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Autoregulation of Cerebral Blood Flow during Halothane and Morphine Anesthesia in Dogs

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Abstract The effects of halothane and morphine anesthesia on autoregulation of cerebral blood flow under the conditions of normo-, hypo-, and hypercapnia were studied in eleven dogs. The cerebral blood flow (CBF) from the sagittal sinus was continuously measured by electromagnetic flowmeter. Induced hypertension and hypotension were obtained with intravenous infusion of phenylephrine and blood withdrawal, respectively. In 1.5-per cent end-tidal halothane group at normocapnia (39 mmHg), the mean CBF did not change significantly within a range of mean cerebral perfusion pressure (CPP) from 100 to 138 mmHg, and at hypocapnia (25 mmHg), within mean CPP from 41 to 169 mmHg. At hypercapnia (65 mmHg), change in CPP from 43 to 142 mmHg was accompanied by similar directional change in CBF, resulting in complete loss of autoregulation. In 2-mg/kg morphine group at normocapnia (35 mmHg) and hypocapnia (24 mmHg) the mean CBF remained unchanged, and at hypercapnia (60 mmHg) it was unchanged within mean CPP from 84 to 169 mmHg. These results suggest that cerebral autoregulation is better preserved during morphine anesthesia than halothane, and is ameliorated by hypocapnia and impaired by hypercapnia.

Key Words: Brain; circulation, autoregulation. Anesthetics; halothane, morphine. Circulation; brain, autoregulation, carbon dioxide

Introduction

One of the major goals of anesthetic management is to provid adequate cerebral blood flow consistent with cerebral metabolic demands. During anesthesia arterial blood pressure and carbon dioxide level change either accidentally or intentionally, exceeding physiological range. In normal subjects, cerebral blood flow (CBF) is maintained constant over a wide range of cerebral perfusion pressure (CPP) ; i.e., autoregulation is complete or unimpaired[1]. The autoregulation of CBF changes with the level of $Paco_2$ in the awake brain; it is impaired with hypercapnia, and better maintained with hypocapnia than with normocapnia[2]. However, in anesthetized subjects it has been reported that autoregulation was impaired or preserved depending on anesthetic circumstances and $Paco_2$ levels[3-6]. Miletich et al[5] reported that impaired autoregulation with halothane, known as a cerebral vasodilator, was exaggerated by hypercapnia while it was ameliorated by hypocapnia. The present study was designed to compare the

effects of morphine, known as a cerebral vasoconstrictor, on autoregulation at different $Paco_2$ levels, with those of halothane.

Materials and Methods

Eleven unpremedicated dogs (weight 12–23 kg) were anesthetized with halothane (1.0–2.0 per cent inspired). Succinylcholine (2mg/kg intramuscularly) was given to facilitate tracheal intubation and thereafter to maintain muscular paralysis. Both femoral arteries were cannulated for blood sampling, pressure monitoring, and blood withdrawal, and both femoral veins were cannulated for infusion of drugs and lactated Ringer's solution The surgical preparation used in this study for the measurement of CBF was a venous outflow technique, originally described by Michenfelder et al[7]. After the animal was heparinized by an initial dose of 3mg/kg (1mg/kg/hr, subsequently), cannulation of the sagittal sinus was performed. A suitably sized electromagnetic flowmeter probe with a lumen diameter of 3mm was placed around the cannula 1-cm distal from the site of cannulation. To insure exact measurements, the electromagnetic flowmeter (Nihon Kohden MF-46) incorporated a non occlusive zero and a 1.0-sec time constant, and was frequently calibrated by direct timed measurement of sagittal sinus blood flow. The blood flow from the sagittal sinus was drained through the cannula and directly returned to the facial or mandibular vein. Cerebral venous pressure was measured immediately distal to the electromagnetic flowmeter. The percentage of the total brain weight drained from the sagittal sinus was determined by injecting vinyl acetate at the completion of each experiment and was used to convert units of flow ml/min to ml/100g/min. Cerebral vascular resistance (CVR) was calculated as the ratio of CPP to CBF. CPP was calculated as mean arterial pressure (MAP) minus cerebral venous pressure. After completion of surgery, the dogs were ventilated on 0.2-per cent inspired halothane in oxygen for a one-hour stabilization period. because any possible effects of residual halothane on CBF could be kept constant throughout the study. Ventilation was controlled with a Harvard pump. Pao_2 was maintained at 178±11 mmHg (± SEM) by adjustment of inspired concentration of oxygen. An epidural thermister was placed to monitor the brain temperature, which was maintained at 37± 0.2°C with the aid of an electric heating pad. Hemoglobin levels were maintained at 13±0.8g/dl. Before the study, $Paco_2$ levels were changed from 25 to 55 mmHg and it was verified that CO_2 responsiveness of cerebral blood vessels was intact. Desired $Paco_2$ levels were obtained by changing inspired CO_2 concentration. The dogs were randomly divided into two groups, halothane (five dogs) and morphine (six dogs). In halothane group, halothane concentration was increased to 1.5-per cent end-tidal. The concentration of end-tidal halothane was measured by gas chromatograph. In morphine group, 2mg/kg of the drug was injected for 5 minutes intravenously. CBF measurement started 30 min after increase of halothane or injection of morphine. Hypertension at two different levels was achieved stepwise by increasing MAP with the intravenous infusion of phenylephrine, which has been reported to have no direct effect on cerebral vessels[8]. Hypotension at two different levels was achieved stepwise by withdrawing blood. Autoregulation was tested for CBF which had been stable for at least 2 min after the change in MAP

Table 1 Experimental Conditions at Different $Paco_2$.

$Paco_2$ level	Anesthetic	$Paco_2$ mmHg	Pao_2 mmHg	pH	Hb g/dl	Cerebral epidural temp.°C
Hypocapnia	Halothane	25±2.1*	168±31	7.46±0.02	13±0.4	37±0.2
	Morphine	24±0.4*	207± 7	7.54±0.03*	17±0.5	37±0.2
Normocapnia	Halothane	39±2.8	178±22	7.37±0.02	11±1.2	37±0.4
	Morphine	35±0.6	240±18	7.40±0.02	13±0.5	36±0.2
Hypercapnia	Halothane	65±2.5*	183±20	7.17±0.03*	12±1.5	37±0.3
	Morphine	60±0.8*	210± 6	7.19±0.02*	13±0.6	36±0.2

Mean±SEM, *Significantly different from values at normocapnia ($P<0.05$).

Table 2 Autoregulation during Halothane Anesthesia

Cerebral hemodynamics	Hypotension		Control	Hypertension	
Hypocapnia					
CPP mmHg	41± 5*	81± 3*	99± 3	141± 7*	169± 8*
CBF ml/100g/min	47± 8	64± 9	64± 6	66± 7	77±10
CVR mmHg/ml/100g/min	1.0±.3*	1.4±.2*	1.6±.2	2.3±.3*	2.4±.4*
Normocapnia					
CPP mmHg	44± 6*	74± 4*	100± 4	138± 6*	168±11*
CBF ml/100g/min	51± 5*	69± 7*	79± 8	82±10	104±16*
CVR mmHg/ml/100g/min	1.0±.2*	1.1±.2	1.4±.2	1.8±.3*	1.7±.3
Hypercapnia					
CPP mmHg	43± 2*	77± 1*	93± 2	125± 3*	142±9*
CBF ml/100g/min	63±16*	83±26*	140±25	160±23*	194±28*
CVR mmHg/ml/100g/min	.9±.3	.9±.2	.7±.1	.8±.1	.8±.1

Means±SEM, n=5, *Significantly different from control ($P<0.05$).

Table 3 Autoregulation during Morphine Anesthesia

Cerebral hemodynamics	Hypotension		Control	Hypertension	
Hypocapnia					
CPP mmHg	40± 4*	86± 6*	108± 4	141± 3*	170± 5*
CBF ml/100g/min	47± 4	50± 3	45± 2	48± 5	52± 5
CVR mmHg/ml/100g/min	.9±.1*	1.7±.1*	2.4±.1	3.1±.3	3.5±.4*
Normocapnia					
CPP mmHg	48± 3*	86± 5*	107± 2	145± 3*	176± 4*
CBF ml/100g/min	49± 4	49± 3	53± 4	50± 6	65± 9
CVR mmHg/ml/100g/min	1.1±.2*	1.8±.2	2.1±.2	3.1±.3*	3.0±.4*
Hypercapnia					
CPP mmHg	44± 3*	84± 6*	104± 3	136± 3*	169± 7*
CBF ml/100g/min	53± 5*	107±19	116±23	127±22	136±33
CVR mmHg/ml/100g/min	.9±.1	.9±.1	1.1±.2	1.3±.3*	1.6±.4*

Means±SEM, n=6, *Significantly different from control ($P<0.05$).

At any CPP level three determinations were made for 10 min, and these were averaged to provide the mean CBF for each animal at each CPP. Autoregulation of CBF was measured with dogs at hypo-, normo-, and hypercapnia. MAP and $Paco_2$ levels were randomly manipulated. All data was subjected to unpaired t-test for experimental conditions (table 1), and paired t-test for the autoregulation (table 2, 3), and $P<0.05$ were considered to be significant.

Results

Experimental conditions at different $Paco_2$ levels are shown in Table 1. The mean $Paco_2$, pH Hb, and epidural temperature were not significantly different between halothane and morphine group. The mean CPP, CBF and CVR in halothane and morphine are shown in Tables 2 and 3, respectively. In halothane group at normocapnia, mean

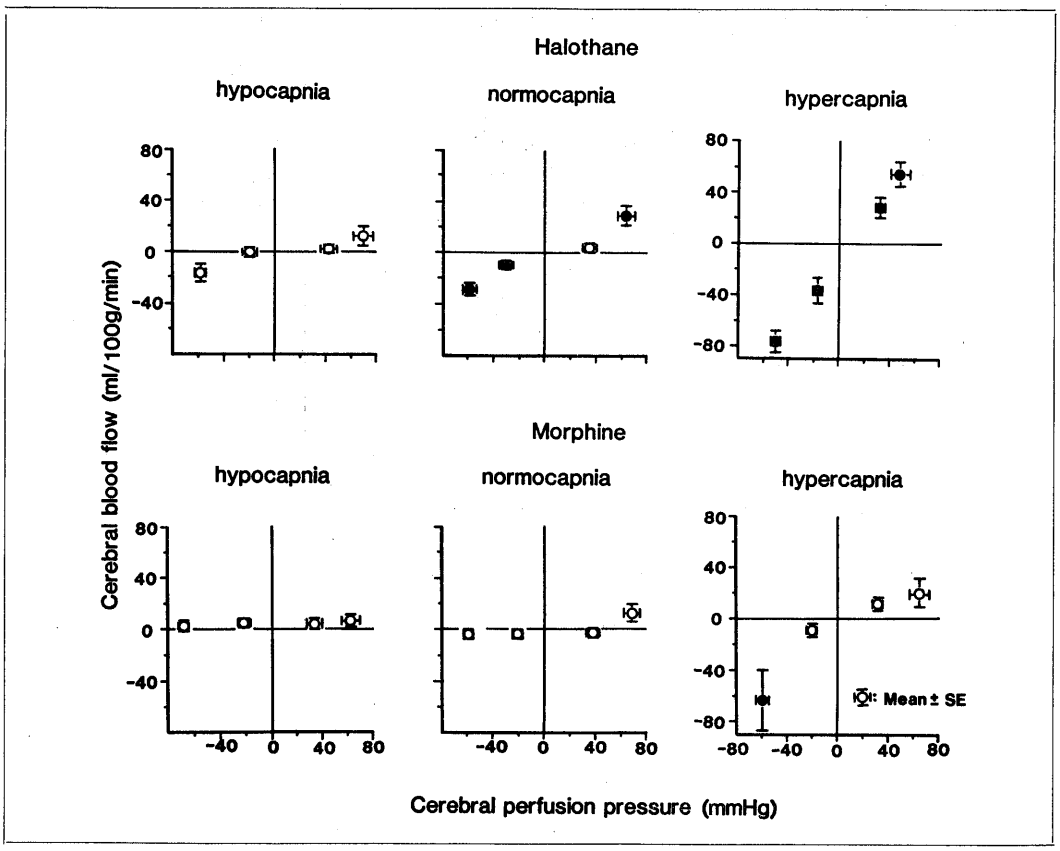

Fig. 1 Autoregulation of CBF during halothane and morphine anesthesia. Mean changes in CBF from control are plotted as a function of mean changes in CPP. Note the linear relationship between CBF and CPP during halothane anesthesia at hypercapnia, and no significant change in CBF despite the change in CPP during halothane and morphine anesthesia at hypocapnia. Closed and open circles indicate significant and insignificant change from control, respectively.

CBF changed significantly from control at mean CPP of 44, 74 and 168 mmHg. At hypocapnia, mean CBF did not change significantly within a range of mean CPP from 41 to 169 mmHg. At hypercapnia, change in CPP was accompanied by directional change similar to that in CBF, resulting in a steep linear relationship, and there was nearly constant CVR over a range of mean CPP from 43 to 142 mmHg. In morphine group, at both normocapnia and hypocapnia, mean CBF remained unchanged. At hypercapnia, mean CBF significantly decreased at CPP of 44 mmHg, but CBF remained unchanged with hypertension. The mean changes in CBF from control in both groups are plotted as a function of changes in CPP to facilitate comparison (Fig. 1).

Discussion

The present study clearly indicates that $Paco_2$ level modifies autoregulation of CBF during halothane or morphine anesthesia. At normocapnia, 1.5 per cent halothane impaired the ability of the cerebral vessels to respond to a decrease in CPP. Morita et al[6]

reported that autoregulation was intact during 0.5 per cent halothane and 66 per cent nitrous oxide anesthesia at CPP ranging from 50 to 100 mmHg, but began to fail at 1.0 per cent halothane, and that complete loss of the autoregulation occurred during 2 per cent halothane and 66 per cent nitrous oxide anesthesia in monkeys. Miletich et al[5] studied the autoregulation during halothane (0.5 and 1 minimum alveolar concentration) anesthesia at normocapnia in the goat and concluded that halothane 1 minimum alveolar concentration abolished autoregulation. Although exact comparison is difficult because of difference of methodology, anesthetic circumstances and species, there were considerable differences between their results and ours. Morita et al[6] plotted per cent control of CBF and CVR as a function of CPP, and control values were obtained during 66 per cent nitrous oxide anesthesia preceding exposure to halothane. We believe that the autoregulation can be measured at a particular level of anesthesia and that a control value must be obtained at the blood pressure level at the specific anesthetic condition. Miletich et al presented their results from data collected for only 1 min after the start of blood pressure change[5], but it should be stressed that autoregulation may not take place instantaneously[9]. In our study, an increase in mean CPP to 138 mmHg did not cause any significant change in CBF, and 32 per cent increase in CBF was observed at 168 mmHg. A decrease in CPP to 74 and 44 mmHg was accompanied by 13 and 35 per cent decrease in CBF, respectively. However it must be added that if 13 per cent decrease in CBF at 74 mmHg is considered as a magnitude of slight impairment of autoregulation, these changes in CBF within a range of CPP from 74 to 138 mmHg may have no clinical significance. It has been well documented that autoregulation of CBF in normal brain can be impaired or lost with hypercapnia, and better preserved with hypocapnia[2,9]. During halothane anesthesia, autoregulation was completely abolished with hypercapnia and was better preserved with hypocapnia. Ekström-Jodal et al[10] studied pressure-flow relationship at different basal flow levels by changing $Paco_2$ and suggested that in vasodilated states the pressure range, within which cerebral blood flow autoregulation against pressure increases is present, becomes gradually narrower. This may be the case during hypertension at hypercapnia in our study. At 60 to 65 mmHg of $Paco_2$, cerebral vessels can dilate almost maximally, and decrease in CPP will result in no further dilatation of cerebral vessels and hence will decrease CBF[2]. However, preexisting vasoconstriction due to hypocapnia was enough to counteract vasodilatation produced by halothane, Miletich et al[5] reported that impaired autoregulation during halothane anesthesia was potentiated by hypercarbia and antagonized by hypocarbia. In our study, autoregulation during halothane at hypocapnia remained intact and was better maintained than normocapnia.

During morphine anesthesia, there was better preservation of autoregulation than during halothane. Jobes et al[4] examined autoregulation during 2 mg/kg morphine and 70 per cent nitrous oxide anesthesia at normocapnia in man, and concluded that with $Paco_2$ constant at 40 mmHg morphine-nitrous oxide anesthesia does not significantly affect autoregulation between 120 and 60 mmHg of MAP. In our study, morphine did not cause any significant change in autoregulation at three different $Paco_2$ except 54 per cent decrease in CBF at 44 mmHg of CPP at hypercapnia. This is in sharp contrast to halothane. Thus, differences between halothane and morphine depend on whether the particular drug dilates or constricts cerebral vessels.

In clinical practice, there may be wide variation of blood pressure during anesthesia either accidentally or incidentally. For better

maintenance of CBF autoregulation during anesthesia, cerebral vasoconstrictor may be preferable to vasodilator. However, patients with pre-existing neurologic disease such as intracerebral hemorrhage or infarction may have altered autoregulation mechanisms and respond differently. Hypocapnia provided better maintenance of autoregulation, but it is known that extreme hypocapnia less than 20 mmHg must be avoided because of possible cerebral hypoxia[1]. The adequacy of cerebral oxygenation must be evaluated not only by the absolute value of CBF but also by metabolic demand. During halothane and morphine anesthesia, metabolic demand of the brain decreases 10 to 20 per cent. Therefore, decrease in CBF produced by hypotension and/or hypocapnia does not necessarily imply inadequate blood flow for oxygen demand, and the present study does not provide information on the critical value of CBF at which cerebral hypoxia may occur. In such circumstance, EEG monitoring, cerebrospinal fluid chemistry, and internal jugular venous oxygen tension would be desirable monitoring for the evaluation of cerebral oxygenation. Increase in CBF during anesthesia at hypercapnia may provide greater oxygen supply to the brain, but it is certainly harmful in patients with low intracranial compliance. In neurosurgical anesthesia, it is essential to keep MAP within narrow physiological range regardless of anesthetic used, and to avoid hypercapnia. In conclusion, autoregulation of CBF is better maintained with morphine than halothane and with hypocapnia than hypercapnia.

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