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Ineffectiveness of Burst Suppression Therapy in Mitigating Perioperative Cerebrovascular Dysfunction

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Background: **Cerebral injury is among the most common and disabling complications of open heart surgery. Attempts to provide neuroprotection have yielded conflicting results. We assessed the potential of propofol-induced burst suppression during open heart surgery to provide cerebral protection as determined by postoperative neuropsychologic function.**

Methods: **Two hundred twenty-five patients undergoing valve surgery were randomized to receive either sufentanil or sufentanil plus propofol titrated to electroencephalographic burst suppression. Blinded investigators performed neurologic and neuropsychologic testing at baseline, postoperative day (POD) 1 (neurologic testing only), PODs 5–7, and PODs 50–70. Neuropsychologic tests were compared with the results of 40 nonsurgical patients matched for age and education.**

Results: **Electroencephalographic burst suppression was successfully achieved in all 109 propofol patients. However, these patients sustained at least as many adverse neurologic outcomes as the 116 controls: POD 1, 40% *versus* 25%, $P = 0.06$; PODs 5–7, −18% *versus* 8%, $P = 0.07$; PODs 50–70, −6% *versus* 6%, $P = 0.80$. No differences in the incidence of neuropsychologic deficits were detected, with 91% of the propofol patients *versus* 92% of the control patients being impaired at PODs 5–7, decreasing to 52 and 47%, respectively, by PODs 50–70. No significant differences in the severity of neuropsychologic dysfunction, depression, or anxiety were noted.**

Conclusions: **Electroencephalographic burst suppression surgery with propofol during cardiac valve replacement did not significantly reduce the incidence or severity of neurologic or neuropsychologic dysfunction. The authors' results suggest that neither cerebral metabolic suppression nor reduction in cerebral blood flow reliably provide neuroprotection during open heart surgery. Other therapeutic approaches must be evaluated to address this important medical problem. (Key words: Cerebral; embolism; neurologic; neuroprotective; propofol.)**

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CENTRAL nervous system dysfunction after cardiac valve replacement surgery continues to pose a significant challenge, with stroke occurring in up to one fourth of patients undergoing open heart procedures and detectable neurologic abnormalities in up to one half.[1–3] The reported incidence of neuropsychologic dysfunction has not been extensively studied in this patient population, although the incidence is believed to be at least as high as that for coronary artery bypass graft (CABG) surgery, with dysfunction occurring in up to 79–88% of patients within a week of surgery.[4–6] Perioperative neurologic and neuropsychologic dysfunction are of profound significance because they lead to increases in mortality rate and resource use, *i.e.*, prolongation of intensive care unit

and hospital stays and increased need for long-term rehabilitation.[2,7]

Despite widespread recognition of the problem, few advances have been made in preventing or treating cerebral complications precipitated by cardiac surgery. Efforts have been focused on reducing cerebral embolization with the use of arterial filters and membrane oxygenators, alterations in management of the ascending aorta, and surgical air-evacuation maneuvers.[2] A mainstay of neuroprotective therapy has been systemic hypothermia, although recent reports differ regarding its effectiveness in the setting of cardiopulmonary bypass.[8–11] Pharmacologic cerebral protection has been proposed, including calcium-channel antagonists[12] and electroencephalographic (EEG) burst suppression with thiopental.[13,14] However, the former has not been proven to be effective, and the latter approach remains controversial. Although one study of thiopental showed significant protection in patients undergoing open-chamber procedures,[13] a subsequent study failed to show neuroprotection in CABG patients.[14] Furthermore, the doses of barbiturates necessary for EEG burst suppression have been associated with significant myocardial depression, increased need for vasopressors, and prolonged time to tracheal extubation.[13,14] Thus, the use of barbiturates for cerebral protection in this setting currently is not widespread, with attention focusing on other methods of attaining EEG burst suppression.

Propofol has been shown to have effects similar to thiopental on cerebral metabolism and blood flow.[15] It has a favorable pharmacokinetic profile, having been used successfully in CABG surgery without significant myocardial depression or prolonged sedation.[16,17] In addition, it also has been shown to have antioxidant properties[18] and perhaps calcium-channel antagonism[19] that may reduce the impact of cerebral injury during cardiac surgery. Therefore, we designed a prospective, randomized clinical trial to determine whether propofol titrated to EEG burst suppression reduces the incidence or severity of cerebral injury associated with valve surgery using neuropsychologic function 2 months postoperatively as the primary endpoint. To assess possible effects on a broad spectrum of cerebral injuries, we used a strategy of testing for neurologic and neuropsychologic abnormalities with validated testing instruments at repeated intervals. Finally, to assess safety, we ascertained the effects of burst suppression doses of propofol on hemodynamics and time to extubation.

Methods

After institutional review board approval at each site and obtaining informed consent, we studied 225 patients undergoing aortic or mitral valve surgery at the San Francisco Kaiser-Permanente Medical Center, the Duke University Medical Center, and the University Hospital, University of Western Ontario, with central analysis performed by the Ischemia Research and Education Foundation. To be eligible for the study, patients had to be between 21 and 79 yr old, hemodynamically stable, and scheduled to undergo elective valve repair or replacement (with or without CABG). Exclusion criteria included pregnancy, history of cerebral infarction or significant neurologic illness, recent seizure history, an ejection fraction less than 0.40, cardiogenic shock, recent history of drug abuse, recent participation in another investigational trial, and inability or unwillingness to comply with the protocol. Patients were randomized for each surgeon at each medical center in balanced blocks.

Intraoperative Management

Patients were premedicated with lorazepam, 0.03–0.06 mg/kg orally, and morphine sulfate, 0.10–0.15 mg/kg 60–90 min before surgery. All routine cardiovascular medications were continued through the morning of surgery. Before induction of anesthesia, catheters were inserted into the radial and pulmonary arteries. EEG monitoring was performed using a Neurotrac II system (Moberg Medical, Ambler, PA) and consisted of 10 leads affixed in a standard parasagittal bipolar block montage using 10-mm gold cups with collodion. The raw EEG was monitored and recorded continuously with an amplitude adjusted to 5 μV/mm. Impedance was maintained below 5,000 Ω throughout the study.

For all patients, anesthesia was induced with sufentanil, 5 μg/kg, followed by infusion at 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$. If necessary, additional boluses of 1 μg/kg were given for indications of light anesthesia, with incremental increases in the infusion rate of 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ with each bolus. After induction of anesthesia, patients randomized into the propofol treatment group received propofol, *via* computer-assisted continuous infusion titrated to achieve EEG burst suppression (60 s between bursts from previous aortic cannulation through chest closure). Heart rate was maintained at less than 120% of baseline, and systolic blood pressure was maintained within 20% of baseline (determined as the mean of three preoperative determinations) by adjusting the level of

anesthesia, administering volume, or administering vasopressors, β blockers, or vasodilators as clinically indicated.

Cardiopulmonary bypass was managed with membrane oxygenators, α-stat blood gas management, 20-μm arterial blood filters, nonpulsatile perfusion at 2.0–2.6 l · m^{-2} · min^{-1}, and systemic hypothermia to 25–28°C (nasopharyngeal). Mean arterial blood pressure was maintained between 50 and 90 mmHg, using phenylephrine or sodium nitroprusside as indicated. Hematocrit was maintained at more than 18%, and glucose was maintained less than 200 g/dl with insulin, if necessary.

Neurologic and Neuropsychologic Assessments

Patients underwent a battery of neurologic and neuropsychologic tests preoperatively administered by trained nurse specialists with intra- and interobserver validity ensured. Standardized neurologic testing consisted of the National Institutes of Health Stroke Scale[20] and the Western Perioperative Neurologic Scale.[5] The neuropsychologic battery consisted of the Digit Symbol subtest of the Wechsler Adult Intelligence Scale—Revised, the Paired Associated Learning Subset of the Wechsler Memory Scale, the Trails A and B test, the Grooved Pegboard test, and the Letter Cancellation test, all administered using a computer installed with Bowman Gray's Automated Behavioral Assessment System software program (courtesy of Dr. David A. Stump, Wake Forest University School of Medicine, Winston-Salem, NC). In addition the Spielberger State Anxiety Inventory, the Spielberger Trait Anxiety Inventory and the Beck Depression Inventory were administered to all patients.

Neurologic testing was repeated on postoperative days (PODs) 1 and 2, PODs 5–7, and PODs 50–70. Changes in neurologic function were assessed by determining the frequency and severity of the score change from baseline at the test periods on PODs 1 and 2 and PODs 50–70. Patients were considered to have adverse neurologic outcomes if they showed a change of more than three points on either scale (National Institutes of Health Stroke Scale, Western Perioperative Neurologic Scale). Severity of neurologic outcome was determined by combining the change score of the National Institutes of Health and the Western Perioperative Neurologic Scale examinations. The summation of scores has the effect of emphasizing factors common to both scales and deemphasizing but still accounting for factors used on only one scale. Frequency of adverse neurologic outcome was determined by the number of test periods in which the patient was classified as positive for neurologic outcome.

Neuropsychologic testing was performed before surgery (baseline) and repeated on PODs 5–7 and PODs 50–70. Data obtained from the neuropsychologic battery were assigned to one of four domains: verbal learning, motor dexterity, visual scanning, and psychomotor speed. Each test was scored and the scores of the two testing periods (PODs 5–7 and PODs 50–70) were compared to the preoperative baseline test scores. When the change score from baseline of any test was below the fifth percentile of normative change scores (based on a substudy of 40 nonsurgical volunteers matched for age, gender, and education and tested at identical intervals to the study population), the patient was considered positive for neuropsychologic outcome, with deficits in two or more domains considered to be a severe neuropsychologic outcome. To be considered calculable at each testing period, the patient had to complete testing in each of the four domains or test positive in at least one domain. Severity of neuropsychologic outcome in each testing period was determined by the number of domains in which the patient had a positive outcome. Frequency of adverse neuropsychologic outcome was determined by the number of times the patient tested positive across the two testing periods.

Statistical Methods

For categoric variables, the homogeneity of the odds ratios was evaluated and the general association between treatment and primary endpoints was derived, after controlling for center and coronary artery disease using the Cochran–Mantel–Haenszel method. For continuous variables, a general linear model test (adjusted for center and grouped by center) was used and, if the results were not consistent, the Kruskal–Wallis median test was used. All tests were two tailed, with $P \leq 0.05$ considered significant.

Results

A total of 225 patients were enrolled in the study and randomized to either group A (propofol; 109 patients) or group B (sufentanil only; 116 patients). Demographic medical history and surgical data were similar between groups (table 1). There were no differences between groups with respect to neurologic history, type or duration of surgery, or time to extubation (table 2).

Table 1. Demographics

	Group A Propofol + Sufentanil Anesthesia	Group B Sufentanil Anesthesia	*P* Value
Number of patients evaluable	109	116	
Age (yr)			
Mean ± SD	63 ± 12.9	63 ± 11.5	0.72
(range)	(22–78)	(28–79)	
Height (cm)			
Mean ± SD	170 ± 9.9	169 ± 10.6	0.47
(range)	(137.5–197.0)	(142–190.5)	
Weight (kg)			
Mean ± SD	78 ± 14.6	77 ± 15.7	0.32
(range)	(46.9–124.3)	(42.8–136)	
Sex			
Male	75 (68.8%)	66 (56.9%)	0.054
Female	34 (31.2%)	50 (43.1%)	
Highest education level			
Attended grade school	8 (7%)	15 (13%)	0.1924
Attended high school	24 (22%)	28 (25%)	
High school graduate	32 (30%)	27 (24%)	
Attended college	27 (26%)	16 (14%)	
College graduate	10 (9%)	17 (15%)	
Postgraduate degree	7 (6%)	10 (9%)	
Medical history			
Cardiac history			
Coronary artery disease (CAD)	55 (50.5%)	42 (36.2%)	0.03
Stable angina	31 (28.4%)	28 (24.1%)	0.48
Unstable angina	5 (4.6%)	3 (2.6%)	0.44
Myocardial infarction	11 (10.1%)	10 (8.6%)	0.68
Previous CABG surgery	4 (3.7%)	4 (3.4%)	0.86
PTCA history	3 (2.8%)	3 (2.6%)	0.91
Congestive heart failure (CHF)	46 (42.2%)	52 (44.8%)	0.43
Arrhythmia	39 (35.8%)	37 (31.9%)	0.54
Cardiac risk factors			
Smoking history	69 (63.3%)	63 (54.3%)	0.20
Hypertension	50 (45.9%)	50 (43.1%)	0.72
Diabetes mellitus	5 (4.6%)	11 (9.5%)	0.16
Hypercholesterolemia	12 (11.0%)	23 (19.8%)	0.07
Carotid bruit	3 (2.8%)	8 (6.9%)	0.18
Neurologic/neuropsychologic history			
TIA history	4 (3.7%)	4 (3.5%)	0.94
Impaired sensory/motor function	1 (0.9%)	2 (1.7%)	0.60
Psychosis	1 (0.9%)	1 (0.9%)	0.97
Seizure	2 (1.8%)	3 (2.6%)	0.65
ASA classification			0.52
Class II	1 (0.9%)	0	
Class III	6 (5.5%)	5 (4.3%)	
Class IV	102 (93.6%)	111 (95.7%)	

Burst Suppression

Patients in the sufentanil (control) group received a total of 1,040 ± 583 μg of sufentanil per patient, compared with 767 ± 280 μg of sufentanil in the propofol group ($P = 0.0004$). To achieve initial burst suppression, 150 ± 132 mg propofol was used, with a total dose of 3,062 ± 2,040 mg necessary for maintenance of EEG burst suppression (mean time 3.2 ± 0.9 h).

Neurologic and Neuropsychologic Outcomes

Patients in the propofol group tended to have a higher incidence of adverse neurologic outcomes at PODs 1 and 2 (40 *vs.* 25%, $P = 0.06$), and PODs 5–7 (18 *vs.* 8%, $P = 0.07$), but these differences had resolved by PODs 50–70 (6.2 *vs.* 6.2%, $P = 0.80$) (table 3). There were no significant differences in severity or frequency of neurologic outcome between the two groups at any time period.

Table 2. Perioperative Procedures and Events

	Sufentanil Group A Propofol + Anesthesia	Sufentanil Group B Anesthesia	*P* Value
Number of patients	109	116	
Type of surgery			0.64
Valve surgery	72 (66%)	80 (69%)	
Valve + CABG surgery	37 (34%)	36 (31%)	
Type of cardiac valve surgery			0.71
Aortic valve surgery	32 (29.4%)	40 (34.5%)	
Redo aortic valve surgery	8 (7.3%)	9 (7.8%)	
Aortic valve + CABG surgery	27 (24.8%)	20 (17.2%)	
Redo aortic valve + CABG surgery	0	3 (2.6%)	
Mitral valve surgery	22 (20.2%)	24 (20.7%)	
Redo mitral valve surgery	7 (6.4%)	5 (4.3%)	
Mitral valve + CABG surgery	8 (7.3%)	11 (9.5%)	
Redo mitral valve + CABG surgery	0	1 (0.9%)	
Aortic and mitral valve surgery	2 (1.8%)	1 (0.9%)	
Redo aortic and mitral valve surgery	1 (0.9%)	1 (0.9%)	
Aortic and mitral valve + CABG surgery	1 (0.9%)	0	
Redo aortic and mitral valve + CABG surgery	1 (0.9%)	1 (0.9%)	
Surgical conditions			
Aortic cross-clamp timed (h)	1.3 ± 0.5 (n = 106)	1.3 ± 0.6 (n = 116)	0.73
Cardiopulmonary bypass timed (h)	2.1 ± 0.7 (n = 108)	2.1 ± 0.8 (n = 116)	0.71
Duration of operation (h)	4.7 ± 1.4 (n = 106)	4.6 ± 1.5 (n = 106)	0.70
Hemodynamics			
Hypotension*			
Prebypass	74%	43%	<0.01
Bypass	78%	50%	<0.01
Postbypass	56%	41%	0.02
Hypertension†			
Prebypass	30%	38%	0.09
Bypass	15%	28%	0.01
Postbypass	12%	9%	
Vasoconstriction use (phenylephrine)	5.0 ± 5.3 mg	2.5 ± 5.6 mg	<0.01
IABP use	6%	2%	0.11
Pacemaker use	71%	68%	0.89
Extubation median time (h) (range)	19.4 (6.5 ~ 327)	18.3 (6.5 ~ 208)	0.09***

Values are mean ± SD.

* Hypotension: SBP < 80% baseline pre-CPB-MAP < 50 on CPB, SBP < 90 post-CPB for ≥ 5 min.

† Hypertension: SBP > 120% baseline pre-CPB-MAP > 90 on CPB, SBP > 140 post-CPB for ≥ 5 min.

Statistical include tests of significance (*P* values).

‡ Nonparametric Kruskal-Wallis test.

Neuropsychologic deficits were present in 91% of the propofol patients *versus* 92% ($P = 0.73$) of the sufentanil patients at PODs 5–7 decreasing to 52 and 47% ($P = 0.58$), respectively, by PODs 50–70. Likewise, neither the severity nor the frequency of neuropsychologic outcomes differed significantly between treatment groups at any postoperative test period (table 4), nor were there differences for the depression or state–trait anxiety scales.

Intraoperative Hemodynamic and Surgical Factors

There were no significant differences between groups for aortic cross-clamp time, cardiopulmonary bypass time, or duration of operation. Hemodynamic analysis revealed that the propofol group had a significantly higher incidence of hypotension prebypass (74 *vs.* 43%, $P < 0.001$), during bypass (78 *vs.* 50%, $P < 0.001$), and postbypass (56 *vs.* 41%, $P < 0.02$). This coincided with a twofold difference in use of phenylephrine intraoperatively (5.0 ± 5.3 mg *vs.* 2.5 ± 5.6 mg, propofol *vs.* sufentanil, $P = 0.002$). The sufentanil group had a significantly higher incidence of hypertension during bypass (28 *vs.* 15%, $P = 0.01$). Use of an intraaortic balloon pump was similar (6 *vs.* 2%, $P = 0.11$), as were the need for a pacemaker (71 *vs.* 68%, $P = 0.89$), use of inotropes

Table 3. Incidence of Neurologic Outcome

	Group A Propofol + Sufenta Anesthesia (n = 109) (%)	Group B Sufenta Anesthesia (n = 116) (%)	*P* Value
POD 1			
Neurologic deficit	40/101 (40)	27/110 (25)	0.06
POD 6			
Neurologic deficit	18/98 (18)	8/103 (8)	0.07
POD 60			
Neurologic deficit	5/81 (6)	5/81 (6)	0.80

or vasopressors, and median time to extubation (19.4 *vs.* 18.3 h) (table 2). Finally, the in-hospital mortality rate from all causes was 3.1%, without difference between groups (propofol 4.5%, sufentanil 1.7%, $P = 0.27$).

Discussion

This multicenter study is the first report of the neurologic and neuropsychologic effects of propofol-induced EEG burst suppression during cardiac surgery. Our randomized clinical trial of 225 patients undergoing valve surgery showed that propofol-induced EEG burst suppression did not reduce adverse neurologic or neuropsychologic outcomes up to 2 months after surgery. Neurologic outcomes persisted in 6.2% of patients in each group at 2 months without significant differences in severity. Approximately half of the patients in each group showed neuropsychologic deficits at 2 months, also without significant differences in severity.

Because neuroprotective agents generally limit the size of cerebral infarct rather than the incidence of infarction,[21] we designed this trial to assess the severity of insult and the incidence. Because of the logistic difficulties and expense associated with perioperative imaging studies, we used neurologic scales that have been shown to be sensitive in detecting neurologic injury[5] and to correlate with infarct size.[20] Neuropsychologic dysfunction over time also correlates with the extent of injury[22]; hence, we repeated testing at several intervals up to PODs 50–70. Testing several months postoperatively also minimizes potential confounders such as pain, concomitant medications, and environmental stimulation that may interfere with perioperative neuropsychologic assessments.[23]

Previous Studies

Animal Studies. Studies of the neuroprotective effects of propofol in animal models have yielded inconsistent findings. Kochs *et al.*[24] demonstrated improvement in neurologic outcomes and neuronal damage in propofol-treated rats subjected to right common carotid artery occlusion. However, Ridenour *et al.*[25] detected no improvement in neurologic outcomes or cerebral infarct volumes after ligation of a middle cerebral artery in rats given propofol compared to rats given halothane. Propofol protected against transient forebrain ischemia-induced delayed hippocampal neuronal death in a gerbil model, although it did not improve survival.[26]

Studies in Patients. Many changes in surgical or cardiopulmonary bypass techniques have been thought to diminish cerebral injury associated with cardiac surgery. Although there is evidence to suggest arterial filters,[27]

Table 4. Incidence of Neuropsychologic Outcome

	Group A Propofol + Sufentanil Anesthesia (%)	Group B Sufentanil Anesthesia (%)	*P* Value
Incidence			
At POD 5–7	83/91 (91)	93/101 (92)	0.73
At POD 50–70	35/67 (52)	31/66 (47)	0.58
Severity Score*			
POD 5–7			0.90
0	8/85 (9)	8/86 (9)	
1	23/85 (27)	38/86 (44)	
2	34/85 (40)	34/86 (40)	
3	14/85 (16)	5/86 (6)	
4	6/85 (7)	1/86 (1)	
POD 50–70			0.45
0	32/63 (51)	35/60 (58)	
1	23/63 (37)	21/60 (35)	
2	3/63 (5)	2/60 (3)	
3	0/63 (0)	0/60 (0)	
4	5/63 (8)	2/60 (3)	
Severity ≥ 2†			
POD 5–7	58/109 (53)	46/116 (40)	0.07
POD 50–70	9/109 (8)	7/116 (6)	0.60

* Severity score is number of domains positive for adverse outcomes. Four domains were tested: verbal learning, motor dexterity, visual scanning, and psychomotor speed. The Severity Score therefore can range from 0 (no domains positive) to 4 (all domains positive). Patients must have been tested in all domains at each testing period to be scored.

† Not necessary to be tested in all four domains for this measurement.

membrane oxygenators,[28] and surgical evacuation of intracardiac air may decrease cerebral embolism, little evidence supports claims of improved central nervous system outcomes associated with these techniques. Currently, a great deal of attention has been focused on management of the diseased proximal aorta. Although some studies have shown promise, no prospective randomized study has convincingly shown the effectiveness of any of the suggested techniques.[7,29]

In contrast, both arterial blood-gas management and temperature and have been studied in prospective, randomized trials. Murkin *et al.*[5] demonstrated an improvement in neuropsychologic outcomes with α-stat blood-gas management. Regarding hypothermia, some investigators have demonstrated improved cerebral outcomes with hypothermia[9,11,30]; other investigators have detected no differences between normothermic and hypothermic patients.[8,10] Interpretation of these studies is confounded by differences in study design, including untreated hyperglycemia during bypass[9,30] and the use of bladder rather than nasopharyngeal temperatures.[8,9,30]

Pharmacologic protection from cerebral ischemia has been an elusive goal. Barbiturates, calcium-channel blockers, and other agents, including adenosine-regulating agents, have been tested in patients undergoing cardiac surgery. Calcium-channel antagonists may block the flow of calcium into ischemic cells, interrupting the ischemic cascade and improving postischemic hypoperfusion. However, only L-channel blockers, such as nimodipine, are clinically available, and these do not prevent central excitatory neurotransmitter release. An investigation of nimodipine in cardiac surgical patients was discontinued early because of excess mortality and bleeding without evidence of neuroprotective effects.[12]

Acadesine, an adenosine-regulating agent, was found in one study to be associated with a decreased incidence of stroke after CABG from 4.5% to 0.5%.[31] A meta-analysis of other studies (n = 2013) showed a trend toward reduced incidence of stroke ($P = 0.10$).[32] These studies suggest potential for adenosine-regulating drugs to reduce strokes after cardiac surgery.

Although animal studies with thiopental have shown smaller infarct size after transient focal ischemia, only one study in patients undergoing open chamber cardiac surgery has shown any benefit in humans.[13] Although this report initially was received with enthusiasm, the side effects of hemodynamic depression and prolonged sedation coupled with a subsequent report showing no benefit in coronary artery bypass surgery[14] have led to skepticism of the role of thiopental in providing neuroprotection in the setting of cardiac surgery.

The differences in results of the Nussmeier *et al.*[13] and Zaidan *et al.*[14] studies may be explained by a number of factors. Perhaps most notably, the studies were performed in different patient populations—open-chamber *versus* coronary artery bypass procedures. Although there may be considerable overlap in the causes of cerebral injury between the two types of procedures, open-chamber procedures are associated with a much higher incidence of air embolism and valve debris; CABG procedures are more likely to result in embolism from aortic atheromas.[2] It has been postulated that air emboli lead to temporary cerebral arterial occlusion, which may be more likely to benefit from intraoperative therapy than atheromatous emboli, which form permanent occlusions.[33] In addition, management of cardiopulmonary bypass in the Nussmeier *et al.*[13] study used several techniques that may increase cerebral embolization or worsen neurologic outcomes, *i.e.*, bubble oxygenators,[28,34] relative normothermia (temperature $\geq$ 34°C),[8,11,30] *p*H-stat blood-gas management,[5] no arterial filters,[7] and glucose priming solutions.[35] If one or more of these techniques worsen neurologic outcomes, a neuroprotective effect would be easier to detect.

Although it remains unclear whether thiopental provides cerebral protection in the setting of cardiac surgery, it clearly limits cerebral damage caused by focal ischemia in animal models.[36,37] Despite its benefits in animal models, the mechanisms of protection remain uncertain. Classically, the cerebral protectant effects of barbiturates were attributed to their ability to depress cerebral metabolism.[38] However, it has been shown that the amount of energy used by the cells for functional metabolism is significantly less than the total amount of energy necessary for maintenance of cellular stability.[39] In addition, other drugs that depress metabolic function have not yielded consistent cerebral protection.[40–43] Other proposed mechanisms include scavenging of free radicals,[44] membrane-stabilizing effects,[45] attenuation of free fatty acid accumulation,[46] and the possibility of decreased numbers of cerebral emboli because of decreased cerebral blood flow with thiopental.[47]

Current Study Findings and Clinical Implications

Propofol has effects similar to thiopental on cerebral metabolism and cerebral blood flow, although it maintains flow–metabolism coupling better than thiopental.[15] Propofol also appears to possess antioxidant properties[18] and calcium-channel antagonist effects,[19] which

may be beneficial in limiting cerebral damage resulting from focal ischemic insults. Thus, we hypothesized that propofol may provide cerebral protection similar to thiopental. Therefore, we designed our trial using a similar patient population and degree of burst suppression and controlled for other potential confounders.

Despite the theoretical advantages of propofol, we were unable to detect any cerebral protectant effects at our primary 2-month endpoint, as shown by an extensive battery of neurologic and neuropsychologic testing. The lack of neuroprotection may have been caused by several factors, including the possibility that propofol lacks neuroprotective effects. Other potential reasons for the lack of a protective effect include management techniques believed to minimize cerebral injury such as α-stat blood-gas management, hypothermia, use of arterial filters and membrane oxygenators, and relatively tight control of glucose. If these techniques in fact decrease the likelihood of cerebral injury, they also would diminish the power to discern a protective effect of propofol. It is also possible the trend toward worse neurologic outcomes at PODs 1 and 2 and PODs 5–7, with improvement by PODs 50–70, represents a neuroprotective effect over the long-term. More likely, the worsened in-hospital dysfunction represents residual drug effects that had dissipated by PODs 50–70, or possibly the fact that some unforeseen action of propofol actually may lead to a detrimental effect, as recently has been shown with nimodipine.[12]

The findings of this study have several important implications for application of drugs thought to have cerebral protectant properties because of suppression of cerebral metabolism. Although propofol quite effectively provided EEG burst suppression for more than 3 h, it did not provide meaningful neuroprotection. This finding supports the hypothesis that profound cerebral cortical metabolic depression does not, in itself, confer protection from focal insults. This is in keeping with a recent study finding that EEG burst suppression is not necessary for maximal neuroprotection with pentobarbital.[37] In addition, it has been postulated that the reduction in cerebral blood flow accompanying EEG burst suppression with agents such as thiopental may reduce the delivery of emboli into the cerebral circulation, and thereby reduce cerebral injury. If this were the case, it would be expected that propofol would provide similar benefit because it also significantly reduces cerebral blood flow. More likely, other properties are responsible for any neuroprotective capabilities of drugs such as barbiturates.

Limitations

Although we used an extensive battery of neurologic and neuropsychologic tests, the tests may not be sensitive enough to reliably detect differences in cerebral infarct size. In addition, this study was powered to detect differences in neuropsychologic outcome—the primary endpoint—and not neurologic outcomes, *per se,* which would have required many more patients. However, because we detected no difference in neurologic outcomes at 2 months, increasing our sample size is unlikely to yield different results. Finally, although hypothermia clearly has been shown to be neuroprotective, use of hypothermic cardiopulmonary bypass necessitates rewarming before discontinuation of bypass. Because most emboli occur during clamp removal and resumption of pulsatile flow[2] when brain temperature may actually exceed 37°C, the brain may be even more susceptible to injury. However, this effect would have been similar between groups and should not affect our conclusions.

Summary

In summary, we were unable to detect any neurologic or neuropsychologic benefit from using propofol-induced EEG burst suppression during cardiac valve surgery. Approximately one half of these patients demonstrate abnormal cognitive functioning at 2 months postsurgery, with 6.2% demonstrating neurologic deficits. Burst suppression with propofol is associated with vasodilation but is otherwise well-tolerated, with similar times to extubation. This study shows that drugs that decrease cerebral metabolism and cerebral blood flow do not necessarily provide cerebral protection during open-chamber cardiac surgery. Future investigations should focus on other potential mechanisms of pharmacologic neuroprotection.

References

1. Sotaniemi KA: Cerebral outcome after extracorporeal circulation: Comparison between prospective and retrospective evaluations. Arch Neurol 1983; 40:75–7

2. Mangano DT, Mora Mangano CT: Perioperative stroke encephalopathy and CNS dysfunction. J Intensive Care Med 1997; 12:148–60

3. Inoue K, Luth JU, Pottkamper D, Strauss KM, Minami K, Reichelt W: Incidence and risk factors of periperative cerebral complications: Heart transplantation compared to coronary artery bypass grafting and valve surgery. J Cardiovasc Surg 1998; 39:201–8

4. Shaw P, Bates D, Cartildge NEF, Heaviside D, Julian DG, Shaw DA:

Early neurological complications of coronary artery bypass surgery. Br Med J 1985; 291:1384–7

5. Murkin JM, Martzke JS, Buchan AM, Bentley C, Wong CJ: A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. J Thorac Cardiovasc Surg 1995; 110:349–62

6. McKhann GM, Goldsborough MA, Borowicz LM, Selnes OA, Mellits ED, Enger C, Quaskey SA, Baumgartner WA, Cameron DE, Stuart RS, Gardner TJ: Cognitive outcome after coronary artery bypass: a one-year prospective study. Ann Thorac Surg 1997; 63:510–5

7. Roach GW, Kanchuger M, Mora Mangano CT, Newman MF, Nussmeier NA, Wolman R, Aggarwal A, Marschall K, Graham SH, Ley C, Ozanne G, Mangano DT, for the Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Adverse cerebral outcomes after coronary bypass surgery. N Engl J Med 1996; 335:1857–63

8. McLean RF, Wong BI, Naylor CD, Snow WG, Harrington EM, Gawel M, Fremes SE: Cardiopulmonary bypass, temperature, and central nervous system dysfunction. Circulation 1994; 90:II-250–5

9. Martin TC, Craver JM, Gott JP, Weintraub WS, Ramsay J, Mora CT, Guyton RA: Prospective, randomized trial of retrograde warm-blood cardioplegia: Myocardial benefit and neurologic threat. Ann Thorac Surg 1994; 57:298–304

10. Plourde G, Leduc AS, Morin JE, DeVarennes B, Latter D, Symes J, Robbins R, Fosset N, Couture L, Ptito A: Temperature during cardiopulmonary bypass for coronary artery operations does not influence postoperative cognitive function: A prospective, randomized trial. J Thorac Cardiovasc Surg 1997; 114:123–8

11. Regragui I, Birdi I, Bashar M, Black AMS, Lopatatzidis A, Day CJE, Gardner F, Bryan AJ, Angelini GD: The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: A prospective randomized trial. J Thorac Cardiovasc Surg 1996; 112:1036–45

12. Legault C, Furberg CD, Wagenknecht LE, Rogers AT, Stump DA, Coker L, Troost BT, Hammon JW: Nimodipine neuroprotection in cardiac valve replacement: Report of an early terminated trial. Stroke 1996; 27:593–8

13. Nussmeier NA, Arlund C, Slogoff S: Neuropsychiatric complications after cardiopulmonary bypass: Cerebral protection by a barbiturate. ANESTHESIOLOGY 1986; 64:165–70

14. Zaidan JR, Klochany A, Martin W: Effect of thiopental on neurologic outcome following coronary artery bypass grafting. ANESTHESIOLOGY 1991; 74:406–14

15. Newman MF, Murkin JM, Roach G, Croughwell ND, White WD, Clements FM, Reves JG, the CNS Subgroup of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Cerebral physiologic effects of burst suppression doses of propofol during nonpulsatile cardiopulmonary bypass. Anesth Analg 1995; 81:452–7

16. Jain U, Body SC, Bellows W, Wolman R, Mora Mangano CT, Mathew J, Youngs E, Wilson R, Zhang A, Mangano DT, for the Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Multicenter study of target-controlled infusion of propofol-sufentanil or sufentanil-midazolam for coronary artery bypass graft surgery. ANESTHESIOLOGY 1996; 85:522–35

17. Wahr JA, Plunkett JJ, Ramsay JR, Reeves J, Jain U, Ley C, Wilson R, Mangano DT, for the McSPI Research Group: Cardiovascular responses during sedation following coronary revascularization: Incidence of myocardial ischemia and hemodynamic episodes with propofol versus midazolam. ANESTHESIOLOGY 1996; 84:1350–60

18. Murphy PG, Davies MJ, Columb MO, Stratford N: Effect of propofol and thiopentone on free radical mediated oxidative stress of the erythrocyte. Br J Anaesth 1996; 76:536–43

19. Introna RP, Pruett JK, Yodlowski EH, Grover E: Direct effects of propofol on canine artery ring tension. Gen Pharmacol 1993; 24:497–502

20. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V, Rorick M, Moomaw CJ, Walker M: Measurements of acute cerebral infarction: A clinical examination scale. Stroke 1989; 20:864–70

21. Zivin JA, Choi DW: Stroke therapy. Scientific American 1991; 265:56–63

22. Stump DA: Selection and clinical significance of neuropsychologic tests. Ann Thorac Surg 1995; 59:1340–4

23. Murkin JM, Newman SP, Stump DA, Blumenthal JA: Statement of consensus and assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995; 59:1289–95

24. Kochs E, Hoffman WE, Werner C, Thomas C, Albrecht RF, Schulte am Esch J: The effects of propofol on brain electrical activity, neurologic outcome, and neuronal damage following incomplete ischemia in rats. ANESTHESIOLOGY 1992; 76:245–52

25. Ridenour TR, Warner DS, Todd MM, Gionet TX: Comparative effects of propofol and halothane on outcome from temporary middle cerebral artery occlusion in the rat. ANESTHESIOLOGY 1992; 76:807–12

26. Arcadi FA, Rapisarda A, De Luca R, Timmarchi GR, Costa G: Effect of 2,6-diisopropylphenol on the delayed hippocampal cell loss following transient forebrain ischemia in the gerbil. Life Sci 1996; 58:961–70

27. Pugsley W, Klinger L, Paschalis C, Treasure T, Harrison M, Newman S: The impact of microemboli during cardiopulmonary bypass on neuropsychological functioning. Stroke 1994; 25:1393–9

28. Muraoka R, Kokota M, Aoshima M, Kyoku I, Nomoto S, Kobayashi A, Nakano H, Ueda K, Saito A, Hojo H: Subclinical changes in brain morphology following cardiac operations as reflected by computed tomographic scans of the brain. J Thorac Cardiovasc Surg 1981; 81:364–9

29. Davila-Roman VG, Barzilai B, Wareing TH, Murphy SF, Kouchoukos NT: Intraoperative ultrasonic evaluation of the ascending aorta in 100 consecutive patients undergoing cardiac surgery. Circulation 1993; 84:III-47–52

30. Mora CT, Henson MB, Weintraub WS, Murkin JM, Martin TD, Craver JM, Gott JP, Guyton RA: The effect of temperature management during cardiopulmonary bypass on neurological and neuropsychological outcomes in coronary revascularization patients. J Thorac Cardiovasc Surg 1996; 112:514–22

31. The Multicenter Study of Perioperative Ischemia (McSPI) Research Group: Effects of acadesine on morbidity and mortality following coronary artery bypass graft surgery. ANESTHESIOLOGY 1995; 83: 658–73

32. Mangano DT, Browner WS, Hollenberg M, Li JM, Tateo IM, SPI Research Group: Long-term cardiac prognosis following noncardiac surgery. JAMA 1992; 268:233–9

33. Todd MM, Hindman BJ, Warner DS: Barbiturate protection and cardiac surgery: A different result (editorial). ANESTHESIOLOGY 1991; 74:402–5

34. Padayachee TS, Parsons S, Theobold R, Linley J, Gosling RG, Deverall PB: The detection of microemboli in the middle cerebral artery during cardiopulmonary bypass: A transcranial Doppler ultrasound investigation using membrane and bubble oxygenators. Ann Thorac Surg 1987; 44:298–302

35. Lanier WL, Stangland KJ, Schecthauer BW, Milde JH, Michenfelder JD: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. ANESTHESIOLOGY 1987; 66:39–48

36. Michenfelder J, Milde J, Sundt T: Cerebral protection by barbiturate anesthesia: Use after middle cerebral artery occlusion in Java monkeys. Arch Neurol 1976; 33:345–50

37. Warner DS, Takaoka S, Wu B, Ludwig PS, Pearlstein RD, Brinkhous AD, Dexter F: Electroencephalographic burst suppression is not required to elicit maximal neuroprotection from pentobarbital in a rat model of focal cerebral ischemia. ANESTHESIOLOGY 1996; 85:1475–84

38. Michenfelder JD: The interdependency of cerebral functional and metabolic effects following massive does of thiopental in the dog. ANESTHESIOLOGY 1974; 41:231–6

39. Steen PA, Newberg L, Milde JH, Michenfelder JD: Hypothermia and barbiturates: Individual and combined effects on canine cerebral oxygen consumption. ANESTHESIOLOGY 1983; 58:527–32

40. Keykhah M, Smith D, O'Neil J, Harp J: The influence of fentanyl upon cerebral high-energy metabolites, lactate, and glucose during severe hypoxia in the rat. ANESTHESIOLOGY 1988; 69:566–70

41. Nehls DG, Todd MM, Spetzler RF, Drummond JC, Thompson RA, Johnson R: A comparison of the cerebral protective effects of isoflurane and thiopental during temporary focal ischemia in primates. ANESTHESIOLOGY 1987; 66:453–64

42. Guo J, White JA, Batjer HH: Limited protective effects of etomidate during brainstem ischemia in dogs. J Neurosurg 1995; 82:278–83

43. Drummond JC, Cole DJ, Patel PM, Reynolds LW: Focal cerebral ischemia during anesthesia with etomidate, isoflurane, or thiopental: A comparison of the extent of cerebral injury. Neurosurgery 1995; 37: 742–8

44. Smith DS, Rehncrona S, Siesjo BK: Inhibitory effects of different barbiturates on lipid peroxidation in brain tissue *in vitro*. ANESTHESIOLOGY 1980; 53:186–94

45. Demopoulos HB, Flamm ES, Seligman ML: Antioxidant effects of barbiturates in model membranes undergoing free radical damage. Acta Neurol Scand 1977; 56:152–3

46. Shiu G, Nemoto EM: Barbiturate attenuation of brain free fatty acid liberation during global ischemia. J Neurochem 1981; 37:1448–56

47. Woodcock TE, Murkin JM, Farrar JK, Tweed WA, Guiraudon GM, McKenzie FN: Pharmacologic EEG suppression during cardiopulmonary bypass: Cerebral hemodynamic and metabolic effects of thiopental or isoflurane during hypothermia and normothermia. ANESTHESIOLOGY 1987; 67:218–24

Appendix

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