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Original Papers

The Effect of Infusions of Adrenaline, Noradrenaline and Dopamine on Cerebral Autoregulation Under Isoflurane Anaesthesia in an Ovine Model

J. A. MYBURGH*, R. N. UPTON†, C. GRANT‡, A. MARTINEZ§

Department of Anaesthesia and Intensive Care, University of Adelaide, Adelaide, South Australia

SUMMARY

The effects of infusions of adrenaline, noradrenaline and dopamine on cerebral autoregulation under steady-state isoflurane anaesthesia were compared with the awake state.

Six studies each were conducted in two cohorts of adult ewes: awake sheep and those anaesthetized with 2% isoflurane anaesthesia. In random order, each animal received ramped infusions of adrenaline, noradrenaline (0-40 μg/min) and dopamine (0-40 μg/kg/min).

Cerebral blood flow was measured continuously from changes in Doppler velocities in the sagittal sinus. Autoregulation was determined by linear regression analysis between cerebral blood flow and mean arterial pressure.

Isoflurane did not significantly alter cerebral blood flow relative to pre-anaesthesia values ($P>0.05$). All three catecholamines significantly and equivalently increased MAP from baseline in a dose dependent manner in both the awake and isoflurane cohorts. Although adrenaline significantly increased cerebral blood flow from baseline in the awake cohort ($P<0.01$), none of the catecholamines significantly increased cerebral blood flow during isoflurane anaesthesia. No significant differences were demonstrated between the slopes and intercepts of regression lines for adrenaline, noradrenaline and dopamine within either cohort (ANCOVA). Inter-cohort comparisons between the two autoregulation curves demonstrated no significant difference between the slopes of the autoregulation curves for the awake (pooled slope=0.39) and isoflurane cohorts (pooled slope=0.28) ($P>0.05$).

Over a specific dose range, systemic hypertension induced by adrenaline, noradrenaline and dopamine did not significantly increase cerebral blood flow under 2% isoflurane anaesthesia. The concomitant administration of isoflurane and the catecholamines was not associated with altered autoregulatory function compared to the awake state.

Key Words: CATECHOLAMINES: adrenaline, noradrenaline, epinephrine, norepinephrine, dopamine. CEREBRAL BLOOD FLOW: autoregulation. ANAESTHESIA, ANESTHESIA: isoflurane

Cerebral autoregulation is defined as the maintenance of cerebral blood flow at constant levels in the presence of changing systemic pressures. Also termed "myogenic" autoregulation, this phenomenon is attributed to changes in cerebrovascular resistance, although a number of metabolic systems have been implicated[1]. The capacity of this complex physiological system to maintain cerebral autoregulation may be influenced by volatile anaesthetic agents[2-4].

Infusions of catecholamines such as adrenaline, noradrenaline and dopamine are frequently used during anaesthesia to defend systemic blood pressure. During neuroanaesthetic procedures using volatile agents such as isoflurane, these catecholamines may also be used to augment or maintain cerebral perfusion pressure.

Volatile anaesthetics have variable effects on cerebral blood flow and autoregulation. Under these conditions, catecholamines may exert direct or indirect effects on the cerebral circulation, which may result in alterations in cerebral autoregulatory

*M.B., B.Ch., Ph.D., D.A.(S.A.)., F.A.N.Z.C.A., F.J.F.I.C.M.
†Ph.D., Principal Medical Scientist.
‡M.Med.Sci.
§Technical Officer.

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

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activity[5]. The direct effect of catecholamines on the cerebral circulation under awake and anaesthetized conditions remains contentious, due to variability of experimental models and methods of measurement of cerebrovascular mechanics.

The aim of this study was to determine the effects of adrenaline, noradrenaline and dopamine on cerebral autoregulation under steady-state isoflurane anaesthesia. These effects were compared with each other and with awake animals state.

The Animal Ethics Committee of the University of Adelaide approved the studies. Animals were handled in accordance with the 1997 edition of the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes issued by the National Health and Medical Research Council of Australia.

METHOD

Studies were performed in two cohorts of adult female merino sheep: awake and anaesthetized with steady-state isoflurane.

Animal preparation

Adult merino ewes of similar ages and body mass were used. One to two weeks prior to performing the studies, the animals were instrumented under thiopentone and halothane anaesthesia as described previously[6]. In brief, a 2 cm frontal craniotomy was performed anterior to the trifurcation of the frontal and parietal sutures. A bony plug was removed using a trephine and the extradural portion of the sagittal sinus exposed.

An ultrasonic, range-gated Doppler transducer (Tritonics Medical Instruments, Iowa, U.S.A.) was placed on the dorsal sagittal sinus. The Doppler transducer was secured under the replaced bone plug that was fixed with a plate and bone screws.

The animal was then turned supine and the femoral triangle exposed. A 7F catheter (Multipurpose A1 catheter, Cordis Corporation, Miami, U.S.A.) was inserted into the femoral artery for measurement of mean arterial pressure and into the femoral vein for drug and fluid delivery.

A single dose of penicillin/streptomycin was administered perioperatively for antibiotic prophylaxis. Catheter patency was maintained by intraluminal heparin (10 IU/ml) locks.

The animal was then recovered and returned to housing crates and allowed free access to food and water.

A period of five to ten days elapsed between insertion and measurements to allow a fibrous scar to develop around the flowmeter 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.

The sample size required to determine baseline stability within and between cohorts and reproducibility of each intervention was determined from previous studies using our experimental preparation[7,8]. Due to the homogeneity and stability of the preparation, six studies for each intervention (i.e. catecholamine infusion) were considered appropriate. Stability and reproducibility were evaluated by determining normality of distribution and 95% confidence interval analysis.

On the day of measurement, the animal was moved to a specific study laboratory.

The animal was supported by a canvas sling and extraneous noise was minimized to reduce changes in cerebral blood flow induced by startling. Monitoring lines were connected and the animal was allowed to settle so that a period of baseline stability was achieved before commencement of infusions.

Prior to anaesthesia, the output of the Doppler probe and mean arterial pressure catheter was recorded with the animal in an awake, calm state.

Anaesthesia was induced with thiopentone 1000 mg and isoflurane delivered by a vaporizer (Isotec 3, Ohmeda BOC Group, U.K.) in 100% oxygen to maintain an expired concentration of 2%, measured by a volatile agent detector (Capnomac, Datex Instrumentarium Corp, Helsinki, Finland).

Selection of isoflurane dose

Whilst minimum alveolar concentration (MAC) has an established place in clinical anaesthesia and is a useful method of comparing relative potencies of anaesthetic agents, it has limitations in animal pharmacokinetic or pharmacodynamic studies. A surgical incision is a difficult stimulus to standardize and there are cross species differences. Such pharmacodynamic studies may be standardized by establishing a depth of anaesthesia that may be assessed by reproducible stimuli, such as with analgesiometry, or by performing studies at variable levels of steady-state concentration[9]. These concentrations may be determined using end-tidal expired gas concentrations of the volatile agent in question with specific expired gas analysers. The selection of 2% isoflurane was based on previously published animal studies using isoflurane that demonstrated adequacy of anaesthesia and stability of cerebrovascular volumes over a range of P_aCO_2 [10]. The effects of isoflurane on carbon dioxide cerebrovascular reactivity in doses of 1.5% and 2% have been described[11].

The animal was turned supine and endotracheally intubated. Ventilation was controlled using a volume control ventilator (7000 Ventilator, Ohmeda, Madison, WI, U.S.A.) in 100% oxygen. End-tidal CO_2 was measured with an infrared analyser (Capnomac, Datex Instrumentarium Corp, Helsinki, Finland) and mechanical ventilation was adjusted to maintain end-tidal CO_2 at 40 mmHg.

The animal was placed on the side position for studies.

After 1.5 hours to allow the induction agent to clear and assuming steady-state anaesthetic conditions, baseline measurements of cerebral blood flow and mean arterial pressure were recorded. This interval has been determined in previous studies from our laboratory[12].

Interventions

In random order, each animal received a ramped intravenous infusion of noradrenaline, adrenaline or dopamine through the femoral venous catheter. Noradrenaline and adrenaline were made up as 3 mg/50 ml 0.9% saline. Using a syringe driver, a delivery rate of 1 ml/h is equivalent to 1 μg/minute. Dopamine was constituted as 200 mg/50 ml 0.9% saline. A delivery rate of 1 ml/h is approximately equivalent to 1 μg/kg/min for a 50 kg sheep.

A dosing profile designed to produce a significant physiological response was selected. Principally, this was directed at significantly increasing mean arterial pressure. As adrenaline and noradrenaline have hydroxyl groups on the β carbon atom of the side chain, this is associated with 100 times greater potency than dopamine[13]. Consequently, the catecholamine concentrations may be regarded as functionally equivalent. Doses were reported as ml/h.

Catecholamines were administered as ramped infusions in five minute intervals in doses of 10, 20 and 40 ml/h through the femoral venous catheter. Each animal acted as its own control. On reaching the target dose, infusions were ceased. An elimination period of 15 minutes lapsed following catecholamine infusion to ensure clearance of the preceding drug, manifested by restoration of cardiovascular parameters to baseline values. Subsequent studies were conducted 60 minutes after completion of the elimination period.

Hydration was maintained throughout all studies by intravenous infusion of 1 litre per hour of normal saline. Temperature was maintained at baseline levels via humidification of inspired gases using a heat and moisture exchanger.

Following the studies, the animal was recovered and transferred to holding crates and allowed free access to food and water.

Measurements

Changes in cerebral blood flow were inferred from changes in the outputs from the Doppler probe. Once a period of baseline stability was established, Doppler frequencies were expressed as a percentage of the reading obtained in the baseline period. This was sampled at 1 Hz using an analogue to digital card (Metrabyte DAS 16-G2) and a personal computer (Microbits 486-based IBM compatible) and recorded digitally on computer disc. This method of quantifying cerebral blood flow with a range-gated Doppler ultrasound probe venous outflow has been validated in sheep as a measure of global cerebral blood flow against angiographic, retrograde dye and timed venous outflow studies[6]. This method represents 75% total cerebral blood flow and has been demonstrated to be in agreement with measurements made using the Kety-Schmidt nitrous oxide method in sheep[14]. Due to the anatomical structure of the sagittal sinus in sheep, this vessel in not subject to large variations in vessel diameter. Over the range of flows studied, constant correlation between flow and sinus blood velocities is maintained.

Mean arterial pressure was recorded using a standard transducer and amplifier (78342A, Hewlett Packard Company, U.S.A.) and recorded through the same computerized acquisition system. Following zero calibration, mean arterial pressure was recorded as mmHg and averaged over two minutes after the change in catecholamine infusion rate. This was done in accordance with the expected half-lives of the catecholamines, namely five to seven minutes.

Blood was sampled for blood gas analysis from the femoral arterial catheter and measured using a standard blood gas analyser (ABL 625, Radiometer Medical, Copenhagen, Denmark). Samples were taken at five-minute intervals during the catecholamine infusions for measurement of arterial carbon dioxide tension to ensure normocapnia and calibration of end-tidal carbon dioxide.

Data analysis

Normal distribution of datapoints before parametric analyses was determined using the using the Kolmogorov-Smirnov (KS) test. The effect of isoflurane on cerebral blood flow (pre-anaesthesia vs 1.5 hours post anaesthesia) was examined using a paired t-test.

Data for changes in cerebral blood flow and mean arterial pressure over time for each catecholamine

under each condition was averaged into five-minute intervals using data compression and averaging software programs. These values corresponded to the changes in rates of infusion.

The data for cerebral blood flow were normalized to an arterial carbon dioxide tension of 35 mmHg to remove the influences of small differences in carbon dioxide tensions on cerebral blood flow. This was done by determining the correlation between cerebral blood flow and measured P_aCO_2 during the catecholamine infusions using linear regression analysis. Cerebral blood flow measurements were then adjusted using the derived slope and intercept for a P_aCO_2 of 35 mmHg. The normalized values of cerebral blood flow were subsequently adjusted by the degree of change in cerebral blood flow induced by isoflurane, and expressed as a percentage of baseline.

Comparison of the effects of catecholamines on cerebral blood flow and mean arterial pressure from baseline was determined using two-way analysis of variance and Bonferroni corrections for multiple time points. Significance was determined by 95% confidence intervals, assuming a t-distribution. A P value of <0.05 was considered to be statistically significant.

Cerebral autoregulation was defined as the change in cerebral blood flow for change in mean arterial pressure. This was determined using linear regression analysis. Comparisons between regression lines were determined using an analysis of covariance, using the pooled data for each dataset. These analyses were performed using a commercial statistical software program (GraphPad Prism, GraphPad Software, San Diego, California, U.S.A.).

RESULTS

Studies with each catecholamine were conducted in six animals for each catecholamine in the awake state and under isoflurane anaesthesia.

Isoflurane anaesthesia did not significantly change cerebral blood flow (88.45% of baseline, $P=0.39$) or mean arterial pressure (97.6% of baseline, $P=0.76$) from pre-anaesthetized baseline.

The effects of each catecholamine on cerebral blood flow and mean arterial pressure are shown in Figure 1. All three catecholamines significantly

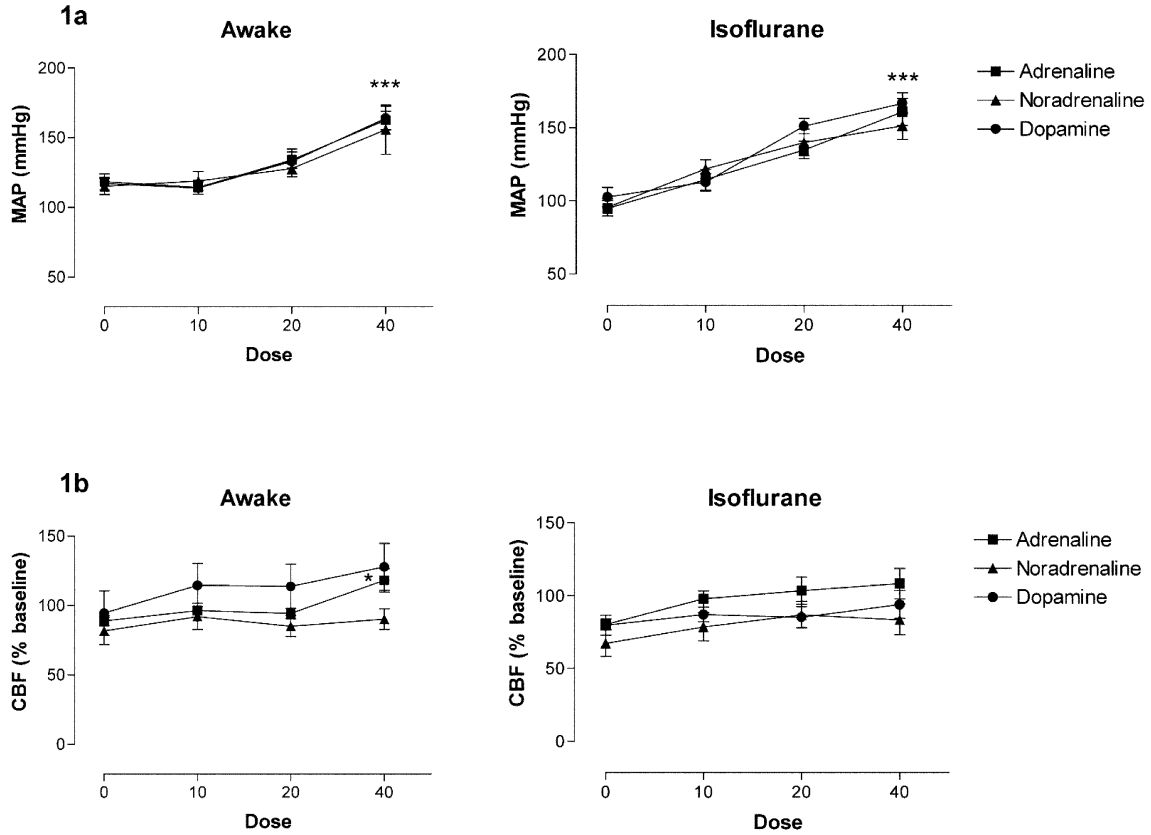

FIGURE 1: The effects of infusions of adrenaline, noradrenaline and dopamine on mean arterial pressure (mmHg) (Figure 1a) and normalised cerebral blood flow (expressed as % baseline) (Figure 1b) in awake sheep (left hand panels) and during steady state isoflurane anaesthesia (2%) (right hand panel). Dose is expressed as ml/h. Data are expressed as mean±SEM. Asterisk (***) represents $P<0.001$ and refers to adrenaline, noradrenaline and dopamine in Figure 1a; (*)= $P<0.01$ in Figure 1b above adrenaline.

TABLE 1

Individual regression analyses for adrenaline, noradrenaline and dopamine under awake conditions and during steady-state isoflurane anaesthesia (2%). Data for slope (cerebral blood flow % baseline/mmHg) and intercept (cerebral blood flow % baseline) are expressed as mean±SEM

	Awake			Isoflurane		
	Adrenaline	Noradrenaline	Dopamine	Adrenaline	Noradrenaline	Dopamine
r^2	0.81	0.16	0.59	0.86	0.87	0.62
Slope	0.53±0.18	0.11± 0.16	0.45±0.27	0.40±0.11	0.33±0.09	0.15±0.08
Intercept	29.4±29.2	73.6±21.8	52.2±36.3	46.8±14.8	37.5±11.7	66.3±11.4

increased mean arterial pressure from baseline in a dose dependent manner ($P<0.001$) in both the awake and isoflurane cohorts (Figure 1a). In the awake cohort, only adrenaline significantly increased cerebral blood flow from baseline ($P<0.01$). During isoflurane anaesthesia, none of the catecholamines significantly increased cerebral blood flow from baseline ($P>0.05$) (Figure 1b). There was no statistically significant difference between the effects of each catecholamine in any of the cohorts ($P>0.05$).

Individual regression analyses between cerebral blood flow and mean arterial pressure for adrenaline, noradrenaline and dopamine under awake conditions and during isoflurane are shown in Table 1.

The resultant slopes and intercepts for each catecholamine in each cohort were compared by analysis of covariance. The *P* values for each comparison are shown in Table 2.

No statistically significant difference between the slopes for adrenaline, noradrenaline and dopamine within each cohort were demonstrated ($P>0.05$). Significant differences in intercepts were demonstrated between dopamine and noradrenaline ($P=0.01$) in the awake cohort; and between adrenaline and noradrenaline ($P=0.002$) and adrenaline and dopamine ($P=0.03$) in the isoflurane cohort.

The effects on the autoregulation curves for the awake and isoflurane cohorts are shown in Figure 2. The data is presented using pooled data for the three catecholamines, as there was no significant difference between the slopes for each catecholamine within each cohort.

TABLE 2

Summary of the analysis of covariance comparing the differences in the slope and intercepts of the regression lines for individual catecholamines in awake sheep and during steady-state isoflurane anaesthesia (2%). Data are the P values for individual regression comparisons. (*) indicates significant results where P<0.05

	Awake		Isoflurane	
Comparison	Slope	Intercept	Slope	Intercept
Adrenaline v noradrenaline	0.16	0.08	0.65	0.002*
Adrenaline v dopamine	0.84	0.06	0.15	0.03*
Dopamine v noradrenaline	0.36	0.01*	0.23	0.12

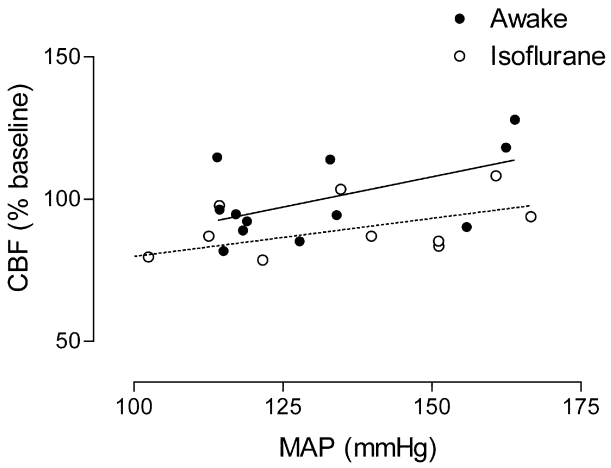

FIGURE 2: Linear regression lines between normalised cerebral blood flow (expressed as % baseline) and mean arterial pressure (mmHg) in awake sheep (closed circles) and during steady state isoflurane anaesthesia (2%) (open circles) during infusions of adrenaline, noradrenaline and dopamine. Catecholamines have been pooled in each cohort.

Comparisons between the two autoregulation curves demonstrated that there was no significant difference between the slopes of the awake (pooled slope=0.39) and isoflurane cohorts (pooled slope=0.28) ($P=0.50$). However, there was a statistically significant difference between the intercepts ($P=0.02$) of the two cohorts.

DISCUSSION

This study analysed the effects of catecholamine-induced hypertension on cerebral autoregulation during steady-state isoflurane anaesthesia. Using real time measurements, we assessed the simultaneous response of cerebral blood flow to dynamic increases in mean arterial pressure. These autoregulatory responses were compared to awake animals.

Cerebral autoregulation is a complex physiological process, involving metabolic and myogenic mechanisms. This study was designed to assess the relationship between cerebral blood flow and mean arterial pressure, using induced hypertension as the primary

perturbation. In order to determine this relationship, stability of the metabolic components of autoregulation were standardized. These metabolic components include arterial and cerebral carbon dioxide tension, systemic and cerebral oxygen consumption and temperature.

In a study using the same animal preparation, we determined carbon dioxide reactivity in awake sheep and under steady-state propofol anaesthesia[15]. This study demonstrated that over a range of arterial carbon dioxide tensions from 18 to 63 mmHg, carbon dioxide reactivity under propofol was significantly different from that in awake sheep. To remove the influences of carbon dioxide on cerebral autoregulation, studies under anaesthesia were conducted using mechanical ventilation, so that arterial carbon dioxide tensions and pH were maintained at normal levels. Accordingly, cerebral blood flow data measured during the ramped infusions of adrenaline, noradrenaline and dopamine were normalized to an arterial carbon dioxide tension of 35 mmHg.

We have quantified the systemic and cerebral metabolic effects of catecholamines in awake sheep and under propofol anaesthesia[16]. Whilst propofol anaesthesia decreases cerebral oxygen consumption relative to systemic levels, no difference between the catecholamines was demonstrated. Temperature was maintained at a constant level throughout the studies.

Over a specified dose range, adrenaline, noradrenaline and dopamine induced equivalent, significant systemic hypertension in awake sheep and during isoflurane anaesthesia.

In the presence of catecholamine-induced systemic hypertension, the effects on cerebral blood flow under these two states were slightly different. Whilst adrenaline caused a moderate, but statistically significant increase in cerebral blood flow in the awake cohort, noradrenaline and dopamine did not increase cerebral blood flow. Under isoflurane anaesthesia, which did not significantly alter cerebral blood flow or mean arterial pressure from baseline, none of the catecholamines increased cerebral blood flow.

Analysing each cohort separately, there was no significant difference between the effect of adrenaline, noradrenaline and dopamine on cerebral blood flow within each cohort.

The autoregulatory curves define these effects. The slope of the cerebral blood flow/mean arterial pressure regression line is representative of the degree of autoregulation. Maintenance of a horizontal line represents the ability to maintain cerebral blood flow at a constant rate over a range of increasing blood pressure. Elevation of the slope represents progressive exhaustion of autoregulatory capacity to a point where cerebral blood flow ultimately becomes dependent on mean arterial pressure. Despite qualitative differences between the effects of the catecholamines under awake and isoflurane anaesthesia, there was no difference between the slopes of the regression lines in these cohorts. The major difference was demonstrated in the intercept of the regression lines. This correlated to the small but non-significant reduction in cerebral blood flow induced by isoflurane compared to the awake state (i.e. 88.45% of baseline). These findings suggest that cerebral blood flow and autoregulation is preserved under isoflurane anaesthesia similar to the awake state, during catecholamine-induced hypertension.

Studies of cerebral autoregulatory function under isoflurane anaesthesia have been conducted using various methods of measurement of cerebral blood flow/mean arterial pressure relationships. Ideally, these measurements should be simultaneous and continuous, thereby assessing the response of the dependent variable (cerebral blood flow) over a range of cerebral perfusion pressures.

Similarly, autoregulatory relationships have been determined a number of methods. These include regression analysis between mean arterial pressure and cerebral blood flow[3] or cerebrovascular resistance[17], dynamic and static measurements of cerebral blood flow responses to changes in mean arterial pressure[18,19], and derived indices such as the autoregulatory index[20].

Isoflurane anaesthesia causes a relative increase in cerebral blood flow by uncoupling flow and metabolism[10,11,21]. As this phenomenon is directly dose and time dependent[4,10], interpretation and comparisons of studies of autoregulatory function requires consideration of dose, duration of anaesthesia and methods of measurements. Consequently, there are diverse conclusions about the effects of isoflurane anaesthesia on cerebral autoregulation.

In a lapine preparation, Patel studied the effects of induced hypertension by angiotensin II, noradrenaline and phenylephrine on global and regional cerebral blood flows (measured by radioactive microspheres) during 1.0 MAC isoflurane anaesthesia[5]. The slopes of pressure/flow curves produced by noradrenaline and phenylephrine were significantly steeper than that produced by angiotensin II in all cerebral blood flow regions. Patel concluded that noradrenaline and phenylephrine caused indirect cerebral vasodilation, whilst angiotensin II caused vasoconstriction during 1.0 MAC isoflurane. However, deductions about specific vascular effects of

vasoactive agents from the slope of regression curves must be made with circumspection. Factors that determine autoregulatory relationships are more complex than solely attributing changes to vasoreactivity. The difference in the conclusion from our study may, in part, be explained by the difference in cerebral blood flow measurement—intermittent (microsphere) versus continuous (sagittal sinus Doppler).

There are few controlled studies of the effects of isoflurane on autoregulation in humans. Strebel assessed alterations in dynamic autoregulation from the response of middle cerebral artery blood flow velocities in patients anaesthetized with low (0.5 MAC) and high (1.5 MAC) dose isoflurane[18]. Transient step increases and decreases in mean arterial pressure were induced by infusions of phenylephrine and rapid inflation/deflation of thigh cuffs respectively. Patients were compared to those having baseline anaesthesia with fentanyl and nitrous oxide. The study demonstrated that low dose isoflurane delayed autoregulatory responses to changes in systemic blood pressure, whilst high dose isoflurane ablated autoregulation. This study was limited by lack of an intact autoregulatory baseline, the use of intermittent indirect measurements of cerebral blood flow and derived variables for the assessment of autoregulation. However, it does emphasise the importance of dose and autoregulatory function. In our study, steady-state concentrations of isoflurane were used for standard periods of time that demonstrated baseline stability and allowed inter-cohort comparisons.

In another human study, Strebel compared the influence of phenylephrine and noradrenaline blood flow velocities of the middle cerebral and internal carotid arteries, measured by transcranial Doppler, during isoflurane anaesthesia[22]. Following augmentation of mean arterial pressure by 20%, flow velocities were determined in the supine and head-up position. Whilst noradrenaline and phenylephrine significantly increased mean flow velocities in the supine position, these effects were negated in the head-up position. Strebel concluded that these vasoactive agents did not directly affect intracranial haemodynamics under isoflurane anaesthesia, but rather that the observed haemodynamic changes reflected the effect of isoflurane on cerebral pressure autoregulation.

Engelhard compared the effects of 1.5 MAC isoflurane on dynamic cerebrovascular autoregulation compared to the awake state in humans[17]. This was assessed using transcranial Doppler ultrasonography and by deriving an autoregulatory index from an induced change in systemic blood pressure. Autoregulatory responses were delayed under isoflurane anaesthesia compared to the awake state. The difference in our study may be explained by the effects that catecholamines may have on the cerebral vasculature under isoflurane anaesthesia. This has been attributed to isoflurane induced changes in cerebral blood flow and blood-brain barrier permeability[10,11,23] and by the catecholamines themselves if associated induced hypertension exceeds the upper autoregulatory threshold[24,25].

The results of our study require the following considerations. We have previously described the effects of adrenaline noradrenaline and dopamine on cerebral blood flow using a higher dosing regimen. In that study, the drugs were infused to peak doses of 60 ml/h for adrenaline and noradrenaline and 60 ml/h for dopamine[26]. At these doses, dopamine significantly increased cerebral blood flow from baseline. In the current analysis, we limited the dose to 40 ml/h so that linearity between cerebral blood flow and mean arterial pressure was maintained. At higher doses, it is probable that the relationship is non-linear.

Second, we determined regression lines using pooled data for each study rather than individual data. This was done to minimize inter-animal variability.

Third, mean arterial pressure was used as an index of cerebral perfusion pressure. As this was a physiological study conducted in the absence of antecedent raised intracranial pressure and normocapnia, this is an acceptable assumption. However, direct effects of catecholamines on intracranial pressure, once upper autoregulatory thresholds have been exhausted, may be a confounding variable that was not quantified.

There are clinical applications from this animal study. Patients with altered cerebral blood flow and autoregulatory capacity are frequently anaesthetized with isoflurane, (e.g. following traumatic brain injury and aneurysmal subarachnoid haemorrhage). The combination of isoflurane and any of three catecholamines studied did not appear to significantly alter cerebral blood flow or autoregulation in the dose ranges that were analysed. Despite recognised cerebral vasodilatory effects of isoflurane, and potential vascular effects of the catecholamines under isoflurane anaesthesia, there did not appear to be alterations in autoregulatory capacity in this preparation. However, extrapolations of the results from this study to pathophysiological states are speculative and warrant further study.

In conclusion, over a specific dose range, induced systemic hypertension by adrenaline, noradrenaline

and dopamine did not significantly increase cerebral blood flow under 2% isoflurane anaesthesia. The concomitant administration of isoflurane and the catecholamines was not associated with altered autoregulatory function compared to awake sheep.

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