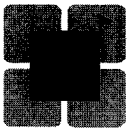

Local cortical blood flow and oxygen consumption during isoflurane-induced hypotension

Results in patients undergoing intracranial aneurysm clipping

STEVEN ROTH, MD; STEPHEN C. JONES, PHD; ZEYD Y. EBRAHIM, MD; HARRY FRIEL, MS; JOHN R. LITTLE, MD

■ Cerebral cortical blood flow (lCoBF) and metabolic rate for oxygen ($lCoMRO_2$) were studied in eight patients undergoing intracranial aneurysm clipping. The patients were anesthetized with fentanyl 10 μg/kg and 70% nitrous oxide combined with 30% oxygen. Hypotension was induced with isoflurane. A thermal diffusion probe was used to measure lCoBF, and arterial and cerebral venous blood samples were obtained for measurement of arterio-cerebral venous O_2 content difference. Measurements were made prior to hypotension, during hypotension (to mean arterial pressure approximately 50 mmHg), and posthypotension. Mean lCoBF decreased from 69 ± 20 mL/100 g/min at normotension to 59 ± 13 mL/100 g/min during hypotension ($P < .03$, NS) and was 61 ± 18 mL/100 g/min upon return to normotension (all values mean ± 1 SD). The $lCoMRO_2$ averaged 3.9 ± 1.6 mL/100 g/min and 3.1 ± 1.5 mL/100 g/min, respectively ($P < .03$, NS) for normotension *v* hypotension. Values for cerebral venous PO_2 and O_2 saturation also did not differ significantly between study periods. These results indicate that isoflurane-induced hypotension during fentanyl-nitrous oxide anesthesia allows maintenance of a constant lCoBF and oxygen delivery.

□ INDEX TERMS: CEREBRAL ANEURYSM; ISOFLURANE □ CLEVE CLIN J MED 1989; 56:766–770

DURING surgical obliteration of an intracranial aneurysm, induced hypotension is frequently employed at critical times to decrease the risk of aneurysm rupture. Isoflurane has been used to induce hypotension in both animals and humans.[1–3] Its advantages include hemodynamic stability, minimal metabolism with no known toxic metabolites,[4] and rapid onset of and recovery from hypotension.

Fentanyl-nitrous oxide-relaxant anesthesia is commonly employed during neurosurgical procedures, because fentanyl has no adverse effect on cerebral autoregulation[5] or CO_2 reactivity,[5] and it decreases the incidence of arrhythmias when epinephrine-containing local anesthetics are used.[6] We evaluated local cortical blood flow (lCoBF) and local cortical metabolic rate for oxygen ($lCoMRO_2$) during isoflurane-induced hypoten-

From the Departments of General Anesthesia (S.R., Z.Y.E.), Cerebrovascular Research Laboratory (S.C.J., H.F.), and Neurosurgery (J.R.L.), The Cleveland Clinic Foundation. Submitted Aug 1988; revision accepted Aug 1989. Dr. Roth is currently on staff at the Department of Anesthesia and Critical Care, The University of Chicago Hospitals and Clinics.

Address reprint requests to Z.Y.E., Department of General Anesthesia, Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

TABLE 1
CLINICAL INFORMATION

Patient no.	Age (yr)	Artery	Grade	Recent SAH?	Other history
1	56	Ant comm	I	No	
2	53	L ant cerebral	III	14 days preoperatively	
3	60	Basilar	I	No	Aneurysm rupture during clipping
4	62	R middle cerebral	I	No	
5	58	R internal cartoid	II	No	
6	33	L post cerebral	0	No	
7	60	R internal carotid	0	No	
8	51	L middle cerebral	I	No	

SAH = subarachnoid hemorrhage; *ant* = anterior; *comm* = commisural; *L* = left; *R* = right.

sion in patients anesthetized with fentanyl and nitrous oxide who were undergoing clipping of an intracranial aneurysm.

METHODS

Eight adults (seven women, one man) undergoing intracranial aneurysm clipping gave written consent to a protocol approved by the Institutional Review Board of the Cleveland Clinic Foundation. Two patients were Hunt and Hess[7] Grade 0, four were Grade I, one patient was Grade II, and the other was Grade III (*Table 1*). One patient had sustained recent subarachnoid hemorrhage, 14 days before operation. Other patients either had not bled from their aneurysms or the hemorrhage had occurred months previously. Patients with cardiovascular, hepatic, renal, or pulmonary disease were not included in the study. Patients received diazepam, 10 mg orally one hour before transport to the operating room. Anesthesia was induced with thiopental 4–5 mg/kg and fentanyl 10 μg/kg. When a stable blood pressure was attained, lidocaine 100 mg and pancuronium 0.1 mg/kg were administered and endotracheal intubation was performed. Anesthesia was maintained with nitrous oxide 70%, oxygen 30%, and isoflurane approximately 0.4% end-tidal as measured by mass spectrometry. The patients were given mechanical ventilation to a $PaCO_2$ between 35 and 40 mmHg. Temperature was maintained within ±1°C of the temperature at the beginning of anesthesia by using heating blankets and a cascade humidifier, or low fresh gas flow rates. All operations were performed with patients in the supine position. Patients were monitored with ECG, radial arterial catheter, end-tidal CO_2, mass spectrometer (Perkin-Elmer Advantage®), esophageal temperature, and a central venous catheter. Pressure transducers (Gould) were zeroed at the level of the right atrium and all waveforms were recorded continuously using a Hewlett-Packard E for M monitor.

After the dura was opened, prior to dissection of the aneurysm, a flow probe (Flowtronics Thermal Diffusion Cerebral Blood Flow Monitor, Flowtronics, Inc., Phoenix, AZ 85019) was placed on the surface of the middle frontal gyrus. The lCoBF was measured using a thermal diffusion technique as previously described.[8–11] The probe was gently held in place with cottonoids or by placement just under the dura. Following a 10-minute stabilization period, lCoBF measurements were made under baseline (normotensive) conditions. The lCoBF measurements did not vary by more than 5% over a 5-minute period, and the average value was recorded. Simultaneous heparinized blood samples were obtained from the arterial catheter and from a cerebral cortical vein adjacent to the flow probe. Analysis of PO_2, PCO_2, and pH was performed with an IL BGM 1312 Blood Gas Analyzer, and oxyhemoglobin saturation with an IL Co-Oximeter 282. Blood gas data were not corrected for temperature. Following completion of baseline measurements, we decreased mean arterial pressure (MAP) to 40–50 mmHg by increasing the end-tidal isoflurane concentration. After 15 minutes at a stable blood pressure, all measurements were repeated. Blood pressure was then returned to baseline value by decreasing the concentration of isoflurane; after a 15-minute stabilization period, the measurements were repeated. No surgical stimulation occurred during the study period. Subsequently, the aneurysm was clipped under hypotensive conditions induced with isoflurane. Patients were monitored postoperatively in the neurosurgical intensive care unit.

Arterial and venous oxygen contents were calculated as:

TABLE 2
CHANGES IN LOCAL CORTICAL BLOOD FLOW AND METABOLISM BEFORE, DURING AND AFTER ISOFLURANE-INDUCED HYPOTENSION (MEAN ± SD)

	Prehypotension	Hypotension	Posthypotension
MAP (mmHg)	83 ± 9	48 ± 5†	79 ± 5
Arterial PCO_2 (mmHg)	40 ± 4	40 ± 4	37 ± 4§
lCoBF (mL/100g/min)	69 ± 20	59 ± 13	61 ± 18
$lCoMRO_2$ (mL/100g/min) x 0.01	3.9 ± 1.6	3.1 ± 1.5	3.4 ± 1.5
AV O_2 difference* (mL/100mL)	5.7 ± 1.9	5.2 ± 1.7	5.7 ± 2.2
Cerebral venous PO_2 (mmHg)	38 ± 9	37 ± 7	36 ± 8
Cerebral venous oxygen saturation (%)	63 ± 10	64 ± 11	61 ± 12
Isoflurane concentration (% end-tidal)	0.5 ± 0.2	1.56 ± .63‡	0.35 ± .24

* Arterial-cerebral venous O_2 content difference.
† $p < .001$ compared to values pre- and posthypotension.
‡ $p < .002$ compared to values pre- and posthypotension.
§ $p < .003$ compared to value at prehypotension.
All other differences not significant.

TABLE 3
LOCAL CORTICAL BLOOD FLOW, METABOLIC RATE, AND CEREBRAL VENOUS PO_2 WITH CHANGES IN MEAN ARTERIAL PRESSURE

	Prehypotension					Hypotension					Posthypotension				
Patient no.	MAP (mmHg)	Isoflurane (% end-tidal)	CBF (mL/100g/min)	CMR O_2 (mL/100g/min)	$CVPO_2$* (mmHg)	MAP (mmHg)	Isoflurane (% end-tidal)	CBF (mL/100g/min)	CMR O_2 (mL/100g/min)	$CVPO_2$* (mmHg)	MAP (mmHg)	Isoflurane (% end-tidal)	CBF (mL/100g/min)	CMR O_2 (mL/100g/min)	$CVPO_2$* (mmHg)
1	92	0.17	78	4.3	40	37	1.53	55	3.1	37	80	0	76	4.3	35
2	97	0.22	70	2.8	41	48	0.94	70	2.7	42	82	0.29	60	2.9	36
3	75	0.40	48	3.5	26	45	1.10	48	2.7	31	71	0.40	50	2.9	31
4	72	0.72	74	2.0	53	48	1.75	59	1.5	48	73	0.74	73	2.6	45
5	82	0.60	88	6.3	37	50	1.20	76	4.9	33	84	0.40	84	6.0	30
6	73	0.55	41	2.0	40	55	2.85	45	1.7	44	79	0.53	44	1.4	49
7	80	0.83	53	4.5	27	48	1.93	43	2.4	37	81	0.17	38	3.6	25
8	90	0.53	97	5.5	38	50	1.14	74	5.9	26	N/A	N/A	N/A	N/A	N/A

*Cerebral venous PO_2.

[(% arterial or venous oxygen saturation/100) × hemoglobin concentration (g/100 mL) × 1.34 mL/g] + 0.003 mL/100 mL/mmHg × PO_2 (mmHg)

(The units of oxygen content are thus mL/100 mL.) Arteriovenous oxygen content difference (AV O_2 difference) was calculated as arterial oxygen content minus venous oxygen content. The $lCoMRO_2$ was calculated as the product of lCoBF and AV O_2 difference multiplied by 0.01. Means of the different variables at hypotensive and normotensive conditions were compared using a paired t-test. To adjust for multiple comparisons, a Bonferroni correction was made. Since three comparisons were made (normotension to hypotension, hypotension to posthypotension, and normotension to posthypotension), the value for statistical significance was set at $P < .05/3$, or $P < .016$.

RESULTS

No complications were attributable to the anesthetic technique, controlled hypotension, or the flow probe. Neurological outcome was excellent in seven patients. One patient sustained residual neurological deficits following intraoperative aneurysm rupture, which occurred after the study period during an attempt to clip the aneurysm. Complete data for normotension, hypotension, and return to normotension were obtained in all patients except one, where time constraints did not allow data collection after return to normotensive status. The results are presented in *Tables 2* and *3*.

Hypotension was induced over an average of eight minutes. The mean (± 1 SD) end-tidal isoflurane concentration was 0.50 ± 0.23% during normotension, 1.56 ± 0.63% during hypotension, and 0.35 ± 0.24% upon return to normotension. Mean lCoBF decreased from 69 ± 20 mL/100 g/min at normotension to 59 ± 13 mL/100 g/min during hypotension, but this change did not achieve statistical significance ($P < .03$). Upon return to normotension, lCoBF increased to 61 ± 18 mL/100 g/min. Mean $lCoMRO_2$ also decreased from 3.9 ± 1.6 mL/100 g/min at normotension to 3.1 ± 1.5 mL/100 g/min during hypotension, but this difference was not statistically significant ($P < .03$). There was an increase in mean $lCoMRO_2$ upon return to normotension (3.4 ± 1.5 mL/100 g/min), but the difference from the mean value at hypotension was not significant ($P < .03$). The MAP decreased from 83 ± 9 mmHg during normotension, to 48 ± 5 mmHg during hypotension, and was returned to 79 ± 5 mmHg. There were no statistically significant differences among the values for AV O_2 difference, cerebral venous oxygen tension, or cerebral venous oxygen saturation during prehypotension, hypotension, and posthypotension. Mean arterial PCO_2 was 40 ± 4 mmHg at normotension and 37 ± 4 mmHg upon later return to normotension, and that difference was statistically significant ($P < .003$), although probably not of a degree to be clinically significant.

DISCUSSION

Isoflurane produced rapid decreases in arterial pressure, a phenomenon that has also been documented by others.[3,12] The desired level of hypotension was easily maintained by adjusting the inspired concentration, and the hypotension was rapidly reversed by decreasing the isoflurane concentration.

The technique used to measure lCoBF has been described previously.[11] The cortical surface is in contact with the probe and the temperature gradient of the probe can be detected to a depth of 4 mm, the thickness of the probe. The lCoBF values therefore are assumed to reflect gray matter flow. Our baseline blood flow measurement (69 ± 20 mL/100 g/min) agrees with previously reported regional determinations of lCoBF, and is similar to the reports of Eintrei et al[13] of isoflurane-nitrous oxide-fentanyl anesthesia using a regional Xe-133 cerebral blood flow (CBF) measurement technique in humans. The thermal diffusion probe provides a continuous recording of lCoBF and it can accurately measure flow at ischemic levels. It has been safely used in humans without complication.

We obtained blood samples from a cerebral cortical vein to measure differences in cerebral arterial-venous oxygen content. This vessel was, in all cases, situated close to the blood flow probe, and therefore our AVO_2 difference and $lCoMRO_2$ values are considered regional determinations. Consequently, our results may differ somewhat from those using global measurements. Eintrei et al[13] also utilized a regional measurement of CBF, with similar baseline lCoBF values, and showed no change in CBF with 1.5% end-tidal isoflurane. Murphy et al[14] and Newman et al[12] report similar findings. However, the findings differ with regard to the effects of isoflurane on $CMRO_2$. Our study indicates a decrease in $lCoMRO_2$ that did not reach significance. Newman et al[12] showed that isoflurane-induced hypotension (2.3 ± 1.0% inspired for at least one hour) with a MAP of 51 ± 7 mmHg produced a 25% decrease in $CMRO_2$. These results agreed with those of Newberg et al[1] in dogs and Van Aken et al[2] in baboons. In contrast, and similar to our data, Hickey et al[15] found no change in CBF or global $CMRO_2$ in dogs with up to 30 min of isoflurane-induced hypotension.

Several reasons may account for differences in our $CMRO_2$ findings. Although the lCoBF probe was located close to the vessel used to sample venous blood, it is possible that the blood samples were contaminated with blood from areas with differing metabolic rates. This could also in part explain our inability to demonstrate a difference in values for $lCoMRO_2$ between hypotensive and nonhypotensive periods. Therefore the possibility of a type II statistical error cannot be entirely excluded. In addition, end-tidal isoflurane concentrations of 1.5 ± 0.6% were lower than those reported to cause decreases in global $CMRO_2$ in humans and dogs. Furthermore, like Hickey et al,[15] we produced hypotension for a much briefer time (15 minutes) than that reported by either Newberg et al[1] or Newman et al,[12] where hypotension was sustained for at least one hour.

One of our patients (Patient 2, *Table 1*) was operated on two weeks following a subarachnoid hemorrhage, and showed no change in lCoBF during hypotension and a decrease in lCoBF upon return to normotension. There was no change in $lCoMRO_2$. These changes suggest disturbed autoregulation following recent subarachnoid hemorrhage, a finding that has been reported previously in animals and humans.[16,17] Therefore, our results may also have been influenced by this possibly abnormal autoregulatory behavior in this particular patient.

In conclusion, we induced hypotension rapidly with isoflurane during fentanyl-nitrous oxide anesthesia for a relatively brief period. During that time, lCoBF,

lCoMRO$_2$, and cerebral venous oxygen tension did not change appreciably. We therefore were unable to demonstrate differences in lCoBF, lCoMRO$_2$, and cerebral venous oxygen tension between hypotensive and nonhypotensive periods. These data are consistent with the concept that isoflurane-induced hypotension is safe during cerebral aneurysm clipping.

REFERENCES

1. Newberg LA, Milde JH, Michenfelder JD. Systemic and cerebral effects of isoflurane-induced hypotension in dogs. Anesthesiology 1984; **60:**541–546.
2. Van Aken H, Fitch W, Graham DI, Brüssel T, Themann H. Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon. Anesth Analg 1986; **65:**565–574.
3. Lam AM, Gelb AW. Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 1983; **62:**742–748.
4. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975; **43:**325–332.
5. McPherson RW, Traystman RJ. Fentanyl and cerebral vascular responsivity in dogs. Anesthesiology 1984; **60:**180–186.
6. Murphy MR, Olson WA, Hug CC Jr. Pharmacokinetics of ^{3}H-fentanyl in the dog anesthetized with enflurane. Anesthesiology 1979; **50:**13–19.
7. Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J Neurosurg 1968; **28:**14–19.
8. Barnett GH, Little JR, Ebrahim ZY, Jones SC, Friel HT. Cerebral circulation during arteriovenous malformation operation. Neurosurgery 1987; **20:**836–842.
9. Carter LP, White WL, Atkinson JR. Regional cortical blood flow at craniotomy. Neurosurgery 1978; **2:**223–229.
10. Carter LP, Crowell RM, Sonntag VKH, Spetzler RF. Cortical blood flow during extracranial-intracranial bypass surgery. Stroke 1984; **15:**836–839.
11. Carter LP, Erspamer R, Bro WJ. Cortical blood flow: thermal diffusion vs isotope clearance. Stroke 1981; **12:**513–518.
12. Newman B, Gelb AW, Lam AM. The effect of isoflurane-induced hypotension on cerebral blood flow and cerebral metabolic rate for oxygen in humans. Anesthesiology 1986; **64:**307–310.
13. Eintrei C, Leszniewski W, Carlsson C. Local application of ^{133}xenon for measurement of regional cerebral blood flow (rCBF) during halothane, enflurane, and isoflurane anesthesia in humans. Anesthesiology 1985; **63:**391–394.
14. Murphy FL Jr, Kennell EM, Johnstone RE. The effects of enflurane, isoflurane and halothane on cerebral blood flow and metabolism in man. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists 1974, pp 61–62.
15. Hickey R, Bunegin L, Albin MS, Gelineau J, Rauschhuber R. Cerebral blood flow responses during varying rates of isoflurane induced hypotension (abst). Anesthesiology 1986; **65:**A580.
16. Pickard JD, Boisvert DPJ, Graham DI, Fitch W. Late effects of subarachnoid haemorrhage on the response of the primate cerebral circulation to drug-induced changes in arterial blood pressure. J Neurol Neurosurg Psychiatr 1979; **42:**899–903.
17. Ishii R. Regional cerebral blood flow in patients with ruptured intracranial aneurysms. J Neurosurg 1979; **50:**587–594.