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Pharmacologic EEG Suppression during Cardiopulmonary Bypass: Cerebral Hemodynamic and Metabolic Effects of Thiopental or Isoflurane during Hypothermia and Normothermia

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We have determined the effects of thiopental or isoflurane upon cerebral blood flow (CBF) and the cerebral metabolic rate for oxygen ($CMRO_2$) when these agents are used in sufficient dose to attain a deep burst suppression pattern on the electroencephalogram (EEG) during hypothermic and normothermic cardiopulmonary bypass (CPB). Thirty-one patients undergoing coronary artery bypass graft surgery were anesthetized with fentanyl 0.1 $mg \cdot kg^{-1}$, and were randomly allocated to one of three groups: control (no further anesthetics during bypass and continuous EEG activity), thiopental treatment (EEG suppression), or isoflurane treatment (EEG suppression). Hypothermia (25–29° C) was routinely induced at onset of nonpulsatile cardiopulmonary bypass. In the treatment groups, thiopental or isoflurane were used during bypass to achieve a deep burst suppression pattern. Cerebral blood flow and cerebral metabolic rate for oxygen were determined during hypothermia and upon rewarming to normothermia (37° C). Pharmacologic EEG suppression with either isoflurane or thiopental was associated with lower cerebral metabolic rate than control values during both hypothermic and normothermic bypass. However, only thiopental-induced EEG suppression was associated with lower cerebral blood flow than control. Cerebral blood flow during isoflurane-induced EEG suppression was similar to control values in spite of the reduced cerebral metabolic rate. (Key words: Anesthesia: cardiovascular. Anesthetics, intravenous: thiopental. Anesthetics, volatile: isoflurane. Brain: blood flow; oxygen consumption. Hypothermia: induced. Monitoring: electroencephalography. Surgery: cardiac.)

IN A RECENT CLINICAL STUDY of the neuropsychiatric sequelae of open heart surgery under normothermic cardiopulmonary bypass (CPB), persistent deficits were found in 7.5% of a control group, while patients subjected to pharmacologic EEG suppression with thiopental during CPB had no persistent deficits.[1] This report provided the first evidence of cerebral protection by a barbiturate in humans, and its efficacy was attributed to the reduction of cerebral metabolic rate for oxygen, though this was not measured. The mean dose of thiopental required to maintain EEG suppression throughout CPB was 39.5 $mg \cdot kg^{-1}$, and the cost of cerebral protection was myocardial depression necessitating increased frequency of administration of inotropic agents, prolonged anesthesia, prolonged time to extubation, and somnolence for up to 3 days. Though it has been stated that this therapeutic modality is now indicated for patients undergoing open chamber heart surgery,[2] the authors urged that ". . . other drugs equally effective in producing EEG suppression without the hemodynamic consequences and persistence of thiopental should be sought."[1] Hypothermia is commonly used during CPB to increase the tolerance of the brain to ischemia by reducing the cerebral metabolic rate,[3] and experimental studies have shown that isoflurane, like the barbiturates, reduces cerebral metabolism in a dose-dependent fashion with maximal effect achieved when EEG suppression occurs, and with no direct toxic effect on cerebral metabolic pathways.[4,5] Though isoflurane is not without hemodynamic effects, these are dose-dependent and non-persistent. As a major physiologic determinant of cerebral protection is considered the reversible reduction of cerebral oxygen consumption at the time of reduced oxygen delivery, our study assessed the cerebral hemodynamic and metabolic effects of pharmacologic EEG suppression with thiopental and compared them to those occurring with isoflurane during hypothermic and normothermic CPB.

Methods

The study was approved by the Institutional Committee on Human Research, and written informed consent to their participation was obtained from patients scheduled for coronary artery bypass graft surgery. Patients with evidence of cerebrovascular disease or valvular heart disease were excluded from this study. Prior to surgery, patients were randomly allocated to control, thiopental, or isoflurane groups.

After premedication with sublingual lorazepam 0.06 $mg \cdot kg^{-1}$ and intramuscular morphine sulphate 0.15 $mg \cdot kg^{-1}$, patients were brought to the operating room where ten EEG leads were affixed in a standard parasagittal bipolar block montage. The EEG was moni-

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tored and recorded continuously throughout surgery with a sensitivity of 7 μv and a pass band filter of 0.5–70 Hz. A radial arterial cannula and peripheral venous cannula were inserted under local anesthesia. A central venous or pulmonary arterial catheter was introduced *via* the right internal jugular vein, either before induction of anesthesia (under infiltration block) or after induction of anesthesia. The same internal jugular vein was then punctured percutaneously, and a 15 cm 16-Fr catheter was passed in a cephalad direction to the jugular bulb to allow sampling of cerebral venous blood. Routine postoperative radiographs were examined to confirm correct placement of these catheters.

Anesthesia was induced and maintained with fentanyl 0.1 $mg \cdot kg^{-1}$, using succinylcholine or pancuronium bromide to facilitate tracheal intubation. Further doses of pancuronium bromide were used to maintain muscle relaxation. The lungs were ventilated using a Bain nonrebreathing system with a fresh gas flow of 60 $ml \cdot kg^{-1} \cdot min^{-1}$ of oxygen. Ten scintillation counters were positioned around the head, five over each hemisphere, and connected to a Novo Cerebrograph 10a® to permit determination of cerebral blood flow (CBF) at five periods during surgery. The first measurements were made following sternotomy prior to cannulation for CPB (pre-CPB), and the last measurements were made following protamine administration after CPB (post-CPB), by intravenous injection of ^{133}Xe 5–10 mCi in 6 ml 0.9% saline. Expired air was continuously sampled from the endotracheal tube to obtain end-tidal Xenon concentration used subsequently to correct for isotope recirculation.[6] Measurements were also made after 15 and 30 min of hypothermic CPB (cold CPB_{15}, cold CPB_{30}; temperature 24.9–29° C), and after rewarming during normothermic CPB (warm CPB; temperature 37° C), by injection of the isotope into the arterial port of the pump oxygenator. In preliminary studies, a scintillation detector placed over the aortic inflow cannula during CPB showed less than 1% recirculation of the original xenon bolus; therefore, a correction for recirculation was not applied. Regional cerebral blood flow (rCBF) under each counter was determined by stochastic (height/area) analysis of the ^{133}Xe washout curve over 15 min.[7,8] The calculated flow values were corrected for changes in the xenon partition coefficient resulting from alterations in hemoglobin concentration and temperature.[9] Mean hemisphere blood flow was calculated from the "hemispheric clearance curve" constructed by summing the outputs of the five detectors on each side.

Blood gas analysis was performed on arterial and jugular venous blood samples at 37° C and corrected to the patients nasopharyngeal temperature by the factors of Kelman and Nunn[10] for determination of oxygen content according to the formula $C_xO_2 = (P_xO_2 \times s) + (Hb \times 1.34 \times S_xO_x)$, where C_xO_2 = oxygen content of sample (either arterial or venous), P_xO_2 = oxygen tension, s = the solubility coefficient of oxygen in blood adjusted for temperature (s = 0.00395 $ml^{-1} \cdot dl^{-1} \cdot mmHg^{-1}$ at 26–28° C, 0.00317 $ml^{-1} \cdot dl^{-1} \cdot mmHg^{-1}$ at 36–38° C), Hb = hemoglobin concentration, and S_xO_2 = oxygen saturation. The cerebral metabolic rate for oxygen ($CMRO_2$) was calculated as the product of the mean right hemispheric CBF and the arterio-jugular oxygen content difference. Hemodynamic parameters were recorded during the first 5 min of CBF determination. Cerebral perfusion pressure (CPP) was calculated as the mean arterial pressure − mean jugular venous pressure.

Prior to aortic cannulation patients were given heparin 3–4 $mg \cdot kg^{-1}$, and subsequent doses as necessary to maintain the activated coagulation time (ACT) beyond 400 s. Bypass technique included the use of a membrane oxygenator without arterial line filter and nonpulsatile pump flows of 2–2.5 $l \cdot m^{-2} \cdot min^{-1}$. The perfusionist attempted to achieve normal arterial *p*H and P_{CO_2} as measured at 37° C without correction for patient temperature.[11,12]

Patients allocated to the control group received no additional anesthetic agents. Patients allocated to thiopental treatment group received intravenous doses of thiopental 8 mg/kg^{13}, plus further doses sufficient to maintain a predominantly isoelectric burst/suppression EEG pattern during CPB, such that the duration of the isoelectric periods always exceeded the bursts (fig. 1). The first three patients received thiopental throughout CPB to an empirically predetermined maximum of 24 $mg \cdot kg^{-1}$, but, as EEG suppression for the full period of CPB could not be consistently maintained within this total dose limit, further patients received thiopental only for the first 15 min of hypothermic CPB (cold CPB_{15}) and upon rewarming to normothermia (warm CPB). In these patients, continuous EEG activity was allowed to resume in the interval between measurement periods cold CPB_{15} and warm CPB, and no measurement was attempted at cold CPB_{30}. Patients allocated to isoflurane treatment group received isoflurane, in air and oxygen, *via* the pump oxygenator in sufficient concentration (read from the vapouriser dial setting) to attain a predominantly isoelectric burst suppression EEG pattern (fig. 1).

Mean arterial pressure during CPB was kept above 40 mmHg by administration of phenylephrine as required. Hypertension (pressure greater than 90 mmHg) was treatd with chlorpromazine (maximum dose 25 mg) or sodium nitroprusside. Immediately before termination of CPB, 0.5–1.0 g calcium chloride was injected *via* the pump for all patients. After termination of CPB, fluids and inotropes were used as necessary to achieve satisfac-

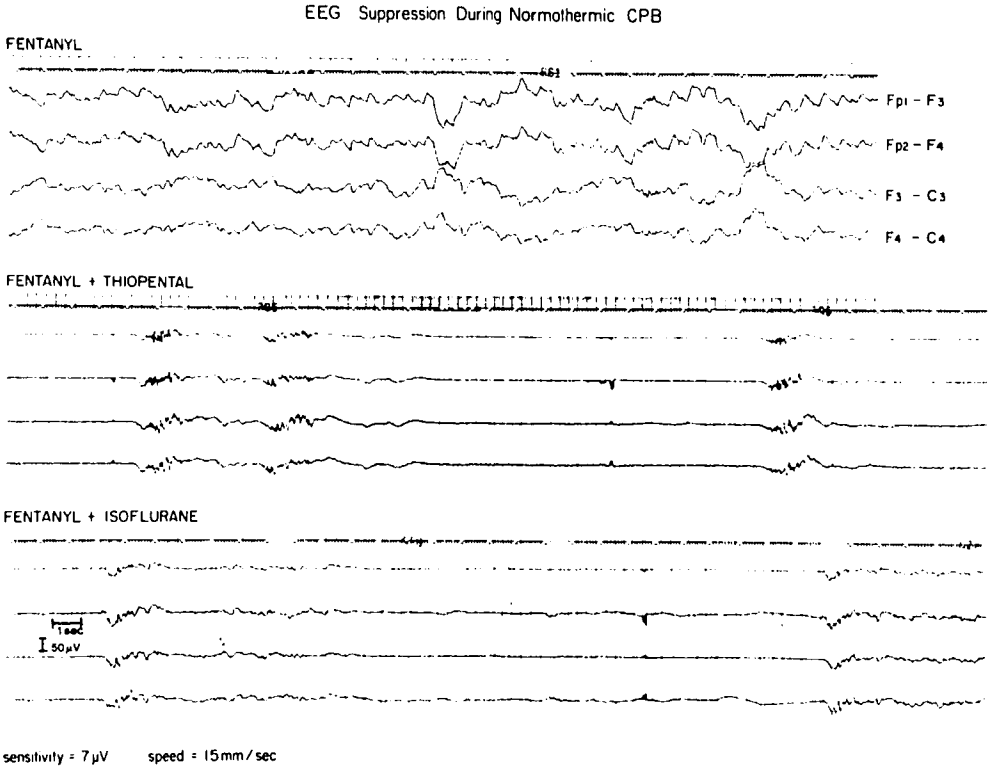

FIG. 1. Representative EEG tracings from three study group patients during normothermic cardiopulmonary bypass. The top tracing is from the control group, and demonstrates characteristic low-voltage activity occurring during high-dose narcotic anesthesia. The middle tracing shows burst suppression in a patient receiving thiopental, while the bottom tracing demonstrates burst suppression resulting from isoflurane administration.

tory hemodynamic parameters. Protamine was administered in sufficient dosage to restore the ACT to pre-CPB values.

Data were submitted to one-way analysis of variance (ANOVA), and Scheffes test for multiple comparisons was used to identify differences when ANOVA was significant to $P < 0.05$. For nonparametric data, chi-square testing using Bonferroni's correction for multiple comparisons, with $P < 0.05/k$, was used to determine significance.

Results

As shown in table 1, there were no significant differences in demographics between groups. Subjects were predominantly male, and the age range was 45–73 yr.

Routine postoperative radiography showed no malposition of the jugular catheters. Nasopharyngeal temperature, arterial carbon dioxide tension, hemoglobin concentration, cerebral perfusion pressure, and mean arterial pressure in each group at each stage of the study are shown in table 2. One hundred and twenty-six acceptable CBF measurements were made in 31 patients (table 2). There were no significant variations in rCBF and intrahemispheric CBF values were comparable. Right hemispheric CBF was utilized for determination of $CMRO_2$ to conform with the side of the jugular bulb catheter.

TABLE 1. Patient Demographics

	Control	Thiopental	Isoflurane
Sex M/F (n)	10/2	6/1	11/1
Age (yr)	50.0 ± 8.1	63.1 ± 6.5	55.5 ± 9.9
Weight (kg)	83.5 ± 11.8	78.1 ± 11.2	79.4 ± 10.2
Duration of CPB (min)	106 ± 37	105 ± 21	104 ± 26

Results are mean ± SD. Results N.S. at $P < 0.05$. CPB = cardiopulmonary bypass.

Compared to either the thiopental group or the control group, phenylephrine was required significantly more often ($P < 0.0005$) when isoflurane was used to suppress the EEG, whereas administration of vasodilators was required more frequently ($P < 0.0005$) in the control group *versus* the other groups.

Continuous low frequency EEG activity was recorded throughout CPB in control group patients (fig. 1). During hypothermic CPB (temperature range 24.9–29° C), 1.1 ± 0.3% isoflurane produced EEG burst suppression, and, during normothermic CPB (temperature range 36.5–38.1° C), 2.4 ± 0.4% isoflurane was required to maintain EEG burst suppression. In the thiopental group, the mean total dose of barbiturate needed to achieve 30–40 min EEG burst suppression was 17 ± 4 mg/kg.

There were no significant differences in pre-CPB values of CBF and $CMRO_2$ (tables 3, 4; figs. 2, 3) EEG

TABLE 2. Intraoperative Variables

	Pre-CPB	Cold CPB_{15}	Cold CPB_{30}	Warm CPB	Post-CPB
Data Measurements (n)					
Control	11	11	6	11	10
Thiopental	7	7	2	7	6
Isoflurane	10	11	8	9	10
Temperature (°C)					
Control	35.5 ± 0.6	26.8 ± 1.0	26.8 ± 1.2	37.1 ± 0.4	35.8 ± 0.3
Thiopental	35.0 ± 0.6	26.5 ± 1.4	(25.0, 25.2)	37.1 ± 0.3	35.8 ± 0.3
Isoflurane	35.7 ± 0.3	26.6 ± 0.9	28.3 ± 0.6†	37.3 ± 0.5	35.6 ± 0.6
Pa_{CO_2} (mmHg)					
Control	36 ± 5	41 ± 3	37 ± 3	34 ± 5	37 ± 3
Thiopental	35 ± 1	42 ± 1	(26, 44)	32 ± 6	37 ± 3
Isoflurane	36 ± 2	42 ± 4	42 ± 8	36 ± 2	37 ± 3
MAP (mmHg)					
Control	95 ± 11	72 ± 14	83 ± 5	60 ± 13	77 ± 13
Thiopental	91 ± 13	54 ± 12*	(61, 61)	58 ± 10	74 ± 2
Isoflurane	89 ± 13	52 ± 8*	59 ± 10*	52 ± 4	73 ± 7
CPP (mmHg)					
Control	84 ± 16	66 ± 19	74 ± 8	52 ± 12	67 ± 12
Thiopental	81 ± 13	44 ± 12*	50 ± 5	48 ± 11	61 ± 5
Isoflurane	75 ± 11	40 ± 9*	50 ± 11	38 ± 3*	58 ± 7
Hb (mg/dl)					
Control	12.3 ± 0.86	8.6 ± 1.0	8.5 ± 0.7	8.4 ± 1.1	9.1 ± 1.0
Thiopental	11.8 ± 1.4	7.6 ± 1.0	(7.2, 6.9)	7.7 ± 0.9	8.4 ± 0.9
Isoflurane	12.4 ± 0.9	8.4 ± 1.0	8.5 ± 0.7	8.4 ± 0.5	8.4 ± 0.4

Pa_{CO_2} at 37°C; MAP = mean arterial pressure; CPP = cerebral perfusion pressure; Hb = hemoglobin concentration; CBF = cerebral blood flow; CPB = cardiopulmonary bypass. Results are mean ± SD. * $P < 0.05$ *vs.* control; † $P < 0.05$ *vs.* thiopental.

suppression with thiopental during hypothermic CPB (cold CPB_{15}) was associated with significantly lower CBF and $CMRO_2$ than control. Only two CBF measurements were obtained at cold CPB_{30} in the thiopental group, and these data points are presented in table 3, but were not subjected to statistical analysis. Thiopental-induced EEG suppression was also associated with significantly lower CBF and $CMRO_2$ than control during warm CPB.

Pharmacologic EEG suppression with isoflurane was associated with a significantly lower $CMRO_2$ than control at each stage of CPB. One patient in the isoflurane group had elevated CBF before CPB (48 ml · 100 g^{-1} · min^{-1}) and during CPB (27 ml · 100 g^{-1} · min^{-1} at cold CPB_{15}; 24 ml · 100 g^{-1} · min^{-1} at cold CPB_{30}) with similar $CMRO_2$ to the other patients in the group, and so was considered an outlier; the values are excluded from statistical analysis. CBF during isoflurane-induced EEG suppression at cold CPB_{15} was intermediate between control and thiopental groups, but was not statistically different from either. At cold CPB_{30} CBF during isoflurane-induced EEG suppression was again somewhat lower than control, but did not reach statistical significance. During warm CPB, CBF during isoflurane-induced EEG suppression was similar to control and greater than thiopental.

Post-CPB measurements were made 15–30 min after termination of CPB, and in EEG suppression groups, after discontinuation of the agent used with return to continuous EEG activity. CBF and $CMRO_2$ values after CPB were similar in all three groups.

In the early post-bypass period, ephedrine or an infusion of inotropic agents were used to increase cardiac contractility in 2/12 control patients, 2/7 patients who had been treated with thiopental, and 2/12 patients who had been treated with isoflurane. A further two patients in the control group and two patients who had received thiopental required mechanical assist devices for left ventricular failure attributable to perioperative myocardial ischemia.

TABLE 3. Cerebral Blood Flow (ml · 100 g^{-1} · min^{-1})

	Pre-CPB	Cold CPB_{15}	Cold CPB_{30}	Warm CPB	Post-CPB
Control	26.9 ± 5.6	14.6 ± 5.5	12.8 ± 4.1	19.5 ± 4.8	25.4 ± 6.0
Thiopental	32.4 ± 6.7	8.2 ± 2.5*	(7.2, 12.1)	14.9 ± 1.0†	21.8 ± 3.7
Isoflurane	24.6 ± 5.8	11.8 ± 2.5	9.2 ± 1.5	19.6 ± 4.7	24.8 ± 3.6

CPB = cardiopulmonary bypass. Results are mean ± SD. * $P < 0.05$ *vs.* control; † $P < 0.05$ *vs.* other groups.

TABLE 4. Cerebral Metabolic Rate for Oxygen (ml · 100 g^{-1} · min^{-1})

	Pre-CPB	Cold CPB_{15}	Cold CPB_{30}	Warm CPB	Post-CPB
Control	1.80 ± 0.32	0.41 ± 0.08	0.48 ± 0.11	1.16 ± 0.21	1.38 ± 0.37
Thiopental	2.36 ± 0.48	0.27 ± 0.02*	(0.23, 0.37)	0.92 ± 0.14*	1.33 ± 0.13
Isoflurane	1.78 ± 0.41	0.29 ± 0.04*	0.30 ± 0.06*	0.76 ± 0.16*	1.17 ± 0.24

CPB = cardiopulmonary bypass. Results are mean ± SD. * $P < 0.05$ *vs.* control.

Discussion

This is the first report of the cerebral metabolic and hemodynamic effects of thiopental or isoflurane-induced EEG suppression during CPB in humans.

The CBF measurement techniques used in the present study (intravenous and intra-aortic injections) will both yield a slight underestimate of "true" CBF due to the presence of Xenon in the extracerebral (scalp) tissues. Estimates of grey matter blood flow obtained by bicompartmental analysis are not significantly affected by this extracerebral contamination,[14] but estimates of white matter and weighted mean blood flows are underestimated by 10–15%.[8]

The use of noncompartmental stochastic analysis (height/area) for calculating mean CBF is less sensitive to this contamination, and integration to 15 min rather than infinity further reduces the effect of the extracerebral compartment. The stochastic method produces estimates of mean CBF which are within 2–5% of the "true" mean flow over a wide range of flow rates.[8]

For determination of $CMRO_2$, sampling of effluent cerebral venous blood from a jugular bulb catheter is representative of the venous drainage from all brain structures due to mixing in the confluence of the venous sinuses.[15] Although there is some drainage of extracerebral tissue *via* the cortical emissary veins, blood sampled from the jugular bulb is contaminated to less than 3% by extracerebral flow.[16]

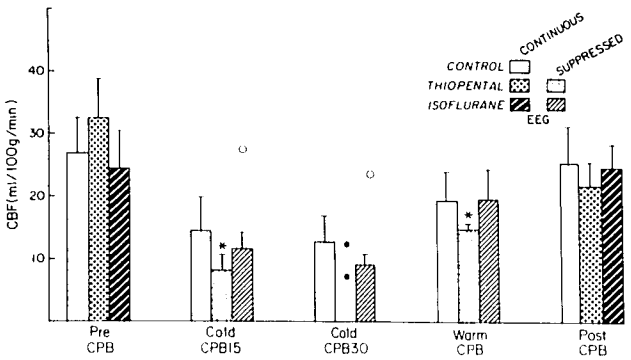

FIG. 2. CBF values in control, thiopental, and isoflurane groups; see text for discussion. Values are mean + SD. O = outlying result excluded from statistical analysis (patient in isoflurane group); ● = individual values for CBF in thiopental group at CPB_{30} (n = 2); CBF = cerebral blood flow; CPB = cardiopulmonary bypass. *$P < 0.05$ *versus* control.

Patients undergoing CPB for closed heart surgery were selected as subjects for this study, as they are less at risk of cerebral embolism[17] which might cause pathologic derangements of CBF, complicating the interpretation of the data. The radioxenon washout technique has previously been used to measure CBF in humans during cardiac surgery in an attempt to elucidate the effects of cardiopulmonary bypass on the cerebral circulation,[18–21] and postoperatively to ascertain the incidence of diffuse cerebral injury.[22,23]

Many factors influence CBF and $CMRO_2$, and it has been reported that CBF is independent of mean arterial pressure over the range 30–110 mmHg using the described bypass technique, implying that cerebral autoregulation is maintained.[18,19] The ventilation parameters used in this study produced mild hypocapnia before and after CPB. Our intention during CPB was to achieve normocapnia on arterial blood gas analysis measured at 37° C and uncorrected for patient temperature,[11,12] and values achieved were comparable between groups at each period (table 2).

The profile of intraoperative CBF and $CMRO_2$ changes seen in the control group for this study is similar to that previously reported from this unit, in which the anesthetic technique varied primarily in the premedication used.[18] The Pre-CPB CBF and $CMRO_2$ values are lower than normal values for the awake patient, and are attributable to anesthesia, mild hypothermia, and hypocapnia (table 2). The Pre-CPB CBF values are comparable to those obtained by Henriksen *et al.*[21] using the Initial Slope Index method following intra-arterial injection of radio-Xenon. Govier *et al.*[19] and Prough *et al.*[20] measured CBF in humans during hypothermic CPB and found low values comparable to the control group presented here. Both this and our previous study have documented the low $CMRO_2$ attained during hypothermic CPB in humans, and we postulate that $CBF/CMRO_2$ coupling is responsible for the low CBF.[18] By contrast, Henriksen *et al.*[21] reported cerebral hyperperfusion during hypothermic CPB, but their bypass technique included the addition of CO_2 to maintain normal temperature-corrected arterial P_{CO_2} values. The effects of acid/base management on CBF and $CMRO_2$ during hypothermic CPB are discussed by us elsewhere.[18]

EEG suppression was achieved in all patients treated with either thiopental or isoflurane. The initial dose of thiopental (8 $mg \cdot kg^{-1}$) was determined from a report by Quasha *et al.* noting its efficacy in inducing prolonged burst suppression during hypothermic CPB.[13] Isoflurane has similarly been shown to be an effective EEG suppressant during hypothermic CPB by Loomis *et al.*[24] They reported onset of burst suppression at a higher average isoflurane vaporizer setting (2.2%), which, exclusive of vaporizer performance, may partly reflect the lower dosage of narcotic their patients had received (average fentanyl 0.07 $mg \cdot kg^{-1}$). In addition, their primary end-point was reduction of MAP rather than induction of EEG burst suppression. We have reported isoflurane-induced EEG suppression during non-cardiac surgery occurring at vaporizer settings similar to those required during normothermic CPB.[25]

$CMRO_2$ at burst/suppression was similar with either agent during hypothermia (approximately 0.3 $ml \cdot 100\ g^{-1} \cdot min^{-1}$ at 28° C), and presumably reflects the basal cerebral oxygen consumption at those temperatures. The proportionate reduction in $CMRO_2$ achieved by pharmacologic EEG suppression from the anesthetized, continuous-EEG control state at either temperature was of the order of 30%, and is in good agreement with the findings of Astrup *et al.* who used pentobarbital or lidocaine to induce EEG suppression in a canine laboratory model of hypothermic and normothermia CPB.[26] Our results also support the hypothesis of Steen *et al.*[27] that thiopental only reduces $CMRO_2$ during CPB by reducing functional electrical activity, and is only additive with hypothermia in the presence of EEG activity. For example, it is evident from our data that hypothermia to 26–30° C, which does not extinguish EEG activity, provides more cerebral metabolic depression than does pharmacologic EEG suppression at 37° C (table 4). We are not aware of any laboratory studies of isoflurane effect on cerebral metabolism during hypothermic CPB, but Newberg *et al.* have demonstrated that isoflurane, like thiopental, only reduces $CMRO_2$ by reducing functional cerebral activity, and that no further reduction in $CMRO_2$ occurs when the EEG becomes isoelectric.[4]

In the thiopental group, CBF was reduced in conjunction with $CMRO_2$. Reductions in CBF would be expected to produce a proportionate reduction in the delivery of emboli to the cerebral circulation. The cerebroprotective effects of thiopental reported by Nussmeier *et al.*[1] may, therefore, be primarily due to cerebral vasoconstriction rather than a primary reduction in $CMRO_2$. A reduction of CBF was not achieved in the isoflurane group. There was a tendency to lower CBF associated with isoflurane-induced EEG suppression during hypothermic CPB, but it did not attain statistical significance in this study. A biphasic effect of isoflurane on CBF has been noted in baboons; at less than 1 MAC isoflurane, CBF is reduced in conjunction with $CMRO_2$, but, at greater than 1 MAC isoflurane, cerebral vasodilatation occurs and CBF returns to baseline levels, despite further reduction in $CMRO_2$.[28] This uncoupling of the CBF/$CMRO_2$ relationship has been documented in humans during isoflurane-induced hypotension[29] and isoflurane-induced EEG suppression.[25] There may, therefore, be a real reduction of CBF during EEG suppression with 1% isoflurane during hypothermic CPB which, because of sample size, this study has failed to confirm statistically. EEG suppression with 2.5–3.5% isoflurane during normothermic CPB is undoubtedly associated with a degree of cerebral hyperperfusion relative to the reduced $CMRO_2$. One possible mechanism for this vasodilatation is an increase in brain cyclic-AMP.[30]

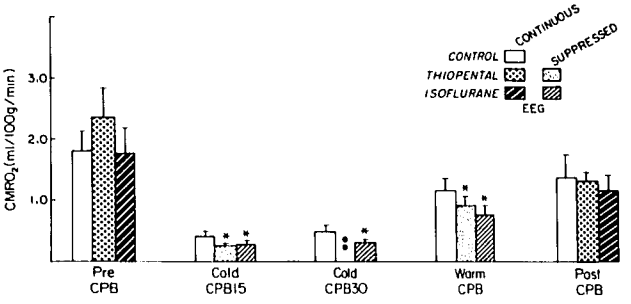

FIG. 3. $CMRO_2$ values in control, isoflurane, and thiopental groups; see text for discussion. Values are mean + SD. ● = individual values for $CMRO_2$ in thiopental group at CPB_{30}; $CMRO_2$ = cerebral metabolic rate for oxygen; CPB = cardiopulmonary bypass. $*P < 0.05$ *versus* control.

A potentially limiting side effect of barbiturate-induced EEG suppression is known to be persistent depression of myocardial contractility. Upon reviewing our preliminary results, we found that three of 22 patients studied up to that point had evidence of severe ischemic left ventricular failure after CPB. Two of them had received thiopental. Though there was no evidence that thiopental was responsible for myocardial ischemia, we were concerned that the barbiturate might reduce the response to inotropic drugs, and felt that we were not justified in continuing to use thiopental in association with our high-dose fentanyl anesthetic technique for patients with ischemic heart disease, as they are not the primary risk group for embolic cerebral complications. At completion of our study, one further patient (in the control group) had sustained severe ischemic left ventricular failure.

In summary, we have demonstrated that EEG suppression with thiopental during CPB in humans reduces both CBF and $CMRO_2$. Isoflurane is also effective in inducing EEG suppression and reducing $CMRO_2$ dur-

ing CPB, although it does not reduce CBF during normothermic CPB when high concentrations are required to maintain EEG suppression. These differences in effect on CBF may be important in considerations of potential cerebral protection against cerebral emboli global or focal ischemia associated with cardiopulmonary bypass. Hypothermia is a potent metabolic depressant and, in the presence of EEG activity, its effects can be augmented by pharmacologic EEG suppression. Clinical outcome studies are indicated to assess the relative benefits of hypothermia and pharmacologic EEG suppression in patients undergoing open or closed heart surgery during CPB.

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