Original Article

Cerebral responses to sevoflurane-induced hypotension and isovolemic hemodilution

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Abstract

The aim of the present study was to evaluate the hemodynamic and cerebral variables in response to sevoflurane-induced hypotension combined with isovolemic hemodilution in dogs. We divided adult mongrel dogs into no-hemodilution (N) and hemodilution (H) groups. In both groups, baseline measurements were taken with sevoflurane in 60%-nitrous oxide, at a mean areterial pressure of 100 mmHg. Hemodilution was performed by replacing blood (20 m*l*/kg) with isovolemic dextran 70 for the H group animals. The animals in both groups then inspired sevoflurane at a mean arterial pressure of 70 mmHg after adjustment of the vaporizer setting. CI, LV dp/dt max, ICP, CCBF and CMBF values showed significant increases and SVR a significant decrease after hemodilution compared to before hemodilution, but HR, mAP, and PtO_2 did not differ. mAP, CI, LV dp/dt max, CCBF, CMBF, and PtO_2 values showed significant decreases after hypotension compared to before hypotension in both groups. ICP showed a significant decrease in group H, but did not differ in group N. However, after hypotensive induction, ICP did not change significantly compared to the baseline condition in both groups. In addition, PtO_2 significantly decreased during the hypotensive period compared to the baseline condition. ICP, CMBF, and PtO_2 did not differ significantly between groups N and H during the hypotensive period. However, CCBF increased significantly more in group H than in group N. Regardless of whether or not hemodilution had been performed, ICP did not change, but PtO_2 decreased significantly compared to the baseline condition after hypotensive induction by sevoflurane.

These results indicate that anesthesiologists should be attentive to cerebral variables when formed hypotension is induced by sevoflurane in patients undergoing neurosurgery. Similarly it involves using acute normovolemic hemodilution.

key words
hemodilution, hypotensive anesthesia
sevoflurane, cerebral responses

Introduction

When reduction in arterial pressure lessens the risk of vessel rupture, as in the resection or ligation of intracranial aneurysm or tumor, induced hypotension may benefit patients. In addition, acute normovolemic hemodilution combined with retransfusion is one of the various techniques proposed to avoid homologous blood transfusion. Preoperative hemodilution with self blood donation is being used increasingly in combination with controlled hypotension to conserve blood.

Isoflurane is often selected when an inhalation anesthetic is needed during intracranial surgery. The present author reported previously that isoflurane has a satisfactory effect on induced controlled hypotensive drug under hemodilution conditions[1]. Conzen et al. demon-

strated that at a mean arterial pressure of 70 mmHg, both isoflurane and sevoflurane anesthetics changed systemic hemodynamic variables to a similar degree[2].

The objective of the present study was to evaluate systemic hemodynamic and cerebral responses during either a non-hemodilution or a hemodilution state, in order to examine the effect of sevoflurane induced controlled hypotension in sevoflurane-anesthetized dogs.

Materials and Methods

Fourteen adult male mongrel dogs weighing 13 to 18kg were randomly allocated to two groups of animals: a no-hemodilution (N) group, and a hemodilution (H) group. The animals were anesthetized with sodium pentobarbital (30mg/kg i.v.). Pancuronium bromide (0.2mg/kg) was administered after an endotracheal tube had been inserted. The animals were ventilated with 1.8 to 2.8% sevoflurane in 60% nitrous oxide using a Harvard respirator, at a mean arterial pressure (mAP) of 100 mmHg, achieved by adjusting the vaporizer setting. The respiratory tidal volume was adjusted to maintain an end-expiratory $ETCO_2$ of 35～40mmHg, which was monitored with an infrated CO_2 analyzer.

The left femoral vein was cannulated for infusion of lactated Ringer's solution with a maintenance dose of 3ml/kg/h and for withdrawal of blood and volume replacement with plasma substitute. The left femoral artery was cannulated for continuously monitoring the systemic arterial pressure and for blood samplings. The left ventricular pressure (LVP) was monitored with a 7-French pigtail catheter cannulated via the right femoral artery. The maximum rate of the left ventricular pressure change (LV dp/dt max) was measured by electrically deriving the LVP wave using an electronic differentiator. A 7.5-French balloon-tripped triple lumen pulmonary catheter (Swan-Gantz catheter) was inserted via the right femoral vein and its top was positioned in a branch of the pulmonary artery for measurements of hemodynamic variables. Cardiac output (CO) was determined by the thermodilution method using 5ml of 0.9% saline at 0°C injected into the right atrium at the end of expiration. The heart rate (HR) was monitored, using a cardiotachometer, from lead II of an electocardiograph.

Cerebral blood flow (CBF) was determined by the hydrogen gas clearance method. Cerebral tissue oxygen tension (PtO_2) was measured using an oxygen partial digital monitor (Unique Medical, Tokyo, Japan). Craniotomy was performed so that hydrogen gas clearance electrode was inserted into the cortex layer at a 2-mm depth and into the medullary layer at a 6-mm depth. Similarly, oxygen electrode was inserted into the cortex layer at a 2-mm depth. Intracranial pressure (ICP) was determined by the extradural method with an ICP-monitoring catheter (Nihon Kohden, Tokyo, Japan).

The dogs were allowed to stabilize for at least 60 min after surgical procedure (baseline condition), and physiological measurements were taken. Hemodilution was then performed by replacing blood (20ml/kg) with isovolemic dextran (6% in saline, MW=70,000) for the group H animals. After a 30min stabilization period, measurements were obtained. The animals then inspired sevoflurane in 3.5～5.2% concentration at a mAP of 70mmHg after adjustment of the vaporizer setting. Further sets of measurements were then obtained in the hypotensive condition at 30min, 60min and 90 min, respectively. The animals were allowed to recover from the sevoflurane concentration to their pre-hypotensive condition. The final measurements were carried out after 30min.

The following parameters were measured in

the animals of both groups: HR, mAP, CO, LVP, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), ICP, cerebral cortex and cerebral medullary blood flow (CCBF and CMBF), and PtO_2. Cardiac index (CI), systemic vascular resistance (SVR) and LV dp/dt max were calculated using the standard formulas.

Data are expressed as mean±standard error (SE). Comparisons between the baseline or hemodilution values (group H, only) and the experimental measurements in each group were made by Student's paired t-test, with $P<0.05$ considered statistically significant. Differences between groups N and H were analyzed by Student's unpaired t-test. Significance was accepted when $P<0.05$.

Results

Blood hemoglobin (Hb) values did not differ significantly between groups N and H under the baseline condition (12.4±1.5g/d*l* and 12.1±2.0g/d*l*, respectively). In group H, Hb value was reduced by isovolemic hemodilution to 6.8±1.5g/d*l*.

Hemodynamic variables are shown in Table 1. Under the baseline condition, hemodynamic variables did not differ significantly between the two groups. CI and LV dp/dt max significantly increased and SVR significantly decreased after hemodilution compared to the values before hemodilution, but HR and mAP did not change. mAP, CI and LV dp/dt max values significantly decreased after hypotension compared to before hypotension in both groups, but HR and SVR did not change. During the hypotensive and recovery periods, SVR in group H decreased significantly compared with that in group N. LV dp/dt max in group H showed a significant increase compared with that in group N during the recovery period. The other hemodynamic variables, however, did not differ significantly between the 2 groups.

The respiratory variables of PaO_2 and $PaCO_2$ during the baseline condition, did not differ significantly between the two groups: In group N, PaO_2 was 178±11mmHg and $PaCO_2$ was 39±2mmHg, whereas in group H the corresponding values were 173±21 and 38±3mmHg, respectively.

Cerebral variables are shown in Table 2. Under the baseline condition, cerebral variables did not differ significantly between the two groups. ICP, CCBF, and CMBF showed a significant increase when comparing the values before and after hemodilution, but PtO_2 did not differ. After hypotensive induction in group N, a change in ICP was not significant, but CCBF, CMBF, and PtO_2 decreased significantly compared with the baseline condition. During the hypotensive condition in group H, PtO_2 decreased compared with that of the baseline condition, but ICP, CCBF and CMBF did not differ. All cerebral variables showed a significant decrease compared with the values before and after hypotension in group H. During the hypotensive period, CCBF in group N decreased significantly compared with that in group H. The other cerebral variables, however, did not differ significantly between the 2 groups.

Discussion

Suggested benefits of normovolemic hemodilution and autotransfusion include reduced erythrocyte loss, decreased blood viscosity, improved tissue perfusion, and enhanced oxygen delivery to the tissues as a result of lower hematocrit and the availability of fresh whole blood. It is generally agreed that myocardium and brain tissues are favored in the redistribution of cardiac output during hemodilution. Messmer et al. reported that local oxygenation of the myocardium and brain tissue remained in

Table 1. Hemodynamic variables in response to hemodilution and hypotension, respectively

	Group	Baseline	HD	30HP	60HP	90HP	Recovery
HR	N	142±8		135±7	133±6	133±6	138±5
	H	137±6	140±6	134±8	134±9	132±9	141±10
mAP	N	102±1		70±1[a]	70±1[a]	70±1[a]	101±2
	H	102±2	101±2	69±1[ab]	70±1[ab]	70±1[ab]	96±3
CI	N	1.8±0.1		1.2±0.1[a]	1.2±0.1[a]	1.2±0.1[a]	1.7±0.1
	H	1.7±0.1	2.0±0.1[a]	1.4±0.1[b]	1.3±0.1[b]	1.2±0.1[b]	1.8±0.1
SVR	N	6510±237		6491±487[c]	6583±534[c]	6597±556[c]	6517±215[c]
	H	6777±581	4802±283[a]	4793±608[a]	5021±472[a]	5277±490[a]	4912±220[a]
LVdp/dt max	N	1667±153		1011± 61[a]	1078± 75[a]	1011± 51[a]	1633±113[c]
	H	1729±71	2114±124[a]	1186±122[ab]	1200±136[ab]	1229±119	2100±184[a]

(n=7)
Data are expressed as mean ± standard error (SE)
HR: heart rate (beats·min^{-1}); mAP: mean arterial pressure (mmHg); CI: cardiac index (l·min^{-1}·m^{-2}); SVR: systemic vascular resistance (dyn·sec·cm^{-5}); LV dp/dt max: maximum rate of left ventricular pressure change (mmHg·sec^{-1})
N: no-hemodilution group, H: hemodilution group
Baseline: baseline condition, HD: 30 minutes after hemodilution, 30HP, 60HP, and 90HP: 30, 60, and 90 minutes after hypotension, Recovery: 30 minutes after cessation of hypotensive procedure
[a]$P<0.05$: from Baseline
[b]$P<0.05$: from HD
[c]$P<0.05$: between group N and H

Table 2. Cerebral variables in response to hemodilution and hypotension, respectively

		Control	HD	30HP	60HP	90HP	Recovery
ICP	N	16±1		15±1	15±1	15±1	17±1
	H	16±1	20±2[a]	17±1[b]	17±2[b]	16±2[b]	19±2[a]
CCBF	N	52±1		47±1[ac]	47±1[ac]	47±1[ac]	52±1
	H	53±3	57±3[a]	54±3[b]	53±3[b]	53±3[b]	56±3[a]
CMBF	N	33±1		30±1[a]	30±1[a]	30±1[a]	32±1
	H	31±1	34±1[a]	31±1[b]	31±1[b]	30±1[b]	32±1
PtO_2	N	51±1		42±3[a]	41±3[a]	39±4[a]	48±1
	H	51±1	48±3	41±2[ab]	41±2[ab]	40±2[ab]	48±3

(n=7)
Data are expressed as mean ± standard error (SE)
ICP: intracranial pressure (mmHg); CCBF: cerebral cortex blood flow (ml·min^{-1}·100g^{-1}); CMBF: cerebra medullary blood flow (ml·min^{-1}·100g^{-1}); PtO_2: cerebral tissue oxygen tension (mmHg)
N: no-hemodilution group, H: hemodilution group
Baseline: baseline condition, HD: 30 minutes after hemodilution, 30HP, 60HP, and 90HP: 30, 60, and 90 minutes after hypotension, Recovery: 30 minutes after cessation of hypotensive procedure
[a]$P<0.05$: from Baseline
[b]$P<0.05$: from HD
[c]$P<0.05$: between group N and H

the normal range during normovolemic hemodilution[3]. Oxygen supply to tissues is maintained following hemodilution by an increased cardiac output and by an increased oxygen extraction from blood. In other words, local tissue hypoxia does not develop despite the decrease in oxygen capacity of the blood by normovolemic hemodilution within physiological compensatory fluctuations. This paper shows that CI, CCBF and CMBF during hemodilution in group H increased significantly compared with that baseline condition values. However, PtO_2 did not differ.

Acute isovolemic hemodilution is used increasingly in combination with induced controlled hypotension as a method of blood conservation. Controlled hypotension may be indicated to decrease transmural pressure across the aneurysm and reduce the risk of rupture during at neurosurgical operations. However, in all forms of controlled hypotension, the risk of cerebral hypoxia owing to

hypoperfusion must be recognized. Inhalation anesthetics in common use produce cerebral vasodilatation and increase cerebral blood flow, but at equianesthetic doses, halothane increases CBF the most. Patients with decreased compliance may develop marked increases in ICP during cerebral vasodilatation, which increases cerebral blood volume. Takahashi et al. showed that ICP increased significantly with 0.5～1.5MAC enflurane and halothane, but not with sevoflurane at any anesthetic concentration[4]. Artru et al. demonstrated that sevoflurane decreased middle cerebral artery flow velocity and caused no epileptiform electroencephalogram activity and no increase to intracranial pressure[5]. Moreover, some investigators have reported that isoflurane is a less potent cerebral vasodilator compared to enflurane or halothane, and prefer it for patients as there is a risk of increased ICP with the latter two[6,7]. With regard to cerebral variables, Scheller et al. found that the effects of sevoflurane on cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRO_2$), ICP and EEG were similar to those of isoflurane[8,9].

Newman demonstrated that CBF is maintained and that the cerebral oxygen supply-demand balance is favorably influenced during isoflurane-induced hypotension[10]. Similarly, Newberg et al. demonstrated that isoflurane produced a significant decrease in cerebral oxygen consumption accompanied by a decrease in CBF and provided protection in circumstances currently cited as appropriate for barbiturate therapy[11,12]. In the present study, after hypotensive induction by sevoflurane, CCBF and CMBF decreased significantly in the 2 groups. For some unknown reason, PtO_2 showed a significant decrease. Moreover, after hypotensive induction in group N, ICP did not change significantly. The present author reported previously that ICP and CBF significantly decreased after isoflurane induced hypotension compared to before isoflurane induced hypotension, regardless of whether or not there was hemodilution[1]. However, PtO_2 did not differ significantly. As a result, hypotensive anesthesia using isoflurane is more effective than sevoflurane regardless of the presence or not of hemodilution.

These findings suggest that anesthesiologists should be attentive to cerebral variables when hypotension is induced by sevoflurane in patients undergoing neurosurgery. Similarly it involves using acute normovolemic hemodilution.

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