Original Article

Cerebral responses to isoflurane induced hypotension and isovolemic hemodilution in isoflurane anesthetized dogs

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Abstract

The aim of the present study was to evaluate the hemodynamic and cerebral variables, in the responses to isoflurane induced hypotension combined with isovolemic hemodilution in dogs. We divided adult mongrel dogs into no-hemodilution (N) and hemodilution (H) groups. In both the groups, control measurements were taken with isoflurane 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 isoflurane at a mean arterial pressure of 70 mmHg by adjustment the vaporizer setting. CI, LV dp/dt max, ICP, and CBF showed significant increases and SVR a significant decrease when comparing the values before and after hemodilution, but HR, mAP, and PtO_2 did not differ. mAP, CI, LV dp/dt max, ICP, and CBF showed significant decrease when comparing the values before and after the induced hypotension in both groups. During the hypotensive period, ICP, CBF, and PtO_2 did not differ significantly between groups N and H. PtO_2 did not differ significantly during all experimental periods in both groups.

These results indicate that, when conbined with hemodilution, isoflurnce acted as a hypotensive agent, at least regarding the cerebral variables.

Introduction

Induced hypotensions is widely used during anesthesia for cerebral aneurysm surgery to reduce the risk of rupture and to facilitate the clipping of the aneurysm. In addition, intraoperative phlebotomy and normovolemic hemodilution is one of the techniques widely used in the prectice on the critical concept of avoiding homologous blood transfusion. It is generally known that inhalation anesthetics produces dose-dependent increases in cerebral blood flow (CBF) and decreases in cerebral oxygen metabolic rate ($CMRO_2$). Isoflurane is often selected when an inhalation anesthetic is needed during intracranial surgery.

The aim of this study was to assess its hypotensive action in neurosurgery, either under no-hemodilution or hemodilution conditions, in order to examine the effect of isoflurane induced controlled hypotension on the cerebral response.

Materials and Methods

Fourteen adult male mongrel dogs weighing from 12 to 17 kg were randomly allocated to 2 groups of animals: a no-hemodilution (N) group, and a hemodilution (H) group. The animals were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Pancuronium

bromide (0.2mg/kg) was administered after an endotracheal tube had been inserted. The animals were ventilated with 1.2 to 2.0% isoflurane in 60% nitrous oxide using a Harvard respirator, at a mean arterial pressure (mAP) of 100mmHg, achieved by adjusting the vaporizer setting. The respiratory tidal volume was adjusted to maintain an end-expiratory $ETCO_2$ of 35～40 mmHg, 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 5 ml 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). Intracranial pressure (ICP) was determined by the extradural method with an ICP-monitoring catheter (Nihon Kohden, Tokyo, Japan). Craniotomy was performed so that hydrogen gas clearance electrodes and an oxygen electrode was inserted into the cerebral cortex layer at a 2-mm depth.

The dogs were allowed to stabilize for at least 60min after surgical procedure (control condition), and physiological measurements were conducted. 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 30 min stabilization period, measurements were obtained. The animals then inspired isoflurane in 2.5～3.6% concentration at a mAP of 70 mmHg by adjusting the vaporizer setting. Further sets of measurements were then obtained in the hypotensive condition at 30min, 60min and 90min, respectively. The animals were allowed to recover from the isoflurane concentration with return to the 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, CBF 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 control 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 $P<0.05$.

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

		Control	HD	30HP	60HP	90HP	Recovery
HR	N	134±6		124±6	125±5	125±4	131±4
	H	133±5	140±5	133±4	133±5	134±5	142±8
mAP	N	101±1		70±1[a]	69±1[a]	70±1[a]	101±1
	H	100±1	100±1	70±1[ab]	69±1[ab]	70±1[ab]	96±4
CI	N	1.9±0.1		1.2±0.1[a]	1.2±0.1[a]	1.2±0.1[a]	1.8±0.1
	H	1.9±0.3	2.4±0.5[a]	1.6±0.3[ab]	1.5±0.2[ab]	1.5±0.2[ab]	1.9±0.3
SVR	N	5782±266		6150±422[c]	6030±376[c]	6337±479[c]	5939±353
	H	5756±917	4632±709[a]	4187±547[a]	4516±582[a]	4793±593[a]	5578±828
LVdp/dt max	N	1838±226		1025±139[a]	1038±119[a]	1063±119[a]	1788±253
	H	1729±221	2014±293[a]	1300±223[ab]	1286±229[ab]	1386±247[ab]	1886±220

(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
Control: control condition, HD: 30 min after hemodilution, 30HP, 60HP, and 90HP: 30, 60, and 90 min after hypotension, Recovery: 30 min after cessation of hypotensive procedure
[a] $P<0.05$: from Control
[b] $P<0.05$: from HD
[c] $P<0.05$: between group N and H

Results

Blood hemoglobin (Hb) values did not differ significantly between groups N and H under the control condition (13.2 ± 1.5g/d*l* and 12.7 ± 1.2g/d*l*, respectively). In group H, Hb value was reduced by isovolemic hemodilution to 7.8 ± 0.5 g/d*l*.

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

The respiratory variables of PaO_2 and $PaCO_2$ during the control condition, did not differ significantly between the two groups: In group N, PaO_2 was 177 ± 26mmHg and $PaCO_2$ was 38 ± 3mmHg, whereas in group H the corresponding values were 166 ± 30 and 37 ± 2 mmHg, respectively.

Cerebral variables are shown in Table 2. Under the control condition, cerebral variables did not differ significantly between the two groups. ICP and CBF showed a significant increase when comparing the values before and after hemodilution, but PtO_2 did not differ. ICP and CBF showed a significant decrease when comparing the values before and after the induced hypotension in both groups. Particularly, after induction of hypotension during the hemodilution, ICP decreased significantly as compared with control condition. During the hypotensive period, none of the cerebral variables differed significnatly between group N and H. On the other hand, PtO_2 did not differ significantly during all experimental periods in both groups.

Discussion

Cerebral blood flow varies regionally in

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

		Control	HD	30HP	60HP	90HP	Recovery
ICP	N	16±1		14±1[a]	14±1[a]	13±1[a]	16±1
	H	16±2	18±2[a]	14±2[ab]	14±2[ab]	13±2[ab]	16±2
CBF	N	43±1		39±1[a]	39±1[a]	39±1[a]	43±1
	H	45±2	48±3[a]	43±2[b]	42±2[b]	43±2[b]	47±2
PtO_2	N	52±3		50±3	46±8	47±9	51±3
	H	51±9	51±10	49±10	49±10	47±9	53±10

(n=7)

Data are expressed as mean ± standard error (SE)

ICP: intracranial pressure (mmHg); CBF: cerebral blood flow ($ml \cdot min^{-1} \cdot 100g^{-1}$); PtO_2: cerebral tissue oxygen tension (mmHg)

N: no-hemodilution group, H: hemodilution group

Control: control condition, HD: 30 min after hemodilution, 30HP, 60HP, and 90HP: 30, 60, and 90 min after hypotension, Recovery: 30 min after cessation of hypotensive procedure

[a] $P<0.05$: from Control

[b] $P<0.05$: from HD

response to change in cellular metabolic activity. Inhalation anesthetics produce cerebral vasodiltation and increase in CBF. However, isoflurane decreases cerebral metabolism to a greater extent than do halothane or enflurane. Compkin[1] has reported that isoflurane is the least potent cerebral vasodilator compared with enflurane or halothane and thus has the least effect on ICP. As a result, Artru[2] suggested that isoflurane may perferable to halothane or enflurane for patients as risk due to increased ICP. As regards cerebral effects, it has been reported that cerebral effects of sevoflurane are similar to those of isoflurane[3~5].

The ideal hypotensive anesthesia should be easy to control, be nontoxic, have a short biological half-life, and should not significantly alter vital orgen perfusion. The ganglionic blocker trimethaphan is often used to control blood pressure in the neurosurgical patient because it does not increase CBF or ICP. However, it has been reported that administration of trimethaphan causes a decrease in regional blood flows[6,7]. Sodium nitroprusside, a drug that has already found wide acceptance in hypotensive anesthesia, dilates cerebral blood vessels while increasing intracranial blood volume. Macnab et al.[8] reported that isoflurane anesthesia with isoflurane induced hypotension, unlike halothane anesthesia with sodium nitroprusside induced hypotension, attenuates the stress response to induced hypotension allowing good control of arterial pressure and heart rate without rebound hypertension. In the present study, ICP and CBF decreased significanly by isoflurane induced hypotension under no hemodilution condition, but PtO_2 did not differ. Similarly, some investigators[9,10] have suggested that cerebral oxygen consumption is decreased and the cerebral oxygen supply-demand balance is favorably influenced during isoflurane induced hypotension.

This study was carried out in order to find out whether isoflurane has a beneficial effect on hypotensive drug use under hemodilution conditions. The basic mechanism that compensates for the fall of oxygen capacity of the diluted blood is due to a rise cardiac output and organ blood flow. In particular, cerebral blood flow appeared to be more affected than flow to the splanchnic organs by hemodilution. In the present study, ICP and CBF were increased significantly by hemodilution. However, it is noteworthy that ICP and CBF during hemodilution combined with hypotension decreased significantly as compared with the corresponding values in the control condition. In addition,

ICP, CBF, and PtO_2 did not differ significantly between groups N and H during isoflurane induced hypotension. This fundametal study in animals has shown that isoflurane as a hypotensive drug acts on the cerebral variables during the hemodilution condition.

Newberg et al.[11] assumed that cerebral metabolic depression without toxicity provides to brain protection. A clinical use of isoflurane is that of cerebral portection in the circumstances currently cited as appropriate for barbiturate therapy. On the contrary, Drummond et al.[12] have reported that the volume of injured brain in isoflurane is significantly larger than that in thiopental anesthesia.

It is generally knowledge that a given concentration of inspired anesthetic suppresses cardiac function in a dose-dependent manner. In our present study, mAP, CI, and LV dp/dt max, after isoflurane induced hypotension, decreased significantly as compared with control condition in both groups. With regard to hemodynamic variables, Schou et al.[13] suggested that isoflurane - induced cardiovascular depression had adverse effects on cardiac output and oxygen delivery during extreme hemodilution, because isoflurane was insufficient to compensate for the myocardial depression. The author[14] reported previously that a more remarkable reduction in the coronary blood flow and oxygen tension of the left ventricular myocardium was seen during hemodilution with an increase in the concentration of inhalated isoflurane. In addition, a decrease in these cardiac variables produced delivery-dependent oxygen consumption and myocardial ischemia. Further detailed studies must be made on hypotensive drugs under hemodilution conditions.

The findings of the present study suggest that when combined with hemodilution, isoflurane acts as a hypotensive agent, at least regarding the cerebral variables.

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