Anaesth Intensive Care 2002; **30:** 725-733

Original Papers

The Cerebrovascular Effects of Adrenaline, Noradrenaline and Dopamine Infusions Under Propofol and Isoflurane Anaesthesia in Sheep

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

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

SUMMARY

Infusions of catecholamines are frequently administered to patients receiving propofol or isoflurane anaesthesia. Interactions between these drugs may affect regional circulations, such as the brain.

The aim of this animal (sheep) study was to determine the effects of ramped infusions of adrenaline, noradrenaline (10, 20, 40 μg/min) and dopamine (10, 20, 40 μg/kg/min) on cerebral blood flow (CBF), intracranial pressure (ICP), cerebrovascular resistance (CVR) and cerebral metabolic rate for oxygen ($CMRO_2$). These measurements were made under awake physiological conditions, and during continuous propofol (15 mg/min) or 2% isoflurane anaesthesia. All three catecholamines significantly and equivalently increased mean arterial pressure from baseline in a dose-dependent manner in the three cohorts ($P<0.001$). In the awake cohort ($n=8$), dopamine ($P<0.01$) significantly increased CBF from baseline whilst adrenaline and noradrenaline did not ($P>0.05$). Under propofol ($n=6$) and isoflurane ($n=6$), all three catecholamines significantly increased CBF ($P<0.001$). Dopamine caused the greatest increase in CBF, and was associated with significant increases in ICP (awake: $P<0.001$; propofol $P<0.05$; isoflurane $P<0.001$) and CVR (isoflurane $P<0.05$). No significant changes in $CMRO_2$ were demonstrated.

Under propofol and isoflurane anaesthesia, the cerebrovascular effects of catecholamines were significantly different from the awake, physiological state, with dopamine demonstrating the most pronounced effects, particularly under propofol. Dopamine-induced hyperaemia was associated with other cerebrovascular changes. In the presence of an equivalent effect on mean arterial pressure, the exaggerated cerebrovascular effects under anaesthesia appear to be centrally mediated, possibly induced by propofol- or isoflurane-dependent changes in blood-brain barrier permeability, thereby causing a direct influence on the cerebral vasculature.

Key Words: BRAIN, BLOOD FLOW: adrenaline, noradrenaline, dopamine, autoregulation. ANAESTHETICS: propofol, isoflurane

Defence of systemic blood pressure forms the cornerstone of intensive care medicine and anaesthesia. This is usually achieved by using infusions of catecholamines such as adrenaline, noradrenaline or dopamine. These drugs are frequently administered to sedated or anaesthetized patients receiving intravenous agents such as propofol, or volatile anaesthetics such as isoflurane.

The direct effect of catecholamines on the cerebral circulation under physiological and pathophysiological conditions remains contentious, due to variability of experimental models and methods of measurement of cerebrovascular mechanics. Within physiological autoregulatory limits, catecholamines do not cross the intact blood-brain barrier, thereby limiting their direct cerebrovascular effects. However, this effect may be altered by changes in blood-brain barrier permeability or by systemic physiological perturbations (e.g. systemic hypertension)[1].

Anaesthetic agents such as propofol or isoflurane may affect the physiological function of the blood-

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

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

Accepted for publication on July 28, 2002.

brain barrier due to alterations of blood-brain barrier permeability[2,3]. Propofol and isoflurane may also affect carbon dioxide (CO_2) reactivity or pressure (myogenic) autoregulation[4]. Consequently, the interaction of exogenous catecholamine infusions under propofol or isoflurane anaesthesia may result in direct effects on the cerebral vasculature.

The aim of this study was to determine the effects of adrenaline, noradrenaline and dopamine on cerebral blood flow, intracranial pressure, cerebrovascular resistance and cerebral metabolic rate for oxygen under continuous propofol and isoflurane anaesthesia. These effects were compared with each other and with the physiological (non-anaesthetized) state.

METHOD

Studies were performed in three cohorts of instrumented adult Merino ewes: awake or anaesthetized with steady state propofol or isoflurane.

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.

Animal preparation

Female Merino sheep of similar ages and body mass were used. The animals were instrumented under thiopentone and halothane anaesthesia as described previously[5]. 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.

Using a Seldinger wire, a 4F polyethylene catheter (Cook Incorporated, Bloomington, U.S.A.) was inserted into the sagittal sinus for intermittent sampling of cerebral venous blood for oxygen content determination. An ultrasonic, range-gated Doppler transducer (Tritonics Medical instruments, Iowa) was placed on the dorsal sagittal sinus. 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. The Doppler transducer, intracranial pressure monitor and sagittal sinus catheter were then secured under the replaced bone plug which 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, 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 perioperatively for antibiotic prophylaxis. Catheter patency was maintained by intraluminal heparin (10 IU/ml) locks.

Sheep were recovered and returned to housing crates where they were allowed free access to food and water.

A period of five 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.

Sample size determination

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[6-8]. 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. This is an appropriate approach for an interventional physiological study.

Awake studies

On the day of study, each sheep was moved to a specific study laboratory. The animal was supported by a sling and extraneous noise was minimized to reduce changes in cerebral blood flow induced by changes its state of arousal. Monitoring lines were connected and the animal was allowed to settle so that a period of baseline stability was achieved before commencement of catecholamine infusions.

Anaesthetized studies

Prior to anaesthesia, the output of the Doppler probes was recorded with the animal in an awake, calm state. Anaesthesia was then induced (see below) and 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 then turned prone and placed in the sphinx position for studies.

Animals anaesthetized with propofol were induced with 200 mg propofol. Propofol was delivered intravenously via a syringe driver (Model 33, Harvard Apparatus, MA, U.S.A.) at a constant rate of 15 mg/min. This rate was selected based on previously published studies from our laboratory analysing the cerebral pharmacokinetics of propofol in sheep[7,9,10].

Animals anaesthetized with isoflurane were induced with thiopentone 1000 mg and isoflurane delivered by a vaporizer (Isotec 3, Ohmeda BOC Group, U.K.) to maintain an expired concentration of 2%, measured by a volatile agent detector (Capnomac, Datex Instrumentarium Corp, Helsinki, Finland). Two per cent isoflurane concentrations were selected in accordance with previous studies demonstrating adequacy of anaesthesia and stability of cerebrovascular volumes[11].

After 1.5 hours to allow the induction agent to clear and for anaesthetic conditions to reach steady state, baseline measurements of cerebral blood flow, mean arterial pressure, intracranial pressure and blood gases were recorded.

Interventions

Using a random number generator (StatMate®, GraphPad Software, San Diego, U.S.A.), each animal received a randomly allocated ramped intravenous infusion of noradrenaline, adrenaline or dopamine through the femoral venous catheter. Each animal acted as its own control. Infusions of noradrenaline and adrenaline (10, 20, 40 μg/min) and dopamine (10, 20, 40 μg/kg/min) were administered for five-minute intervals, followed by a washout period of 20 minutes. One hour elapsed between completion of each study to ensure clearance of each catecholamine and restoration of baseline values.

Hydration was maintained throughout all studies by intravenous infusion of one litre per hour of normal saline. 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, sheep were recovered and transferred to 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. 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 1Hz 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 using a standard transducer and amplifier (78342A, Hewlett Packard Company, U.S.A.) and recorded through the same computerized data acquisition system. Both were recorded as percentage changes from baseline values and averaged over the last two minutes of each rate of catecholamine infusion. This was done in accordance with the expected half-lives of the catecholamine.

An index of cerebrovascular resistance was calculated using the standard formula: cerebral perfusion pressure (mean arterial pressure—intracranial pressure) divided by cerebral blood flow.

Blood was sampled for blood gas analysis from the femoral arterial and sagittal sinus catheters and measured using a standard blood gas analyser (ABL 625, Radiometer Medical, Copenhagen, Denmark). Samples were taken at five-minute intervals throughout each study. Arterial and sagittal sinus oxygen contents were derived from oxygen saturation and haemoglobin. Carbon dioxide tensions and pH were also measured.

Cerebral metabolic rate for oxygen ($CMRO_2$) was calculated using the standard formula: cerebral blood flow x arterio-venous oxygen content difference.

Data analysis

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

Data for changes 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 and into the post-infusion washout period.

Comparison between time intervals and between groups was determined using two-way analysis of variance and Bonferroni corrections for multiple time points[12]. Significance was determined by 95% confi-

dence intervals, assuming a t-distribution. A P value of <0.05 was considered to be statistically significant.

RESULTS

In the awake cohort, studies with each catecholamine were conducted in eight animals, and in six animals for each catecholamine in the propofol and isoflurane cohorts.

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, $P=0.76$).

All three catecholamines significantly increased mean arterial pressure from baseline in a dose-dependent manner in the three cohorts ($P<0.001$). There was no statistically significant difference between each catecholamine in any of the cohorts ($P>0.05$) (Figures 1a, 1b, 1c).

In the awake cohort, cerebral blood flow was significantly increased by dopamine ($P<0.01$), but not by adrenaline or noradrenaline ($P>0.05$) (Figure 2a).

In the propofol cohort, adrenaline, noradrenaline and dopamine significantly increased cerebral blood flow from baseline ($P<0.001$). Dopamine increased cerebral blood flow significantly greater than noradrenaline at the highest infusion concentrations ($P<0.01$) (Figure 2b).

In the isoflurane cohort, adrenaline, noradrenaline and dopamine significantly increased cerebral blood flow from baseline ($P<0.001$). There was no statistically significant difference between each catecholamine under isoflurane ($P>0.05$) (Figure 2c).

Dopamine increased cerebral blood flow significantly greater under propofol than isoflurane anaesthesia ($P<0.001$).

The effects on intracranial pressure are shown in Figures 3a, 3b, 3c. In all cohorts, dopamine significantly increased intracranial pressure from baseline in a dose-dependent manner (awake: $P<0.001$; propofol $P<0.05$; isoflurane $P<0.001$), whilst adrenaline and noradrenaline did not ($P>0.05$).

Dopamine increased intracranial pressure significantly greater than adrenaline and noradrenaline in the awake cohort ($P<0.001$); and noradrenaline in the propofol and isoflurane ($P<0.05$) cohorts.

No statistically significant changes in cerebrovascular resistance from baseline were demonstrated during the infusions of adrenaline and noradrenaline in the awake and propofol cohort ($P>0.05$).

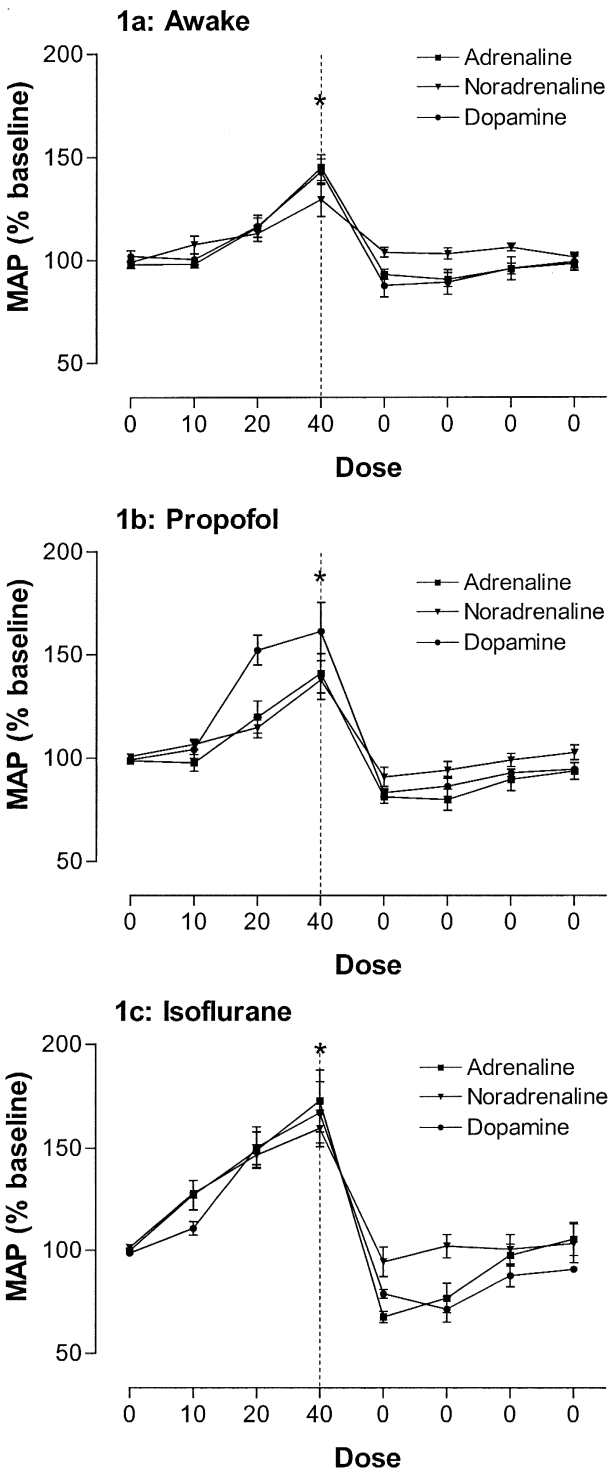

FIGURE 1: Effect of adrenaline, noradrenaline and dopamine infusions on mean arterial pressure (expressed as % change from baseline) under awake (non-anaesthetized) conditions (Figure 1a); during propofol anaesthesia (15 mg/min) (Figure 1b) and during 2% isoflurane anaesthesia (Figure 1c). Dose refers to five-minute intervals in μg/min for adrenaline and noradrenaline, μg/kg/min for dopamine during infusion followed by a 20-minute washout period. Data are expressed as mean±SEM. Asterisk (*) refers to $P<0.001$ for all three catecholamines.

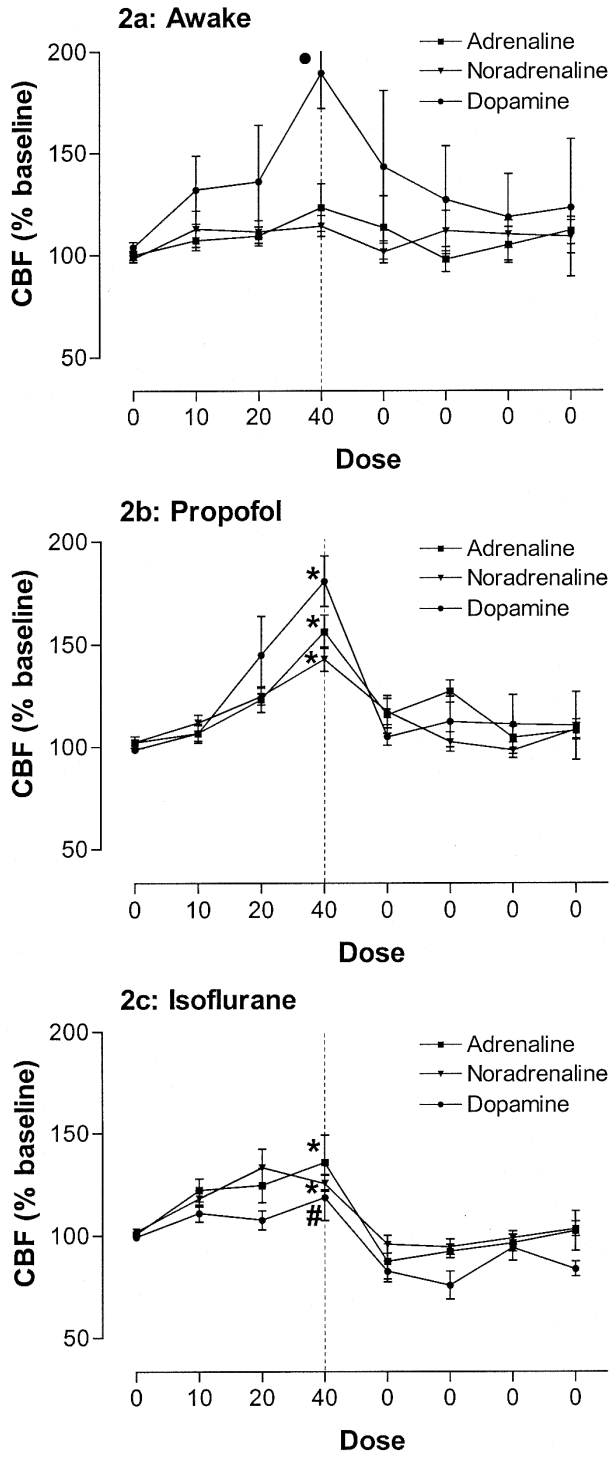

FIGURE 2: Effect of adrenaline, noradrenaline and dopamine infusions on cerebral blood flow (expressed as % change from baseline) under awake (non-anaesthetized) conditions (Figure 2a); during propofol anaesthesia (15 mg/min) (Figure 2b) and during 2% isoflurane anaesthesia (Figure 2c). Dose refers to five-minute intervals in μg/min for adrenaline and noradrenaline, μg/kg/min for dopamine during infusion followed by a 20-minute washout period. Data are expressed as mean±SEM. Asterisk (*) refers to $P<0.001$; hash (#) refers to $P<0.01$, dot (•) refers to $P<0.05$ for each catecholamine for significant changes from baseline.

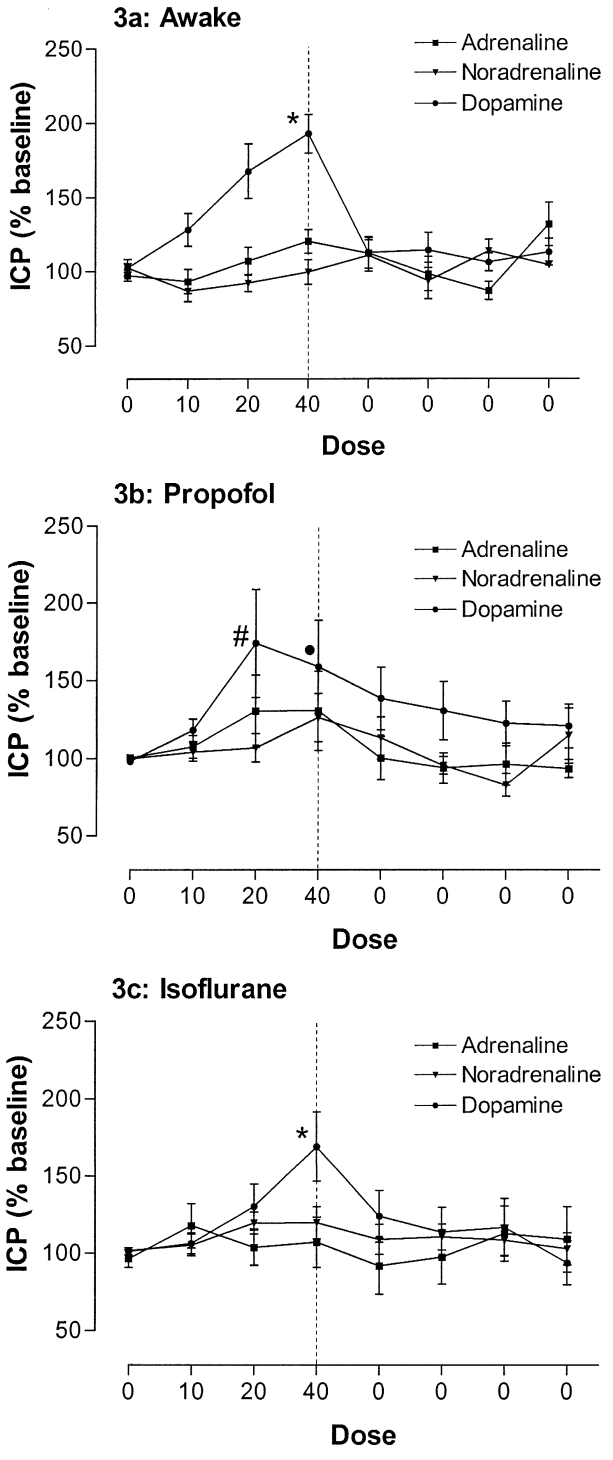

FIGURE 3: Effect of adrenaline, noradrenaline and dopamine infusions on intracranial pressure (expressed as % change from baseline) under awake (non-anaesthetized) conditions (Figure 3a); during propofol anaesthesia (15 mg/min) (Figure 3b) and during 2% isoflurane anaesthesia (Figure 3c). Dose refers to five-minute intervals in (g/min for adrenaline and noradrenaline, μg/kg/min for dopamine during infusion followed by a 20-minute washout period. Data are expressed as mean±SEM. Asterisk (*) refers to $P<0.001$; hash (#) refers to $P<0.01$, dot (•) refers to $P<0.05$ for each catecholamine for significant changes from baseline.

Dopamine significantly increased cerebrovascular resistance from baseline under isoflurane ($P<0.001$), but not in the awake and propofol cohorts (Figures 4a, 4b, 4c).

Prompt reductions in cerebrovascular resistance were demonstrated in all cohorts following cessation of catecholamine infusions. These reductions were only statistically significant following cessation of adrenaline in the awake ($P<0.05$) and isoflurane ($P<0.001$) cohorts, and dopamine in the propofol ($P<0.05$) and isoflurane ($P<0.001$) cohorts.

Adrenaline, noradrenaline and dopamine did not significantly change $CMRO_2$ from baseline during the infusion and post infusion period in any of the cohorts ($P>0.05$) (Figures 5a, 5b, 5c).

$CMRO_2$ during catecholamine infusions was lower under anaesthetized conditions compared to the awake cohort.

DISCUSSION

This study directly compared the effects of three commonly used exogenous catecholamines on cerebrovascular mechanics and metabolism during propofol and isoflurane anaesthesia with the physiological (non-anaesthetized) state. Propofol and isoflurane were chosen because of their predominance in neuroanaesthesia. Propofol is increasingly being used as a sedative agent in critically ill patients.

There are few studies quantifying and comparing the effects of catecholamines on cerebrovascular mechanics. King et al compared the effects of adrenaline (6 to 22 μg/min) and noradrenaline (19-73 μg/min) on cerebral blood flow, measured using the nitrous oxide method, in awake human volunteers[13]. Induced hypertension with adrenaline was associated with increased cerebral blood flow that was attributed to increased cerebral metabolism. Noradrenaline was associated with decreased cerebral blood flow that was attributed to increased cerebrovascular resistance in the absence of demonstrable changes in metabolism.

To assess and compare the effects of individual catecholamine(s) on cerebrovascular function under various conditions, it is important to use a standardized dose regimen and validated measurements of cerebral blood flow, intracranial and mean arterial pressures in a homogeneous population.

The doses of catecholamines used were selected to represent a clinically relevant range. Adrenaline and noradrenaline were expressed as μg/minute, whilst dopamine was referenced to body weight (μg/kg/min) for familiarity reasons. These concentrations may be regarded as functionally equivalent.

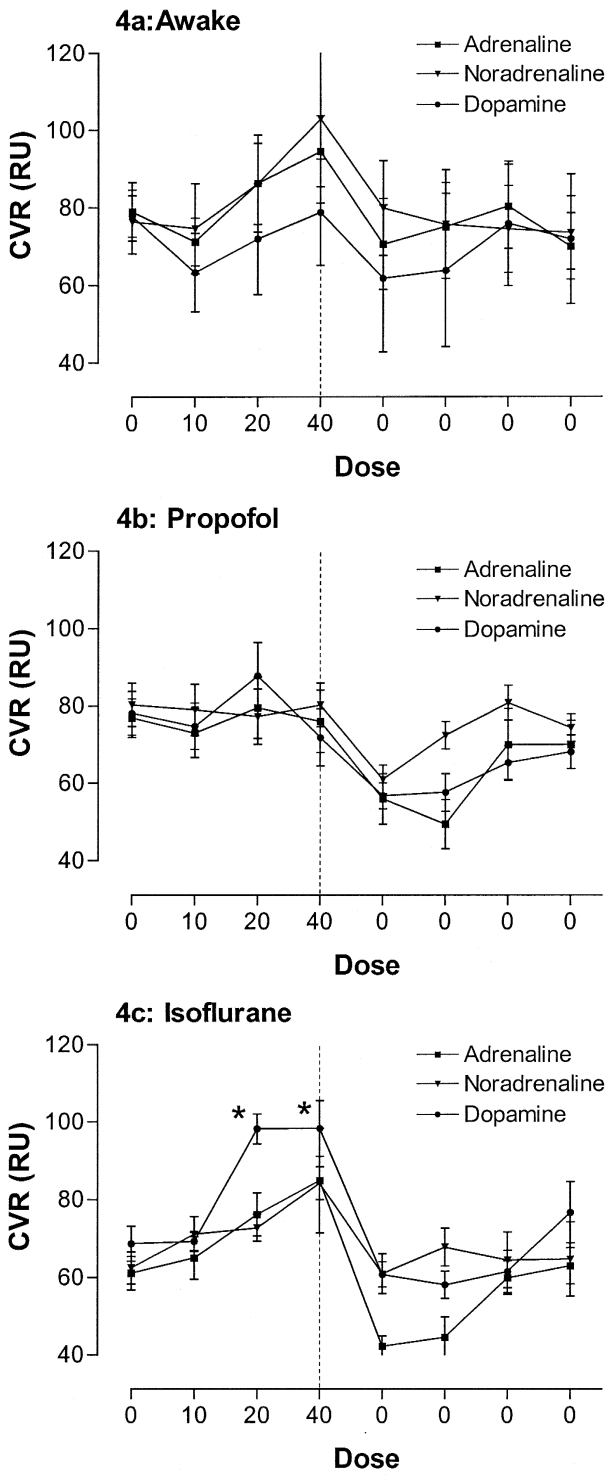

FIGURE 4: Effect of adrenaline, noradrenaline and dopamine infusions on cerebrovascular resistance (expressed as resistance units) under awake (non-anaesthetized) conditions (Figure 4a); during propofol anaesthesia (15 mg/min) (Figure 4b) and during 2% isoflurane anaesthesia (Figure 4c). Dose refers to five-minute intervals in μg/min for adrenaline and noradrenaline, (g/kg/min for dopamine during infusion followed by a 20-minute washout period. Data are expressed as mean±SEM. Asterisk (*) refers to $P<0.001$ for each dopamine for significant changes from baseline.

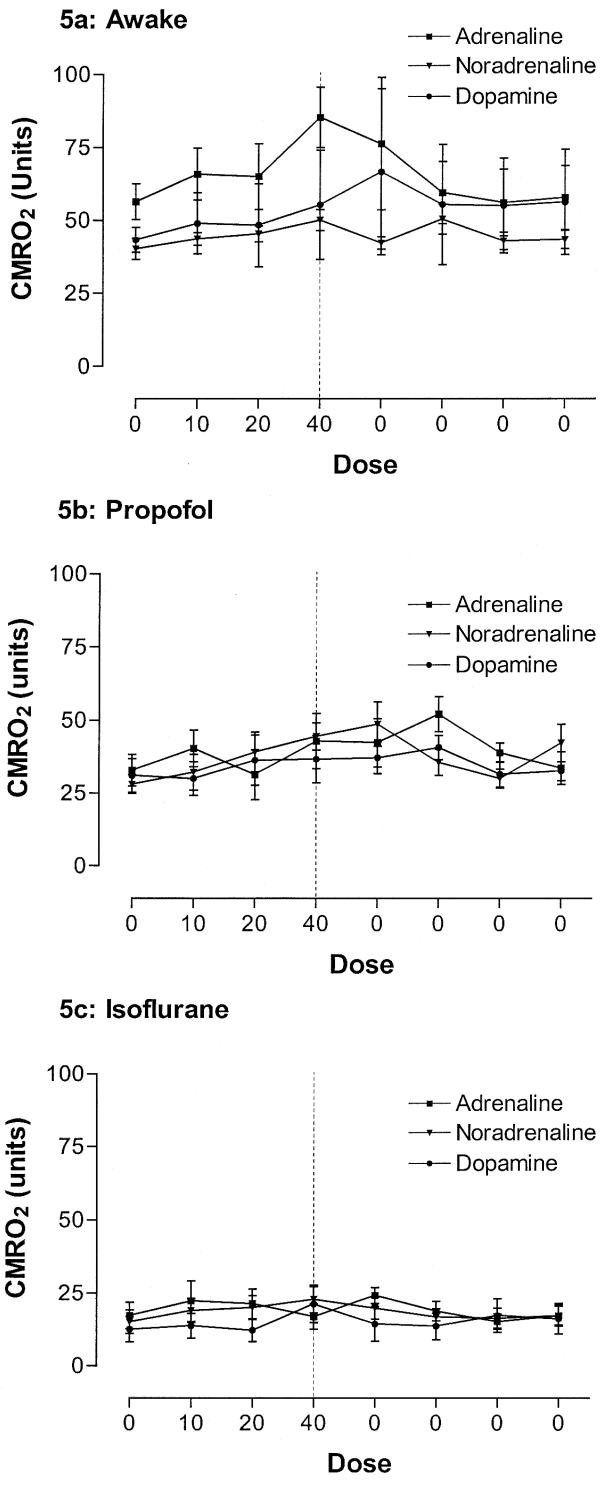

FIGURE 5: Effect of adrenaline, noradrenaline and dopamine infusions on cerebral metabolic rate for oxygen ($CMRO_2$) under awake (non-anaesthetized) conditions (Figure 5a); during propofol anaesthesia (15 mg/min) (Figure 5b) and during 2% isoflurane anaesthesia (Figure 5c). Dose refers to five-minute intervals in μg/min for adrenaline and noradrenaline, μg/kg/min for dopamine during infusion followed by a 20-minute washout period. Data are expressed as mean±SEM. No significant changes from baseline were demonstrated.

Adrenaline and noradrenaline have hydroxyl groups on the β carbon atom of the amine chain, which is associated with a hundred-fold greater potency than dopamine. Dopamine is hydroxylated to form noradrenaline, which is subsequently methylated to form adrenaline[14]. All catecholamines have very short biological half-lives (1 to 2 minutes) and a steady state plasma concentration is achieved within 5 to 10 minutes.

Our laboratory has extensive experience in the measurement of cerebral blood flow using the range-gated Doppler ultrasound probe venous outflow method. Validation studies have been performed that compared this method of cerebral blood flow against angiographic, retrograde dye and timed venous outflow studies[5]. This Doppler method of cerebral blood flow measurement represents 75% total cerebral blood flow. It has also been shown to be in agreement with measurements made using the Kety-Schmidt nitrous oxide method in sheep[15]. Importantly, due to the anatomical structure of the sagittal sinus in sheep, this vessel is not subject to large variations in vessel diameter that may invalidate velocity-based measurements. Validation studies demonstrated that vessel diameters and laminar cerebral blood flow remained constant across a fourfold change in flow. Consequently, flow-velocity relationships remained constant over the range of flows studied, thereby maintaining the correlation between flow and sinus blood velocities.

The data from the awake cohort shows that dopamine significantly increased cerebral blood flow and intracranial pressure in a dose-dependent manner without demonstrable changes in calculated cerebrovascular resistance or cerebral oxygen extraction. The effects of dopamine on cerebral blood flow and intracranial pressure were significantly greater than adrenaline, which increased cerebral blood flow albeit to a lesser extent and noradrenaline, which did not. Of the three catecholamines, noradrenaline had the least effect on cerebrovascular mechanics, despite inducing an equivalent systemic effect to dopamine and noradrenaline, suggesting little or no direct effect on the cerebral circulation. The variance between our results and King's study may be explained by the difference in doses used—a standardized infusion over a dose range compared to disparate doses in different individuals. Cerebrovascular resistance is a derived index that is prone to cumulative measurement errors. Caution should be used when attributing dynamic changes in complex systems to a single derived index.

Under propofol and isoflurane anaesthesia, the

cerebrovascular effects of catecholamines were significantly different from the awake, physiological state. Cerebral blood flow was significantly increased by all three catecholamines under propofol and isoflurane anaesthesia compared to the awake state, with dopamine demonstrating the most pronounced effects, particularly under propofol. Dopamine-induced hyperaemia was associated with other cerebrovascular changes. Dopamine consistently increased both intracranial pressure and cerebrovascular resistance, whilst this was not a feature of noradrenaline and adrenaline, suggesting a greater degree of hyperaemia induced by dopamine. In the presence of an equivalent effect on mean arterial pressure, these cerebrovascular effects appear to be centrally mediated, possibly induced by propofol or isoflurane-mediated changes in blood-brain barrier permeability, thereby causing a direct influence on the cerebral vasculature.

Cerebral metabolic rate for oxygen, used as a surrogate index of cerebral metabolism, was significantly lower under anaesthesia compared to the awake state. The lack of demonstrable effects on cerebral metabolism induced by the catecholamines may be explained by the coupling of flow and metabolism induced by anaesthesia.

The mechanisms for the variable effects of catecholamines on the cerebral circulation under physiological and anaesthetized conditions are speculative, but may be considered by analysing the individual effects that catecholamines and anaesthetic agents have on cerebrovascular function.

Under physiological conditions, exogenous catecholamines do not cross the blood-brain barrier due to anatomical and metabolic mechanisms. The integrity of the endothelial cell lining of the cerebrovascular bed constitutes a morphological blood-brain barrier mechanism to neurotransmitter catecholamines. The small percentage of amines that may pass this membrane are deaminated within the endothelial cells and pericytes of brain microvessels and, in the case of large parenchymal and pial vessels, in the smooth muscle layers[16].

Selective transmission of dopamine may occur across the natural defects in the blood-brain barrier such as the posterior pituitary gland or pineal gland which have specific dopaminergic receptors, or via non-adrenergic central neural mechanisms[17,18].

Brief or sustained hypertensive stimuli that exceed the upper cerebral autoregulatory threshold may transiently open the blood-brain barrier through an effect on endothelial cell linings. High circulating concentrations of catecholamines can also open the morphological barrier, but probably only indirectly by inducing an acute rise in systemic blood pressure[16,19]. Once the blood-brain barrier is open, systemically administered catecholamines may enter the brain parenchyma, where they may induce pronounced changes in cerebral blood flow and metabolism.

The effect of catecholamines such as adrenaline, noradrenaline and dopamine on blood-brain barrier permeability has been demonstrated in a number of experimental models including labelled albumin leakage[20], Evans blue[21] and horseradish peroxidase tracers[22]. The effects of catecholamines on cerebral blood flow and metabolism were demonstrated using various methods of cerebral blood flow measurement including ^{14}C ethanol[23], quantitative autoradiography[19] and hydrogen clearance techniques[24]. A consistent finding in these studies was that blood-brain barrier permeability was altered by induced hypertensive stimuli[19,25], particularly by dopamine and adrenaline[22]. This phenomenon has been implicated in the pathogenesis of hypertensive encephalopathy[26].

Intravenous and inhalational anaesthetics have direct cerebrovascular effects that are complex. Propofol is regarded as an indirect cerebral vasoconstrictor, whilst isoflurane is thought to be a predominant vasodilator. However, these mechanisms remain unclear as there are variable effects on blood-brain barrier permeability, flow-metabolism coupling and myogenic autoregulation[27-30].

Anaesthetic agents may affect blood-brain barrier permeability. Direct effects of isoflurane on blood brain transfer coefficients and capillary permeability-surface area product have been demonstrated with 1 and 2% isoflurane[31]. Propofol has been shown to independently increase the uptake of chemotherapeutic agents such as melphalan and etoposide phosphate across the blood-brain barrier following osmotic disruption[3]. The effects of propofol/nitrous oxide anaesthesia on blood-brain barrier permeability has been shown to be qualitatively and quantitatively more pronounced than isoflurane/oxygen anaesthesia[2].

The clinical implications of this animal study are significant. The use of catecholamine infusions in patients receiving propofol or isoflurane anaesthesia is common, particularly in patients with cerebral pathology such as traumatic brain injury or subarachnoid haemorrhage. If catecholamine-anaesthetic interactions potentially alter blood-brain barrier function under physiological conditions, it is likely that this may be exacerbated under pathophysiological conditions, thereby rendering the cerebral circulation vulnerable to the direct effect of these

agents. This may be of great clinical significance and requires further study.

ACKNOWLEDGEMENTS

Some aspects of these data were presented at the Tenth International ICP meeting on intracranial pressure and neuromonitoring in brain injury, Virginia, U.S.A. 1997. The resulting abstract was published in Acta Neurochir Suppl(Wien) 1998; 71:19-21.

FOOTNOTE

Funded by the National Health and Medical Research Council of Australia. Grant 157952.

REFERENCES

1. Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM. Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. J Neurosurg 1994; 80:857-864.
2. Remsen LG, Pagel MA, McCormick CI, Fiamengo SA, Sexton G, Neuwelt EA. The influence of anesthetic choice, PaCO2, and other factors on osmotic blood-brain barrier disruption in rats with brain tumor xenografts. Anesth Analg 1999; 88:559-567.
3. Fortin D, McCormick CI, Remsen LG, Nixon R, Neuwelt EA. Unexpected neurotoxicity of etoposide phosphate administered in combination with other chemotherapeutic agents after blood-brain barrier modification to enhance delivery, using propofol for general anesthesia, in a rat model. Neurosurgery 2000; 47:199-207.
4. Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology 1995; 83:66-76.
5. Ludbrook GL, Upton RN, Grant C, Grey E.C. An ultrasonic doppler venous outflow method for the continuous measurement of cerebral blood flow in conscious sheep. J Cereb Blood Flow Metab 1994; 14:680-688.
6. Upton RN, Ludbrook GL. A physiological model of induction of anaesthesia with propofol in sheep. 1. Structure and estimation of variables. Br J Anaesth 1997; 79:497-504.
7. Ludbrook GL, Upton RN. A physiological model of induction of anaesthesia with propofol in sheep. 2. Model analysis and implications for dose requirements. Br J Anaesth 1997; 79:505-513.
8. Upton RN, Runciman WB, Mather LE. Regional pharmacokinetics. III. Modelling methods. Biopharm Drug Dispos 1991; 12:1-15.
9. Ludbrook GL, Upton RN, Grant C, Martinez A. A compartmental analysis of the pharmacokinetics of propofol in sheep. J Pharmacokinet Biopharm 1999; 27:329-338.
10. Ludbrook GL, Upton RN, Grant C, Gray EC. Brain and blood concentrations of propofol after rapid intravenous injection in sheep, and their relationships to cerebral effects. Anaesth Intensive Care 1996; 24:445-452.
11. Young WL, Barkai AI, Prohovnik I, Nelson H, Durkin M. Effect of PaCO2 on cerebral blood flow distribution during halothane compared with isoflurane anaesthesia in the rat. Br J Anaesth 1991; 67:440-446.
12. Motulsky H. Comparing groups with confidence intervals. In: Motulsky H, ed. Intuitive Statistics. Oxford: Oxford University Press, 1995; 65-66.
13. King BD, Sokoloff L, Wechsler R. The effects of l-epinephrine and l-norepinephrine upon cerebral circulation and metabolism in man. J Clin Investig 1951; 31:273-279.
14. Runciman WB, Morris JL. Adrenoceptor agonists. In: Feldman AC, Paton W, Scurr C, eds. Mechanisms of Drugs in Anaesthesia. London: Edward Arnold, 1993; 262-291.
15. Doolette DJ, Upton RN, Grant C. Agreement between ultrasonic Doppler venous outflow and Kety and Schmidt estimates of cerebral blood flow. Clin Exp Pharmacol Physiol 1999; 26:736-740.
16. Hardebo JE, Owman C. Barrier mechanisms for neurotransmitter monoamines and their precursors at the blood-brain interface. Ann Neurol 1980; 8:1-31.
17. Teasdale G, McCulloch J. Effect of stimulation of dopaminergic receptors upon local cerebral blood flow. Acta Neurol Scand Suppl 1977; 64:98-99.
18. Yokote H, Itakura T, Nakai K, Kamei I, Imai H, Komai N. A role of the central catecholamine neuron in cerebral circulation. J Neurosurg 1986; 65:370-375.
19. Tuor UI, Edvinsson L, McCulloch J. Catecholamines and the relationship between cerebral blood flow and glucose use. Am J Physiol 1986; 251:H824-H833.
20. Ben Menachem E, Johansson BB, Svensson TH. Increased vulnerability of the blood-brain barrier to acute hypertension following depletion of brain noradrenaline. J Neural Transm 1982; 53:159-167.
21. Suzuki R, Nitsch C, Fujiwara K, Klatzo I. Regional changes in cerebral blood flow and blood-brain barrier permeability during epileptiform seizures and in acute hypertension in rabbits. J Cereb Blood Flow Metab 1984; 4:96-102.
22. Sokrab TE, Johansson BB, Tengvar C, Kalimo H, Olsson Y. Adrenaline-induced hypertension: morphological consequences of the blood-brain barrier disturbance. Acta Neurol Scand 1988; 77:387-396.
23. Johansson B, Hardebo JE. Cerebrovascular permeability and cerebral blood flow in hypertension induced by gamma-hydroxybutyric acid. An experimental study in the rat. Acta Neurol Scand 1982; 65:448-457.
24. MacKenzie ET, Strandgaard S, Graham DI, Jones JV, Harper AM, Farrar JK. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. Circ Res 1976; 39:33-41.
25. Ekstrom-Jodal B, Larsson LE. Effects of dopamine of cerebral circulation and oxygen metabolism in endotoxic shock: an experimental study in dogs. Crit Care Med 1982; 10:375-377.
26. Tamaki K, Sadoshima S, Baumbach GL, Iadecola C, Reis DJ, Heistad DD. Evidence that disruption of the blood-brain barrier precedes reduction in cerebral blood flow in hypertensive encephalopathy. Hypertension 1984; 6:I75-I81.
27. Stephan H, Sonntag H, Schenk HD, Kohlhausen S. Effect of Disoprivan (propofol) on the circulation and oxygen consumption of the brain and CO2 reactivity of brain vessels in the human. Anaesthesist 1987; 36:60-65.
28. Van Hemelrijck J, Fitch W, Mattheussen M, Van Aken H, Plets C, Lauwers T. Effect of propofol on cerebral circulation and autoregulation in the baboon. Anesth Analg 1990; 71:49-54.
29. Todd MM, Weeks J. Comparative effects of propofol, pentobarbital, and isoflurane on cerebral blood flow and blood volume. J Neurosurg Anesthesiol 1996; 8:296-303.
30. Boarini DJ, Kassell NF, Coester HC, Butler M, Sokoll MD. Comparison of systemic and cerebrovascular effects of isoflurane and halothane. Neurosurgery 1984; 15:400-409.
31. Chi OZ, Anwar M, Sinha AK, Wei HM, Klein SL, Weiss HR. Effects of isoflurane on transport across the blood-brain barrier. Anesthesiology 1992; 76:426-431.