Arterial isoflurane concentration and EEG burst suppression during cardiopulmonary bypass

Isoflurane (1.5 to 3.0 vol% in oxygen) was used to control intraoperative hypertension in 10 patients undergoing hypothermic cardiopulmonary bypass surgery. Isoflurane was administered through the membrane oxygenator of the bypass pump and yielded plateau concentrations in arterial blood ranging from 36.6 to 84.4 μg/ml (0.5 and 1.16 vol%, respectively). Isoflurane dosing resulted in prolonged periods (21 to 63 minutes) of EEG burst suppression and isoelectric activity in nine patients. Burst suppression was not a result of hypothermia. There was a close temporal relationship between isoflurane concentration and the onset of burst suppression (mean onset time: 27.3 ± 4.56 minutes after isoflurane was begun). The mean arterial isoflurane concentration at the onset of burst suppression was 46.5 ± 10.7 μg/ml; the nasopharyngeal temperature was 26.0° ± 0.61° C. Isoflurane was eliminated rapidly from blood with a mean apparent $t_{1/2}$ of 18.8 ± 5.46 minutes.(CLIN PHARMACOL THER 1986;40:304-13.)

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For patients undergoing coronary artery surgery, increased arterial blood pressure is a common complication during surgery. Although intraoperative hypertension can be managed with vasodilators such as nitroglycerin or sodium nitroprusside, reflex tachycardia and rebound hypertension occur with their use. Isoflurane is an inhalational anesthetic that decreases arterial blood pressure by reducing total peripheral resistance without depressing myocardial contractility.[1] Inhalational anesthetics also attenuate the sympathetic nervous system response to arterial vasodilation, so reflex increases in heart rate and blood pressure are minimized.[2,3] These characteristics, and the ease and flexibility of isoflurane dosing, make it a useful antihypertensive agent during surgery. Isoflurane has been shown to provide effective control of intraoperative hypertension in patients undergoing coronary artery bypass grafting.[4]

The advantages afforded by isoflurane in the control of intraoperative hypertension are tempered by its effects on EEG activity. Isoflurane produces a dose-dependent reduction in cortical activity, which appears on the EEG as a progressive decrease in electrical activity.[5,6] Isoflurane is unique among the volatile anesthetics in that an isoelectric EEG pattern can be produced in humans at therapeutic concentrations.[7] Although the effects of isoflurane on the brain are completely reversible,[8] burst suppression and isoelectric activity are troublesome during surgery when the EEG is used as a noninvasive monitor of cerebral function.[9,10] For example, reduced cerebral perfusion, which normally leads to characteristic changes in EEG activity,[11-13] may not be detected during isoflurane-induced isoelectric activity. This can lead to unrecognized intraoperative cerebral ischemia.

We have routinely observed periods of EEG burst suppression and isoelectric activity during isoflurane administration in patients undergoing cardiopulmonary bypass surgery. However, the relationship between isoflurane concentration in blood and the development of EEG burst suppression during cardiopulmonary bypass surgery has not been determined. Furthermore, we are not aware of any studies that have reported arterial isoflurane concentrations during cardiopulmonary bypass surgery. The objectives of this study were to determine the time course of arterial isoflurane concentration when used as a vasodilator during cardiopul-

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Table I. Patient data

Patient	*Age (yr)*	*Weight (kg)*	*Sex*	*EF (%)*	*LVEDP (mm Hg)*	*Surgical procedure*	*Neurologic problems*
1	54	95	F	80	—	CABG (double)	None
2	52	93	M	72	20	CABG (quadruple)	None
3	63	60	F	60	17	CABG (triple)	None
4	58	80	M	69	14	CABG (double)	None
5	61	82	M	53	16	CABG (triple)	None
6	39	92	M	60	12	CABG (triple) + IMAI	None
7	43	100	M	31	31	CABG (double) + AVR	None
8	69	89	M	39	17	AVR	None
9	58	67	M	60	18	CABG (triple)	None
10	52	80	M	—	17	CABG (triple)	None

EF, ejection fraction; LVEDP, left ventricular end diastolic pressure; CABG, coronary artery bypass graft; IMAI, internal mammary artery implantation; AVR, aortic valve replacement.

monary bypass surgery, to determine the time course of isoflurane-induced EEG burst suppression during cardiopulmonary bypass surgery, and to examine the relationship between arterial isoflurane concentration and the onset of EEG burst suppression in these patients. Standard anesthetic and surgical conditions for cardiopulmonary bypass surgery were used throughout this study so that these results would reflect normal cardiopulmonary bypass surgery cases.

MATERIAL AND METHODS

This study received ethical approval from the Clinical Investigation Ethics Review Committee. Ten patients (eight men and two women), American Society of Anesthesiologists physical status III, mean age 55 years (range 39 to 63 years) and mean body weight 83.8 kg (range 67 to 100 kg) who were scheduled for coronary artery bypass grafting, internal mammary artery implantation, or cardiac valve replacement were studied. There was no preoperative evidence of neurologic abnormalities in any of the patients. Preoperative patient data are summarized in Table I. Patients were receiving a variety of medications including diuretics, β-adrenergic blocking agents, nitrates, and calcium channel blockers, which were maintained up to the time of surgery. Premedication consisted of morphine (10 mg subcutaneous) and diazepam (10 mg oral) or lorazepam (4 mg sublingual) 1 hour before induction of anesthesia (Tables I to III).

Details regarding the induction and maintenance of anesthesia for each patient are shown in Tables II and III. Isoflurane in oxygen was used to control arterial pressure during cardiopulmonary bypass and was administered by means of a Fortec vaporizer (Cyprane Ltd., Keighley, England) through a Cobe membrane oxygenator (Cobe Canada, Scarborough, Ontario, Canada). The dose of isoflurane was adjusted in each patient to maintain the mean arterial pressure between 50 and 80 mm Hg. The vaporizer setting was not increased at a fixed rate but was adjusted according to the needs of each patient. Arterial and venous gases were monitored continuously during cardiopulmonary bypass with an in-line Bentley Gas-STAT monitoring system (Bentley Labs of Canada, Markham, Ontario, Canada). Arterial pH was maintained between 7.5 and 7.55, P_{CO_2} was maintained between 25 and 32 torr, and P_{O_2} was maintained between 220 and 270 torr. These determinations were made at 37° C and are not temperature corrected. The vaporizer setting, vaporizer flow, pump blood flow, mean arterial pressure, continuous mixed venous oxygen saturation, arterial P_{O_2} and P_{CO_2}, and patient temperature (nasopharyngeal and esophageal) were recorded at the time of each arterial blood sample.

The EEG was monitored continuously with an eight-channel bipolar scalp montage beginning after the in-

Table II. Anesthetic data (induction)

	Induction of anesthesia (mg)			
Patient	*Fentanyl*	*Lidocaine*	*Diazepam*	*Pancuronium*
1	3.0	100	10	14
2	3.0	100	5	14
3	2.0	0	2.5	12
4	3.0	80	10	14
5	2.5	0	5	12
6	3.0	100	10	10
7	2.5	0	5	16
8	2.5	100	10	14
9	3.0	100	10	12
10	2.0	100	2.5	*

All drugs were given as intravenous bolus injections.
*Suxamethonium, 100 mg, used for intubation.

Table III. Anesthetic data (maintenance)

	Maintenance of anesthesia (total dose)					
Patient	*Fentanyl (mg)*	*Pancuronium (mg)*	*Diazepam (mg)*	*Other vasodilators used*	*Hematocrit on bypass (%)*	*Duration of bypass (min)*
1	3.0	4	5	Nitroglycerin Nitroprusside	—	99
2	2.5	—	5	Nitroglycerin Nitroprusside	24	145
3	2.5	4	7.5	Nitroprusside	18	160
4	2.5	4	10		29	95
5	2.5	8	5	Nitroglycerin	23	120
6	5.5	8	10		23	185
7	3.0	4	10	Nitroprusside	28	160
8	3.0	4	15	Nitroprusside	30	105
9	3.5	4	5	Nitroglycerin	23	155
10	3.5	14	7.5	Nitroglycerin Nitroprusside	24	135

All patients received 100% oxygen during surgery.

duction of anesthesia (before the onset of cardiopulmonary bypass). Eight Grass gold cup electrodes were placed on the scalp according to the International 10-20 system and the EEG was recorded on a Grass model 8-16 electroencephalograph (Grass Instrument Co., Quincy, Mass.) with 5 or 7 μV/mm amplification. The amplitude of EEG activity (peak to peak) was determined in each 1-minute segment of the EEG (usually in the last 2 seconds of each epoch unless artifact was present). A decrease in the amplitude of electrical activity below 5 μV was considered to be the onset of burst suppression. The amplitude of electrical activity during burst suppression was generally 1 to 2 μV or amplifier noise. Recordings obtained from the C_3-O_1 (left central to occipital) electrode were chosen for these determinations. All recordings were symmetric in burst suppression activity, indicating that this channel was representative of the scalp EEG. All EEG analyses were conducted by a neurologist (D. B.).

Arterial blood samples (2.0 ml) were withdrawn from a radial artery cannula with 5 ml plastic syringes for the determination of isoflurane concentration. Blood samples were collected: (a) before isoflurane administration, (b) at 5-minute intervals during increasing or decreasing isoflurane concentrations, and (c) at 10- to 20-minute intervals during steady-state isoflurane concentrations. The blood sample was injected immediately into an empty, sealed 10 ml hypovial and kept on ice throughout the experiment. All hypovials were sealed with a butyl rubber septum and capped with an aluminum seal before the study. During injection of the blood sample, atmospheric pressure was maintained inside the hypovial by inserting a 26-gauge needle through the septum. Once the blood sample had been injected, the syringe needle and the 26-gauge needle were withdrawn simultaneously. No chemical treatment of the blood was necessary, and the blood samples were stored at 4° C up to 5 hours before analysis. All blood samples were collected during cardiopulmonary bypass so factors such as hemodilution and the presence of anticoagulants were constant across the samples.

The concentration of isoflurane in arterial blood was determined by GLC using head-space analysis. Hypovials containing the blood samples or blood standards were incubated at 37° C for 30 minutes in a water bath. One milliliter of the head-space gas was then injected onto the GLC column with a 1.0 ml gas-tight syringe. Chromatography was conducted on a Hewlett-Packard Model 5710A gas chromatograph (Hewlett-Packard Co., Palo Alto, Calif.) equipped with a flame ionization detector and a glass column (1.8 m by 4 mm inside diameter) containing 5% Carbowax 20M on 100 to 120 mesh Supelcoport (Supelco Inc., Oakville, Canada). The operating conditions were: injection temperature, 100° C; column temperature, 70° C; detector temperature, 150° C; nitrogen flow rate, 30 ml/min; hydrogen flow rate, 30 ml/min; air flow rate, 240 ml/min; and detector sensitivity, range 10. The retention time of isoflurane under these conditions was 1.13 minutes. The peak area of the isoflurane signal in each standard and blood sample was determined by a Hewlett-Packard Model 3390A integrator.

For each patient, isoflurane standards were prepared with arterial blood (25 ml) taken from the patient while

on cardiopulmonary bypass but before isoflurane dosing. With a 10 μl Hamilton syringe, an aliquot of liquid isoflurane (Ohio Medical Canada Inc., Toronto, Canada) was injected into a sealed hypovial filled with control blood and containing a small magnetic stir bar. The contents were stirred for 15 minutes at 4° C and aliquots of this stock solution (1 mg/ml) were added to sealed hypovials containing control blood to yield isoflurane concentrations of 5, 10, 25, 50, and 100 μg/ml in a final volume of 2.0 ml of blood. The peak area of the isoflurane signal for each blood standard was plotted against the respective isoflurane concentration. The standard curve was linear from 5 to at least 200 μg/ml and the slope and y intercept of the standard curve, determined by regression analysis, were used to calculate the isoflurane concentration in each blood sample. The overall accuracy of the procedure is 97.6% ± 6.58% ($\bar{X}$ ± SD; n = 16), and the within-run coefficient of variance is 4.91% and 1.16% for 5.0 and 50 μg/ml isoflurane, respectively. The apparent elimination rate constant (k_e) and $t_{1/2}$ of isoflurane were determined from the slope of the natural logarithm arterial blood concentration-time curve beginning after isoflurane dosing had been discontinued.

RESULTS

The time course of arterial isoflurane concentration and EEG amplitude during cardiopulmonary bypass for one of the patients in this study are shown in Fig. 1. For clarity, only the EEG amplitude data determined at 5-minute intervals have been included in Fig. 1. Time zero indicates the onset of isoflurane dosing, not the onset of anesthesia or surgery. At time zero, cardiopulmonary bypass was already in progress and control blood had been withdrawn for the preparation of isoflurane standards. Isoflurane dosing was initiated by gradually increasing vaporizer settings until the mean arterial pressure was between 50 and 80 mm Hg. Normal blood pressure was achieved at a vaporizer setting of 2.0% in this patient. This vaporizer setting was maintained for 65 minutes, resulting in steady-state blood concentrations ranging from 42 to 52 μg/ml. As the concentration of isoflurane in blood increased (>30 μg/ml), there was a marked, simultaneous decrease in the amplitude of EEG activity from 20 to 40 μV to less than 5 μV. The onset of burst suppression occurred at 22.0 minutes, with a corresponding arterial isoflurane concentration of 42.6 μg/ml and a nasopharyngeal temperature of 24.9° C. During cardiopulmonary bypass, the mean nasopharyngeal temperature was 24.7° ± 0.23° C, arterial gases were stable, and there were no major changes in the rate of pump blood flow.

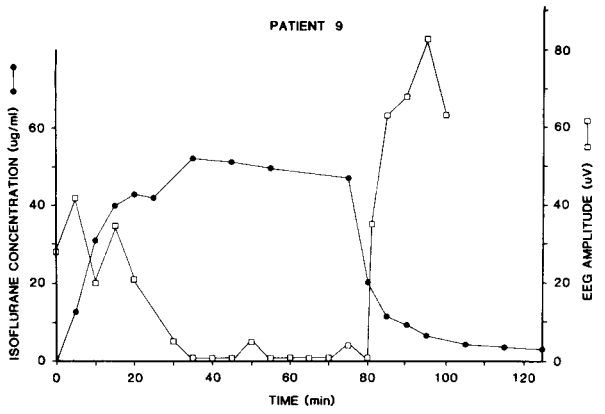

Fig. 1. Time course of arterial isoflurane concentration and the amplitude of EEG activity for one patient during cardiopulmonary bypass surgery. Time zero indicates the onset of isoflurane dosing (cardiopulmonary bypass in progress). In this patient, isoflurane was discontinued at 75 minutes.

Isoflurane was eliminated rapidly from blood with an apparent $t_{1/2}$ of 15.1 minutes; 60 minutes after isoflurane was discontinued the blood concentration in this patient was 3.0 μg/ml.

Selected EEG recordings, taken at various times during surgery, are illustrated in Figs. 2 to 4. Fig. 2 shows the EEG activity during extracorporeal circulation before the administration of isoflurane. The nasopharyngeal temperature at the time of this recording was 25.9° C. The amplitude of electrical activity was reduced compared with prebypass values (data not shown), indicating the effect of hypothermia on the EEG. Although hypothermia did decrease the amplitude of EEG activity, there was no evidence of burst suppression at any time during hypothermic cardiopulmonary bypass before isoflurane dosing. During isoflurane dosing, the amplitude of electrical activity decreased progressively until a characteristic pattern of burst suppression (less than 5 μV amplitude) developed (Fig. 3, *C_3-O_1 electrode*). Dosing with isoflurane resulted in sustained periods of isoelectric activity that were interspersed with brief periods of low-amplitude electrical activity (Fig. 3, *middle*). Burst suppression was evident throughout steady state when blood isoflurane concentrations were maximal. The apparent electrical activity observed in the C_4-O_2 electrode in Fig. 3 is actually an artifact generated by the cardiopulmonary bypass pump and not true electrical activity. Fig. 4 is an EEG recording obtained during rewarming of the patient after isoflurane had been discontinued. The nasopharyngeal temperature at the time of this recording was 30.5° C. The higher amplitude of electrical activity in Fig. 4 as

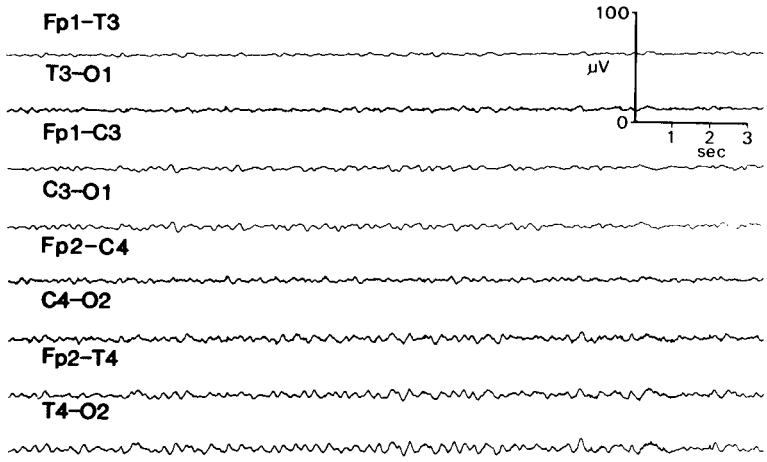

Fig. 2. Representative tracing from one patient shows EEG activity during cardiopulmonary bypass surgery before isoflurane. The nasopharyngeal temperature at the time of this recording was 25.9° C.

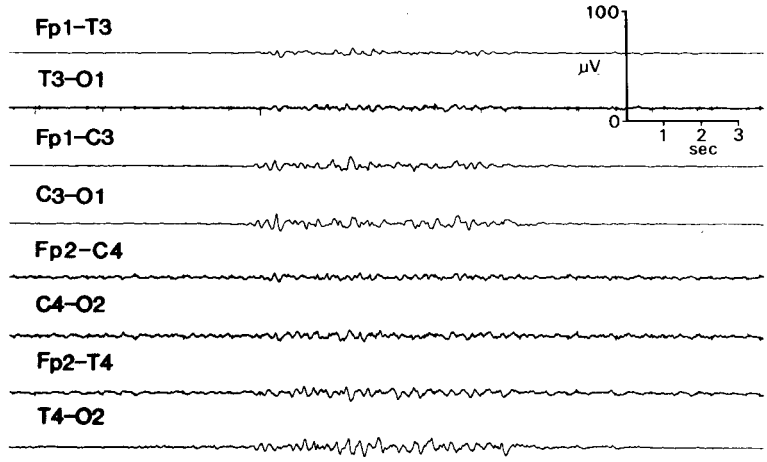

Fig. 3. Representative tracing from one patient (same as Fig. 2) shows the pattern of EEG burst suppression during isoflurane dosing. At the time of this recording, blood isoflurane concentration was 59.8 μg/ml and the nasopharyngeal temperature was 25.4° C.

compared with Fig. 1 is a result of the difference in body temperature at the time of these recordings. After bypass, normal EEG activity was restored and there were no residual effects of the anesthetic or hypothermia on the EEG.

The EEG recordings in Figs. 2 to 4 are typical of the results for the nine patients who developed burst suppression during isoflurane dosing. The results of isoflurane-induced burst suppression during cardiopulmonary bypass for all patients in this study are summarized in Tables IV and V. Variable amounts of isoflurane were required to control intraoperative hypertension as indicated by the plateau concentrations of isoflurane. During isoflurane dosing, a large increase in arterial blood pressure of short duration occurred in eight patients, which required the use of nitroglycerin or sodium nitroprusside (Table III). Generally these drugs were used only once during cardiopulmonary bypass and were given as short intravenous infusions. Prolonged periods of burst suppression developed in nine patients during isoflurane dosing. The mean onset time of burst suppression was 27.3 ± 4.56 minutes (range 20 to 35 minutes), which occurred at a mean vaporizer setting of 2.2% ± 0.43% (range 1.5% to

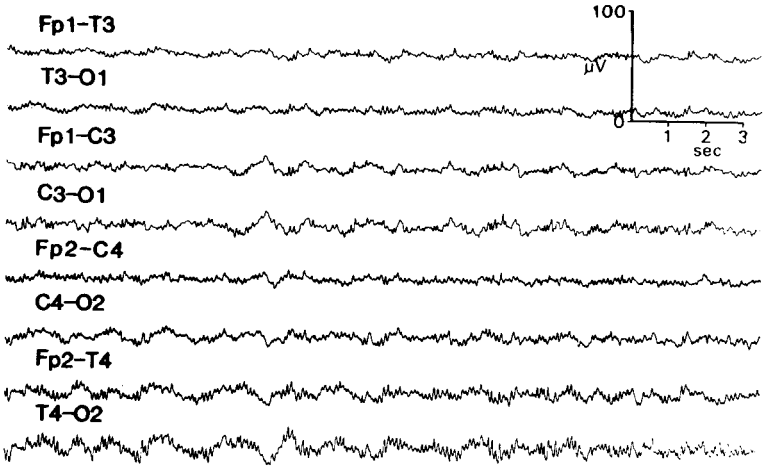

Fig. 4. Representative tracing from one patient (same as Figs. 2 and 3) shows the recovery of EEG activity after isoflurane. At the time of this recording, the nasopharyngeal temperature was 30.5° C and the blood isoflurane concentration was 15.0 μg/ml.

3.0%). The onset of burst suppression occurred at a mean blood isoflurane concentration of 46.5 ± 10.7 μg/ml (range 34.9 to 64.0) and a nasopharyngeal temperature of 26.0° ± 0.61° C (range 24.9° to 26.7°). The mean body temperature for each patient during cardiopulmonary bypass (before rewarming) is shown in Table IV. These data indicate that temperature conditions for all patients were virtually identical during bypass when isoflurane effects were being observed. Recovery from burst suppression occurred at a mean time of 68.0 ± 14.3 minutes (range 48 to 85 minutes), corresponding to a mean duration of burst suppression of 41.1 ± 14.6 minutes (range 21 to 63 minutes). However, rewarming of the patients was already in progress when recovery occurred; the mean nasopharyngeal temperature at the time of recovery was 29.2° ± 3.20° C. Isoflurane-induced burst suppression was absent in only one patient (No. 4) in this study. Fluctuations in EEG activity were observed in patient 4 during maximum blood isoflurane concentrations, suggesting the impending onset of burst suppression. However, burst suppression did not develop. The plateau concentrations of isoflurane in this patient ranged from 41.7 to 58.2 μg/ml and were comparable to other patients in this study. The mean nasopharyngeal temperature during cardiopulmonary bypass did not differ significantly from those patients who developed burst suppression. It would appear that for this patient, arterial isoflurane concentrations that controlled blood pressure adequately were not high enough to induce EEG burst suppression. The apparent $t_{1/2}$ of isoflurane was determined for eight patients and is shown in Table V. Isoflurane was eliminated rapidly from blood with a mean $t_{1/2}$ of 18.9 ± 5.46 minutes. The k_e could not be determined accurately for patients 2 and 6 because there were insufficient isoflurane concentration data points in their respective elimination-time curves.

To verify that burst suppression was the result of isoflurane and not a result of other factors (e.g., hypothermia or fentanyl anesthesia), we examined EEG recordings of several hundred patients undergoing hypothermic cardiopulmonary bypass who did not receive isoflurane. Premedication, anesthetic management, and demographic characteristics of these patients were similar to those of the patients described in Tables I to III. There was no evidence of burst suppression in the continuous EEG recording of any of the non-isoflurane–treated patients we examined, even though all patients who underwent cardiopulmonary bypass surgery had nasopharyngeal temperatures in the range of 24.0° to 26.0° C. The time course of EEG activity during cardiopulmonary bypass for one of the non-isoflurane–treated patients is presented in Fig. 5. The amplitude of EEG activity was measured at 1-minute intervals; however, for the purpose of clarity, only the EEG amplitude data determined at 5-minute intervals have been included. The nasopharyngeal temperature of this patient during cardiopulmonary bypass was approximately 25.0° C, and intraoperative hypertension was controlled with nitroglycerin and sodium nitroprusside. The amplitude of EEG activity during bypass was reduced by hypothermia and ranged from 25 to 35 μV.

Table IV. Isoflurane-induced burst suppression of EEG activity during cardiopulmonary bypass surgery

Patient	*Time of onset (min)*	*Nasopharyngeal temperature at onset (° C)*	*Vaporizer setting at onset (vol% in oxygen)*	*Arterial isoflurane concentration at onset (μg/ml)*	*Plateau concentrations of isoflurane during bypass (range in μg/ml)*	*Mean nasopharyngeal temperature during bypass before rewarming (° C)*
1	29	26.7	1.5	34.9	30.4-41.7	27.1 (0.29)
2	27	26.5	3.0	64.0	72.4-84.5	26.0 (0.45)
3	31	25.2	2.0	36.6	25.1-36.6	25.4 (0.41)
4	—	—	—	—	41.7-58.2	27.0 (0.14)
5	35	26.0	2.5	45.2	38.2-47.7	26.0 (0.52)
6	20	26.6	2.0	41.6	39.0-54.2	26.5 (0.28)
7	28	26.1	2.5	63.1	62.3-70.3	25.8 (0.50)
8	25	25.8	2.0	36.0	36.7-49.7	26.0 (0.32)
9	22	24.9	2.0	42.6	41.9-52.1	24.7 (0.23)
10	29	25.8	2.0	54.6	55.6-68.0	25.8 (0.45)
$\bar{X}$	27.3 (4.56)	26.0 (0.61)	2.2 (0.43)	46.5 (10.7)		

Numbers in parentheses are SDs. No burst suppression was observed in patient 4.

Table V. Elimination of isoflurane from arterial blood during cardiopulmonary bypass surgery

Patient	k_e *(min^{-1})*	$t_{1/2}$ *(min)*
1	0.041	16.9
2	*	—
3	0.038	18.2
4	0.062	11.2
5	0.034	20.4
6	*	—
7	0.038	18.2
8	0.034	20.4
9	0.046	15.1
10	0.023	30.1
$\bar{X} \pm$ SD		18.8 ± 5.46

*Insufficient data points to accurately determine k_e.

However, EEG amplitude never reached the 5 μV threshold for burst suppression at any time during hypothermic bypass. Rewarming of the patient was initiated at 43 minutes and there was a rapid, corresponding increase in the amplitude of EEG activity.

DISCUSSION

Fluctuations in arterial blood pressure are a routine problem during cardiopulmonary bypass surgery. Although hypertensive events can be managed with regular antihypertensive agents, isoflurane is often used by the anesthetist to control blood pressure during cardiopulmonary bypass surgery. Isoflurane decreases systemic arterial pressure by reducing total peripheral resistance, and the ease and flexibility of isoflurane dosing make it useful for this purpose. In this study, doses of isoflurane ranging from 1.5 to 3.0 vol% in oxygen adequately controlled intraoperative hypertension during cardiopulmonary bypass. The doses of isoflurane reported in this study are based on the final vaporizer setting selected for each patient and are not based on inspired concentrations. In a recent clinical study of 20 patients undergoing coronary artery bypass grafting, isoflurane was reported to be effective in controlling intraoperative hypertension that developed during sternotomy or manipulation of the aorta (i.e., before cardiopulmonary bypass).[4] Inspired isoflurane concentrations of 1.5 to 2.0 vol% in oxygen lowered the mean arterial pressure from greater than 110 mm Hg to approximately 80 mm Hg. In our study, comparable doses of isoflurane were required to maintain the mean arterial pressure between 50 and 80 mm Hg during cardiopulmonary bypass.

In our study, isoflurane was administered through the membrane oxygenator of the bypass pump, which must substitute for cardiac and pulmonary function during cardiac surgery. The administration of 1.5 to 3.0 vol% by this route produced plateau concentrations of isoflurane in blood ranging from 36.6 to 84.5 μg/ml, which are equivalent to 0.50 and 1.16 vol%, respectively. Prolonged periods of EEG burst suppression developed in nine patients when isoflurane concentrations were maximal. The mean arterial isoflurane concentration at the onset of burst suppression was 46.5 μg/ml (equivalent to 0.64 vol%). Previous investigations have shown that inspired concentrations of isoflurane in the therapeutic range produce dose-dependent EEG changes in-

Time of recovery (min)	*Nasopharyngeal temperature at recovery (° C)*	*Duration of burst suppression (min)*
50	34.8	21
77	26.7	50
64	26.5	33
—	—	—
73	29.0	38
48	30.2	28
85	25.2	57
54	32.7	29
81	30.6	63
80	26.8	51
68.0 (14.3)	29.2 (3.20)	41.1 (14.6)

cluding burst suppression and isoelectric activity.[5,6] In a study of 100 patients scheduled for a variety of elective and emergency surgical procedures (no cardiac surgery), the majority of patients exhibited patterns of burst suppression at blood isoflurane concentrations of 160 to 210 μg/ml (equivalent to 2.2 and 2.9 vol%, respectively).[6]

The lower blood isoflurane concentration at the onset of burst suppression in our study as compared with previous investigations may be caused by several factors. Under normal ventilatory conditions, the anesthetic concentration in blood, and the anesthetic concentration achieved in the brain, is determined by the production and delivery of an adequate anesthetic concentration for inhalation, distribution of the anesthetic into the lung, uptake from the alveoli into the blood, and distribution from the blood into other tissues including the brain.[14] In our study, isoflurane was administered during cardiopulmonary bypass when both pulmonary and cardiac function was disturbed. The low concentrations of isoflurane in blood therefore may reflect a difference in the uptake of isoflurane into blood from the bypass system as compared with the uptake from the lungs. A change in the blood/gas partition coefficient of isoflurane also would have a dramatic effect on arterial isoflurane concentration. Such a change would be anticipated considering the physiologic alterations that occur during cardiopulmonary bypass surgery. The solubility of isoflurane in blood is known to be reduced by hemodilution,[15] and blood is diluted during cardiopulmonary bypass.[16] On the other hand, the solubility of isoflurane in blood is increased at reduced temperature,[17] which should offset the effect of hemodilution on the blood/gas partition coefficient.

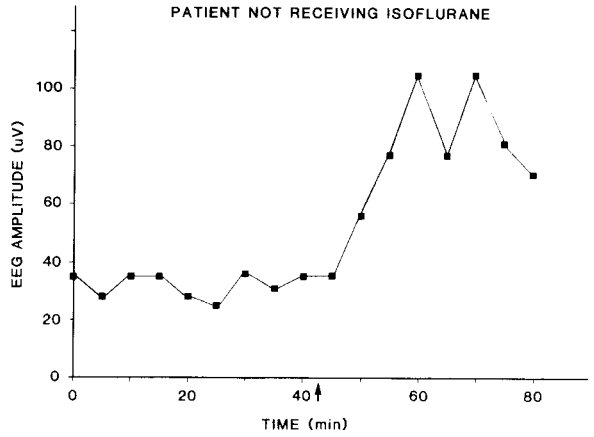

Fig. 5. The amplitude of EEG activity during cardiopulmonary bypass surgery for a patient who did not receive isoflurane. Intraoperative hypertension was controlled with intravenous vasodilators, and the nasopharyngeal temperature during bypass was approximately 25.0° C. Time zero indicates the onset of cardiopulmonary bypass. The arrow on the abscissa indicates the onset of rewarming (43 minutes), and bypass was terminated at 77 minutes.

Disturbances in the pharmacokinetics of several drugs have been reported during cardiopulmonary bypass, including alterations in clearance and the volume of distribution.[16] Plasma fentanyl concentrations have been reported to decrease by 37% during bypass as compared with prebypass values.[18] Currently there are no data regarding the influence of bypass on the pharmacokinetics of isoflurane, but distribution is likely to be affected during extracorporeal circulation. Enhanced distribution into the brain would account for the pronounced effect of isoflurane on the EEG and the low concentrations in blood. Perhaps the most important factor is that previous investigations have used normothermic surgical patients to determine the relationship between blood isoflurane concentration and EEG activity. In our study, patients with hypothermia undergoing cardiac surgery were used. Hypothermia is used in cardiopulmonary bypass surgery to reduce cellular oxygen demand when tissue perfusion is disturbed. Hypothermia reduces cerebral oxygen consumption, resulting in decreased cortical electrical activity and EEG amplitude. Isoflurane also is known to decrease the rate of cerebral oxygen consumption and produce isoelectric activity.[19] A decrease in temperature should enhance the depressant effect of isoflurane on EEG activity, and this appears to be the case in this study. Therefore the lower blood isoflurane concentration at the onset of burst suppression in our investigation is probably a re-

sult of the lower prevailing body temperature in these surgical patients.

Hypothermia reduced the amplitude of EEG activity before isoflurane administration but did not produce burst suppression and isoelectric activity. Furthermore, there was no evidence of burst suppression in the EEG recordings of hypothermic, cardiopulmonary bypass patients who did not receive isoflurane. There was also a close temporal relationship between the rise in blood isoflurane concentration and the onset of burst suppression in this study. Overall, these data suggest that burst suppression and isoelectric activity were a result of isoflurane and not hypothermia.

It is unlikely that the consistent burst suppression observed in this study was the result of changes in cerebral perfusion or hypoxia. Factors that affect cerebral perfusion, such as pump flow, arterial blood gases, and blood pressure, were stable during cardiopulmonary bypass when alterations in EEG activity were observed. Fentanyl in high doses has been reported to influence EEG activity but does not produce burst suppression. In a recent clinical study of six healthy male patients scheduled for elective surgery, the infusion of fentanyl (150 μg/min) progressively slowed the frequency and increased the amplitude of EEG activity.[20] The maximum effect was characterized by δ waves of slow frequency (<4 Hz) and large amplitude (>50 μV), but there was no report of burst suppression. In rats the infusion of fentanyl (200 or 400 μg/kg) induced EEG epileptiform activity, characterized by the appearance of isolated, high-voltage (>100 μV) spike, polyspike, and wave complexes superimposed on a baseline of reduced frequency and voltage.[21] These data indicate that, while fentanyl does affect the activity of the EEG, it does not produce burst suppression and isoelectric activity at anesthetic doses.

Ethical approval for this investigation was granted under the condition that normal anesthetic and surgical procedures be maintained. It was not possible to maintain isothermal conditions during recovery of EEG activity, and in all patients, rewarming was in progress when normal EEG activity appeared. This can be seen by the large interindividual differences in body temperature at the time of recovery (Table IV). Although it is not possible to draw any conclusions about the relationship between anesthetic concentration in blood and the recovery of EEG activity, some recovery data have been included in Table IV for completeness.

In summary, isoflurane (1.5 to 3.0 vol% in oxygen) was administered to control intraoperative hypertension in 10 patients undergoing hypothermic cardiopulmonary bypass surgery. The anesthetic was administered via the membrane oxygenator of the bypass pump and yielded maximum arterial concentrations ranging from 36.6 to 84.4 μg/ml (0.5 and 1.16 vol%, respectively). Isoflurane resulted in prolonged periods (21 to 63 minutes) of EEG burst suppression and isoelectric activity in nine patients. There was a close temporal relationship between the increase in arterial isoflurane concentration and the onset of burst suppression. The relationship between anesthetic concentration in blood and the onset of burst suppression was determined under comparable conditions in all patients. The mean arterial isoflurane concentration at the onset of burst suppression was 46.5 μg/ml with a corresponding mean body temperature of 26.0° C. Hypothermia alone reduced the amplitude of EEG activity but produced no evidence of burst suppression in any of the patients. When isoflurane dosing was discontinued, the anesthetic was eliminated rapidly from blood, with an apparent $t_{1/2}$ of 18.8 minutes. The data indicate that, in the majority of hypothermic, cardiopulmonary bypass patients, the use of isoflurane alone to control intraoperative hypertension leads to EEG burst suppression and isoelectric activity. Therefore if the EEG is used as a noninvasive monitor of cerebral function during cardiopulmonary bypass surgery, control of arterial blood pressure will require the use of lower doses of isoflurane and possibly other vasodilators.

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