady-state propofol (15 mg/min; n=6) and anaesthetized with 2% isoflurane (n=6). Changes in cerebral blood flow were measured continuously from changes in velocities of blood in the sagittal sinus via a Doppler probe. Alterations in the partial pressure of carbon dioxide in arterial blood (P_aCO_2) over the range 18-63 mmHg were achieved by altering either the inspired CO_2 concentration or the rate of mechanical ventilation. Cerebral blood flow/CO_2 relationships were determined by linear regression analysis, with changes in cerebral blood flow expressed as a percentage of the value for a P_aCO_2 of 35 mmHg. Propofol decreased cerebral blood flow by 55% relative to pre-anaesthesia values (P=0.0001), while isoflurane did not significantly alter cerebral blood flow (88.45% of baseline, P=0.39). Significant linear relationships between cerebral blood flow and CO_2 tension were determined in all individual studies (r^2 ranged from 0.72 to 0.99). The slopes of the lines were highly variable between individuals for the awake cohort (mean 4.73, 1.42-7.12, 95% CI). The slopes for the propofol (mean 2.67, 2.06-3.28, 95% CI) and isoflurane (mean 2.82, 2.19-3.45, 95% CI) cohorts were more predictable. However, there was no significant difference between these anaesthetic agents with respect to the CO_2 reactivity of cerebral blood flow.

Key Words: CARBON DIOXIDE: cerebrovascular reactivity, cerebral blood flow, propofol, isoflurane

Under physiological conditions, cerebral blood flow and arterial carbon dioxide tensions (P_aCO_2) have a pseudo-linear relationship: hypercapnia causes cerebral vasodilation, whilst hypocapnia causes vasoconstriction. This mechanism is due to CO_2 induced changes in perivascular cerebral pH resulting in changes in cerebrovascular tone[1]. Cerebrovascular reactivity is also influenced by cerebral tissue oxygenation[2], calcium and potassium fluxes and drugs such as volatile[3,4] and intravenous anaesthetics[5,6]. Although cerebrovascular carbon dioxide reactivity is frequently used as a surrogate index, several mechanisms determine metabolic cerebral autoregulation.

Anaesthetic agents such as propofol and isoflurane have effects on cerebral blood flow, cerebral blood volume and intracranial pressure[7]. These factors may influence CO_2 reactivity, thereby affecting cerebral metabolic autoregulation (flow-metabolism coupling). For example, during propofol anaesthesia, cerebrovascular reactivity of blood flow and blood volume is maintained during hypercapnia but is markedly diminished during hypocapnia[8]. Precise knowledge of the effects of anaesthetic agents on cerebral blood flow/CO_2 reactivity is clearly of clinical importance, considering that these effects contribute to the basis of their selection in neuroanaesthesia and neuro-critical care.

The evidence for these drug specific effects comes from a number of physiological studies using a variety of subjects and methods of measurement[3,8-11]. The array of methods of measurement and study subjects has resulted in conflicting opinion about the effects

*M.B.B.Ch., D.A.(S.A.), F.A.N.Z.C.A., F.F.I.C.A.N.Z.C.A., Senior Lecturer.
†B.Sc., Ph.D., Principal Medical Scientist.
‡M.B.B.S., Ph.D., F.A.N.Z.C.A., Professor.
§Technical Officer.
**Technical Officer.

Address for reprints: Dr J. A. Myburgh, Senior Lecturer, Intensive Care Unit, St George Hospital, Gray Street, Kogarah, N.S.W. 2217.

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of these anaesthetics on CO_2 reactivity. This discrepancy is highlighted further in studies using pathophysiological models[12-14]. Few studies have directly compared the effects of anaesthesia with the awake state, using a consistent measurement of cerebral blood flow.

The aim of this study was to determine the effect of propofol and isoflurane on cerebrovascular CO_2 reactivity and to compare these with the awake state. This study was conducted in a physiologically intact ovine preparation using the same method for measurement of cerebral blood flow in all cohorts.

METHOD

The Animal Ethics Committee of the University of Adelaide approved the study. Animals were handled in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Studies were performed in three cohorts of adult female merino sheep: awake or anaesthetized with steady state propofol or isoflurane. The animals were instrumented under thiopentone and halothane anaesthesia as described previously[15]. In brief, a 2 cm frontal craniotomy was performed anterior to the trifurcation of the frontal and parietal sutures. A bony plate was removed using a trephine and the extradural portion of the sagittal sinus exposed. An ultrasonic, range-gated Doppler transducer (Tritonics Medical Instruments, Iowa) was placed on the dorsal sagittal sinus. In the isoflurane and propofol cohorts, a strain-gauge tipped intracranial pressure monitor (Microsensor ICP Transducer, Codman, Randolph MA, U.S.A.) was placed into the subdural space through the same craniotomy. Both the Doppler transducer and intracranial pressure monitor were secured under the replaced bone flap which was fixed with plate and bone screws.

The animal was turned supine and the femoral triangle exposed. A 7 Fr catheter (Multipurpose A1 catheter, Cordis Corporation, Miami, U.S.A.) was inserted into the femoral artery for measurement of mean arterial pressure, intermittent sampling of arterial blood gases and into the femoral vein for drug and fluid delivery. Through the femoral venotomy, a thermodilution pulmonary artery catheter (Model TD1755H, Biosensors International, Singapore) was inserted and positioned into the pulmonary artery under waveform imaging. A single dose of penicillin/streptomycin was administered peri-operatively for antibiotic prophylaxis. Sheep were recovered from anaesthesia and returned to housing crates where they were allowed free access to food and water. Catheter patency was maintained using intraluminal heparin (10 IU/ml) locks.

A period of two days elapsed between surgery and measurements to allow a fibrous scar to develop around the probe and the sagittal sinus. This ensured minimal movement between the two and a constant angle between the ultrasonic beam and the direction of blood flow.

Awake studies

On the day of study, sheep were moved to a specific study laboratory. The sheep were supported in a comfortable sling and extraneous noise was minimized to reduce changes in cerebral blood flow induced by startling. After a period to allow the animal to settle, 100% oxygen at 20 l/min was administered via a sealed soft plastic mask attached to a semi-open breathing circuit. Carbon dioxide was then introduced into the circuit in increments, while oxygen flow rates were reduced to maintain total flow at 20 l/min. Following each increase in inspired carbon dioxide concentration and when cerebral blood flow had reached a new plateau, an arterial blood sample was taken for gas analysis. The inspired concentration of carbon dioxide was manipulated to keep arterial carbon dioxide tension within the nominal range of 35-60 mmHg.

Anaesthetized studies

Prior to anaesthesia, the output of the Doppler probes was recorded with the animal in an awake, calm state. They were then induced with 200 mg propofol and endotracheal intubation performed (supine position). Thereafter, the studies were performed in the sphinx position. For the isoflurane cohort, maintenance of anaesthesia was with isoflurane delivered via a vaporizer (Isotec 3, Ohmeda BOC Group, U.K.) in the anaesthetic circuit to maintain an end-tidal concentration of 2%. For the propofol cohort, propofol was delivered via a syringe driver (Model 33, Harvard Apparatus, MA, U.S.A.) to maintain a constant infusion rate of 15 mg/min.

For both cohorts, the animals were mechanically ventilated using a volume control ventilator (7000 Ventilator, Ohmeda, Madison, WI, U.S.A.) and 100% oxygen. Expired gas analysis of end-tidal CO_2, tidal volume and volatile agent (if appropriate) were measured using an end-tidal analyser (Capnomac, Datex Instrumentarium Corp, Helsinki, Finland). After 1.5 hours to allow the induction agent to clear, manipulations in CO_2 were performed. Initial measurements were made with the P_aCO_2 titrated to 35 mmHg. The allowed a direct comparison with the

pre-anaesthesia cerebral blood flow value to determine the effect of each anaesthetic agent on cerebral blood flow at normocarbia.

Subsequently, a range of P_aCO_2 levels were induced by randomly increasing or decreasing minute ventilation in a ramped manner by adjusting the tidal volume and respiratory rates on the mechanical ventilator. The minimum value of P_aCO_2 was that achieved by maximal hyperventilation of the animal; the maximum was that achieved by hypoventilating the animal to the point where spontaneous respiration occurred. Typically, six discrete levels of end-tidal carbon dioxide were possible, with each characterized by cerebral blood flow reaching a plateau within approximately five minutes. At this point, an arterial blood sample was taken for blood gas analysis.

Mean arterial and intracranial pressures were recorded throughout the studies using a standard transducer and amplifier (78342A, Hewlett Packard Company, CA, U.S.A.). Temperature was monitored via the pulmonary artery catheter and maintained at baseline levels via humidification of inspired gases using a heat and moisture exchanger. Following the studies, the sheep were recovered from anaesthesia and transferred to their holding crates where they were allowed free access to food and water.

Measurements

Changes in cerebral blood flow were inferred from changes in the outputs from the Doppler probe. This was sampled at 1 Hz using an analog to digital card (Metrabyte DAS 16-G2) and a personal computer (Microbits 486-based IBM compatible) and recorded digitally on computer disk. Mean arterial and intracranial pressures were recorded through the same computerised acquisition system. Both were recorded as percentage changes from baseline values and averaged over 30 seconds when end-tidal CO_2 values stabilized at a discrete level.

Arterial blood gases for measurement of P_aCO_2 and pH where taken from the arterial catheter at the intervals outlined above and measured using a standard blood gas analyser (ABL 625, Radiometer Medical A/S, Copenhagen, Denmark).

Data analysis and statistics

Awake studies were performed on one occasion in six different sheep (n=6). Anaesthetized studies were performed on two occasions in three different sheep (n=6). The significance level was 95% throughout. Analysis of variance was used to test for differences between individual sheep for these data.

The effect of anaesthesia on cerebral blood flow (pre-anaesthesia vs 1.5 hours post anaesthesia) was examined using a paired t-test. Relationships between changes in cerebral blood flow and P_aCO_2 were determined using linear regression analysis using a spreadsheet program (Excel, Microsoft Corporation, U.S.A.), with data normalized to the cerebral blood flow at a P_aCO_2 of 35 mmHg. Thus, the vertical axis of the regression lines represented the percentage increase in cerebral blood flow from the baseline value. Regression was performed on the individual data from each animal. Linear regression was also performed on the pooled data for the propofol and isoflurane cohorts.

Pooled data were expressed as means and 95% confidence intervals. Comparison between cohorts was determined by the calculation of mean differences and 95% confidence intervals assuming a t-distribution using the method described by Motulsky[16].

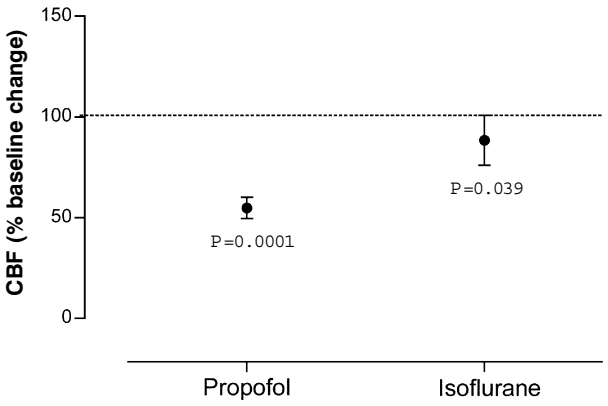
RESULTS

Propofol anaesthesia was characterized by a substantial, statistically significant decrease in cerebral blood flow (55% of baseline, $P=0.001$) and a significant increase in mean arterial pressure (132.4% baseline, $P=0.04$). Isoflurane anaesthesia did not significantly change cerebral blood flow (88.45% of baseline, $P=0.39$) or mean arterial pressure (97.6% of baseline, $P=0.76$) (Figure 1).

Blood pressure, intracranial pressure and temperature did not significantly change from baseline through the period of CO_2 manipulation in all cohorts ($P>0.05$). Significant correlations between mean arterial pressure and P_aCO_2 (awake $r^2=0.46$, $P<0.0001$; isoflurane: $r^2=0.46$, $P<0.0001$; propofol: $r^2=0.43$, $P<0.0001$); and intracranial pressure and P_aCO_2 (isoflurane: $r^2=0.56$, $P<0.0001$; propofol: $r^2= 0.51$, $P<0.0001$) were demonstrated (Figure 2a and 2b).

The range of P_aCO_2 achieved for the awake, propofol and isoflurane cohorts were 31.7-63.2, 18.1-50.6, and 20.6-52.3 mmHg, respectively. Significant linear relationships between cerebral blood flow and P_aCO_2 were found in all individuals (Figure 3a). For the anaesthetized cohorts, the analysis of variance showed no effect of sheep number on the slope of the regressions ($P=0.46$ for propofol, 0.38 for isoflurane), suggesting that intra-animal variability in the data was comparable to inter-animal variability.

In the awake cohort, regression lines demonstrated increased cerebral blood flow for CO_2 although reactivity was highly variable between animals. In



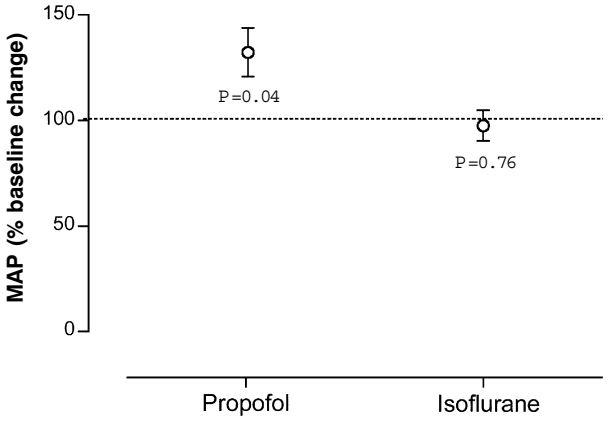


FIGURE 1: The effect of propofol (15 mg/min) and 2% isoflurane anaesthesia on cerebral blood flow (CBF: closed circles) and mean arterial pressure (MAP: open circles) expressed as % baseline change compared to the baseline awake state (dashed line at 100%). Data are expressed as mean±SEM.

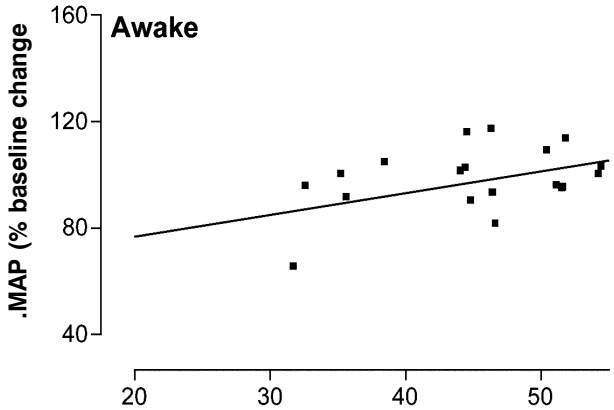
contrast, the reactivity under anaesthesia was more consistent. The pooled data and their regression lines are shown for propofol and isoflurane in Figure 3b.

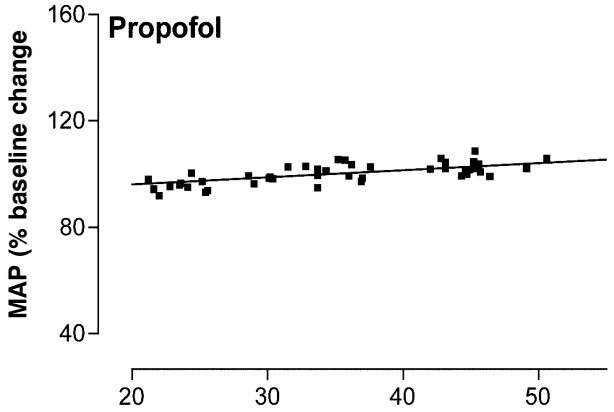
By confidence interval analysis (Table 1), there was no statistically significant difference between the slopes of the regression lines between the awake and anaesthetised cohorts (P=0.21 for awake vs propofol, 0.25 for awake vs isoflurane). There was no statistically significant difference between the slopes between propofol and isoflurane anaesthesia (P=0.68).

TABLE 1

Summary of the linear regression terms for individual cerebral blood flow/carbon dioxide reactivity curves. Data are expressed as mean and (lower to upper 95% confidence intervals)

	r^2	Slope	Intercept
Awake	0.79 (0.57 to1.00)	4.194 (1.186 to 6.49)	–44.68 (–125.7 to 36.35)
Propofol	0.90 (0.85 to 0.96)	2.78 (2.154 to 3.41)	2.689 (–19.24 to 24.62)
Isoflurane	0.92 (0.87 to 0.97)	2.69 (2.09 to 3.29)	3.452 (–15.01 to 21.92)





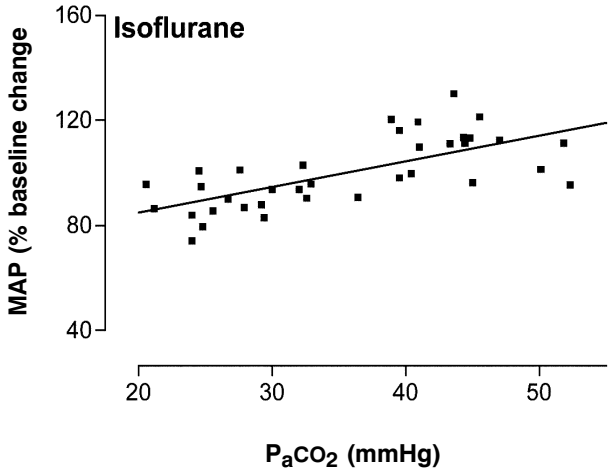


FIGURE 2a: Relationship between mean arterial pressure (MAP: expressed as % baseline change) and arterial carbon dioxide tension (P_aCO_2: mmHg) in the awake (r^2=0.46); isoflurane (r^2=0.46) and propofol (r^2=0.43).

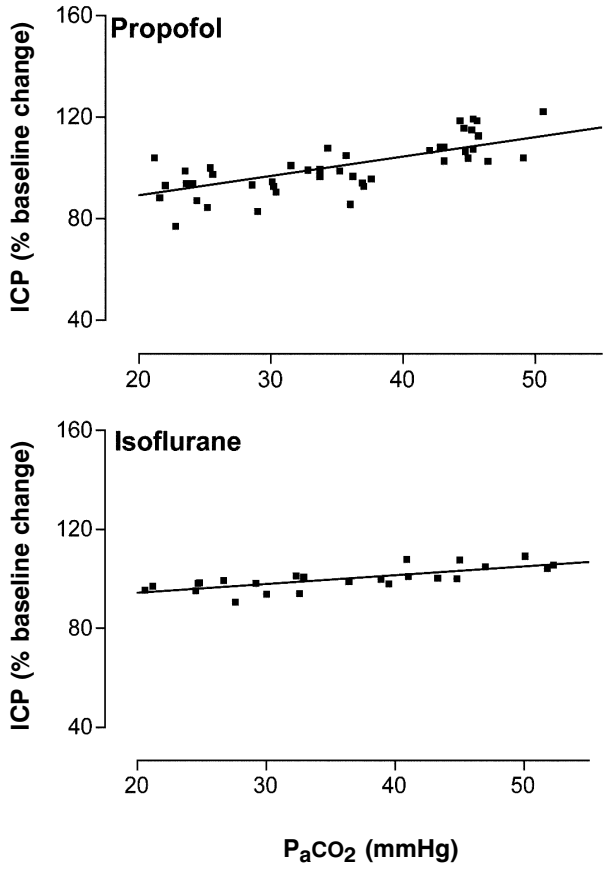


FIGURE 2b: Relationship between intracranial pressure (ICP: expressed as % baseline change) and arterial carbon dioxide tension (P_aCO_2: mmHg) in the isoflurane (r^2=0.56) and propofol (r^2=0.51) groups. There was no significant change from baseline (P>0.05) in any group.

As expected, changes in P_aCO_2 were associated with statistically significant inverse changes in pH: in the isoflurane cohort, the relationship had an r^2=0.95 (P<0.0001), propofol r^2=0.86, (P<0.0001). Statistically significant correlations were demonstrated between changes in cerebral blood flow and pH in the isoflurane (r^2=0.88, P<0.0001) and propofol (r^2=0.70, P<0.0001) cohorts, and are shown in Figure 4.

DISCUSSION

The responsiveness of the cerebral vasculature to changes in P_aCO_2 is an important mechanism for metabolic autoregulation, cerebral volume regulation and cerebral oxygen delivery. These homeostatic mechanisms are influenced under anaesthesia, which may be represented by the slope of the cerebral blood flow/CO_2 response curve.

There have been many studies examining the re-

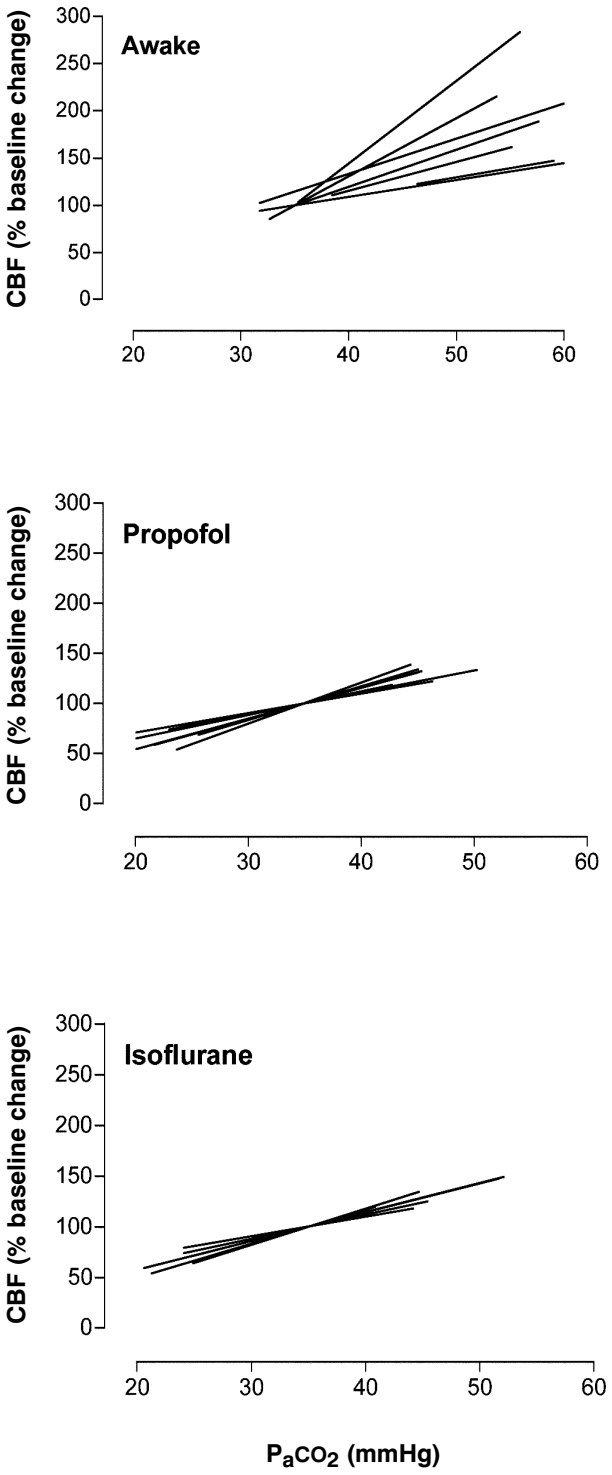


FIGURE 3a: Regression lines of the percent change in cerebral blood flow (CBF) versus arterial carbon dioxide tension (P_aCO_2: mmHg) for each individual study in the awake, propofol and isoflurane cohorts. The r^2 values ranged from 0.72 to 0.99—only the regression lines are shown for clarity. Each line is a goodness-of-fit for the data shown in Table 1. Cerebral blood flow is expressed as percentage change from flow at a P_aCO_2 of 35 mmHg.

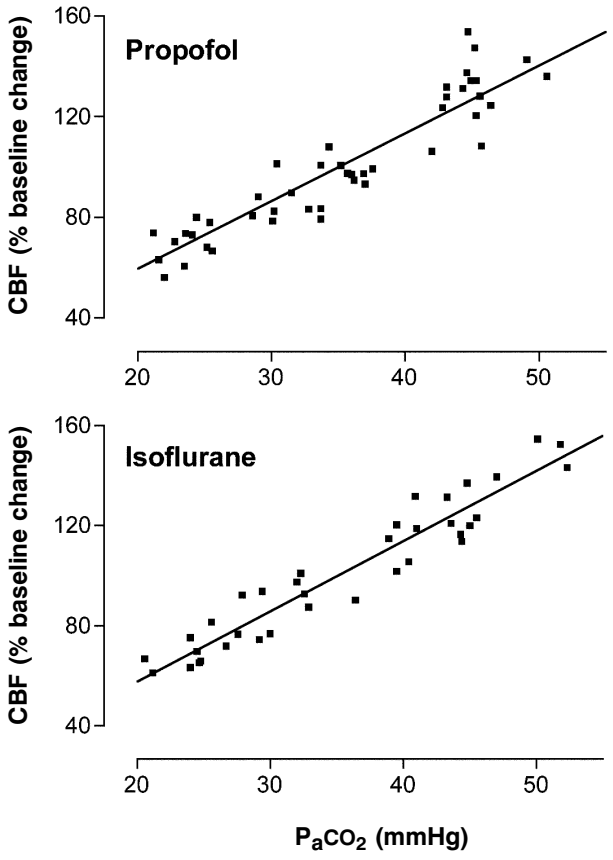


FIGURE 3b: Regression curves for pooled data on cerebral blood flow (CBF) and arterial carbon dioxide tension (P_aCO_2: mmHg) for the propofol ($r^2=0.87$, $P<0.0001$) and isoflurane ($r^2=0.91$, $P<0.0001$) cohorts. CBF is expressed as percentage change from flow at 35 mmHg.

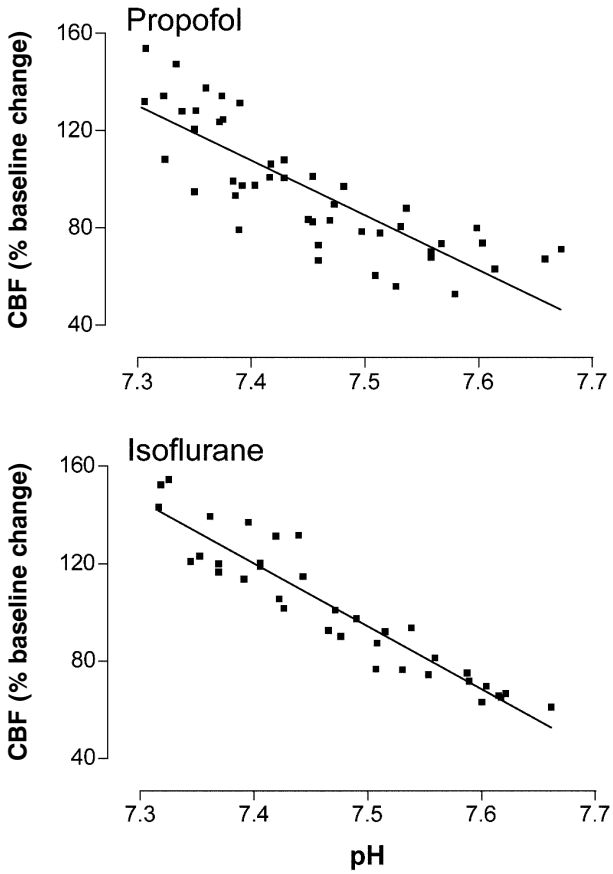


FIGURE 4: Relationship between cerebral blood flow (CBF: expressed as % baseline change) and arterial pH in the isoflurane ($r^2=0.88$, $P<0.0001$) and propofol ($r^2=0.70$, $P<0.0001$) groups.

lationship between cerebral blood flow and P_aCO_2. A variety of methods of measurement of cerebral blood flow are used such as transcranial Doppler[17,18] or microsphere[8] studies. Many of these techniques assume that cerebral blood flow is in a state of equilibrium during such measurements. Despite these disparities, the results and conclusions drawn from such experiments have been remarkably consistent, especially when one considers the variety of species tested and the different experimental conditions used. The (pseudo) linear relationship of cerebral blood flow to P_aCO_2 over a range of approximately 30 to 70 mmHg is repeated in many standard texts of physiology.

The interplay with other factors such as mean arterial pressure and the effects of anaesthetic agents is less clear. Anaesthetic agents have variable effects on cerebral blood flow. Nitrous oxide causes an absolute increase in cerebral blood flow, halothane and isoflurane cause a relative increase by uncoupling cerebral blood flow and metabolism, whilst propofol, thiopentone and benzodiazepines decrease cerebral blood flow[7,10,19,20]. However, as these agents are frequently administered simultaneously in clinical use, the effect of an individual agent on cerebral blood flow and CO_2 reactivity is difficult to quantify.

There are numerous studies analysing CO_2 reactivity under anaesthesia to determine the degree of alteration of cerebral metabolic autoregulation[10,11,17,21]. Most of these studies have been conducted using a number of anaesthetic techniques for a range of surgical procedures, using varied techniques of cerebral blood flow measurements. In studies using patients undergoing cardiopulmonary bypass, factors such as blood pressure and temperature may be potentially confounding variables[22]. Many studies used end-tidal CO_2 measurement to estimate P_aCO_2, which may be

inaccurate in ventilated or hypotensive subjects. Not surprisingly, there are conflicting data about the degree and magnitude of cerebral CO_2 responses under anaesthesia.

An important source of conflicting comparative reports relates to the method of reporting changes in cerebral blood flow in response to CO_2. Absolute changes in cerebral blood flow (usually expressed as ml/100 g/minute/mmHg) may differ from relative changes (expressed as % baseline change). This was highlighted in a study analysing carbon dioxide reactivity during propofol-induced electroencephalographic suppression[5], where absolute CO_2 reactivity was reduced whilst relative CO_2 reactivity was maintained within normal limits within the same subject. In this situation, cerebral blood flow and CO_2 preserve a normal relationship, albeit from a different baseline level. In our study, we quantified the effect of propofol and isoflurane on cerebral blood flow compared to the awake state beforehand, and then made our conclusions about the comparative effects of anaesthesia in this context.

To assess and compare the effects of individual anaesthetic agent(s) on cerebrovascular CO_2 reactivity with awake conditions, it is important to use a validated measurement of cerebral blood flow in a homogeneous study population. The range-gated Doppler ultrasound probe venous outflow method of measuring cerebral blood flow in this study has been validated in sheep as a measure of global cerebral blood flow against angiographic, retrograde dye and timed venous outflow studies. These validation studies demonstrated that this method represents 75% total cerebral blood flow[15]. Furthermore, it has been demonstrated to be in agreement with measurements made using the Kety-Schmidt nitrous oxide method in sheep[23]. Due to the anatomical structure of the sagittal sinus in sheep, this vessel is not subject to large variations in vessel diameter. Previous validation studies of this preparation have demonstrated that vessel diameter did not change across a fourfold change in flow, and the flow-velocity relationship remained constant. The vessel diameter remained constant and cerebral blood flow was laminar over the range of flows studied, thereby maintaining the correlation between flow and sinus blood velocities.

The data from this study demonstrate that under awake conditions there was a linear relationship between cerebral blood flow and P_aCO_2, but that the slope of this relationship was highly variable between animals. There is a neurogenic component to the regulation of cerebral blood flow, which would be more active in the awake state but not under anaesthesia, mediated partly by the sympathetic response to hypercapnia. This was evident during the awake studies when the sheep became visibly agitated as P_aCO_2 increased. We speculated that this additional component was the cause of the variability in the awake studies.

Hypercapnia was induced by different mechanisms in the awake and anaesthetized cohorts—i.e., CO_2 administration compared to alterations in mechanical ventilation. It is unlikely that this had a significant effect on CO_2 reactivity as the ranges of CO_2 produced were not significantly different between cohorts and represented a physiological range. The effects of mechanical ventilation on cerebral blood flow were minimized by maintaining a euvolaemic state and avoiding positive end-expiratory pressure. The levels of alterations of cerebral blood flow under anaesthesia were consistent with other published studies that did not utilize mechanical ventilation[7,20].

While the mean slopes of the reactivity curves did not differ between awake conditions and anaesthesia, this was a function of the high variability of the awake data, and the trend in the data suggests that reactivity under awake conditions is generally higher (i.e. higher slope) than under anaesthesia. What is clear, however, is that the slopes of the lines for isoflurane and propofol were determined with high precision, and that there was no statistically significant difference between the CO_2 reactivity curves for these anaesthetic agents. This suggests that anaesthesia per se, irrespective of the agent used, is the main determinant of alteration of CO_2 reactivity.

Isoflurane and propofol were chosen because of their predominance in neuroanaesthesia. Volatile agents such as isoflurane abolish cerebral autoregulation in a concentration dependent manner. Two per cent isoflurane concentrations were selected in accordance with previous studies demonstrating adequacy of anaesthesia and stability of cerebrovascular volumes over a range of P_aCO_2[21]. Propofol infusion rates were selected following previously published studies from our laboratory analysing the cerebral pharmacokinetics of propofol in sheep[24-26]. No significant changes in mean arterial pressure, intracranial pressure or temperature was observed during these studies during the hypercapnic or hypocapnic ranges. Given the stability of the model, accuracy of cerebral blood flow and P_aCO_2 measurement, and steady-state conditions of anaesthesia, the observed effect of these agents on CO_2 reactivity are attributable to the agent alone.

The linearity of the reactivity curve was maintained over the range of P_aCO_2 studied, making this study at

variance to others that have suggested that cerebral blood flow responses to CO_2 plateau outside of the range 25 to 70 mmHg[27]. However, as the range of P_aCO_2 produced represented a physiological range (18-63 mmHg), we cannot draw any conclusions about the shape of the reactivity curve at CO_2 ranges above or below this range. Flattening of cerebral blood flow is expected at P_aCO_2 levels <20 mmHg: cerebral blood flow responses below this threshold will need to studied specifically to exclude a species-specific phenomenon. The mechanism for this phenomenon remains unclear, but has been attributed to pH-mediated changes in cerebrovascular responsiveness. The strong association between cerebral blood flow and pH demonstrated in Figure 4 is supportive of this hypothesis. Other mechanisms suggested include coupled changes cerebral blood flow and metabolism and alterations in cerebral blood volumes.

This study used a global measurement of cerebral blood flow in a physiologically intact preparation. It therefore does not provide information about regional changes in cerebral blood flow which may be significant, particularly in situations where cerebral autoregulation is impaired by pathological processes. Similarly, the cumulative effects of anaesthetic agents in patients may have significant effects of cerebral autoregulation. Cerebral autoregulation is a complex process involving myogenic and metabolic systems, and varies under pathophysiological conditions[18]. Any deduction about the effect of one aspect of this process on overall autoregulatory function must be made with circumspection.

In conclusion, cerebral blood flow was shown to always increase in a linear manner with increases in P_aCO_2. Isoflurane and propofol anaesthesia produced more predictable CO_2 reactivity curves than for the awake state, which tended to produce steeper reactivity curves (possibly due to an additional reactive autonomic component to cerebral blood flow). However, there was no significant difference between these anaesthetic agents with respect to the CO_2 reactivity of cerebral blood flow.

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