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Association of Perioperative Risk Factors and Cumulative Duration of Low Bispectral Index with Intermediate-term Mortality after Cardiac Surgery in the B-Unaware Trial

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ABSTRACT

Background: Current data suggest that mortality after noncardiac surgery may be associated with persistent hypotension and the cumulative duration of low processed electroencephalogram-based bispectral index (BIS). This study assessed the relationships among cumulative duration of low BIS (BIS < 45), intermediate-term mortality, and anesthetic dose after cardiac surgery.

Methods: The authors studied 460 patients (mean age, 63.0 ± 13.1 yr; 287 men) who underwent cardiac surgery between September 2005 and October 2006 at Washington University Medical Center, St Louis, Missouri. By using multivariable Cox regression analysis, perioperative factors were evaluated for their potential association with intermediate-term all-cause mortality.

Results: A total of 82 patients (17.8%) died during a median follow-up of 3 yr (interquartile range, 2.7–3.3 yr). Comparing patients who died with those who survived, there was no statistically significant difference in the relationship between end-tidal anesthetic gas concentrations during the anesthetic maintenance phase and the BIS. Cumulative duration of low BIS was independently associated with intermediate-term mortality. The 1.29 adjusted hazard ratio (95% CI, 1.12–1.49) for intermediate-term mortality with cumulative duration of low BIS translated into a 29% increased risk of death for every cumulative hour spent with a BIS less than 45. The final multivariable Cox regression model showed a good discriminative ability (c-index of 0.78).

Conclusions: This study found an association between cumulative duration of low BIS and mortality in the setting of cardiac surgery. Notably, this association was independent of both volatile anesthetic concentration and duration of anesthesia, suggesting that intermediate-term mortality after cardiac surgery was not causally related to excessive anesthetic dose.

What We Already Know about This Topic

- ❖ Increased intermediate term mortality has been found to be associated with cumulative time of low bispectral index (BIS < 45) values in patients after noncardiac surgery
- ❖ Whether this applies to cardiac surgery and reflects anesthetic dose is not known

What This Article Tells Us That Is New

- ❖ There is quite likely an association between cumulative time of low BIS values and intermediate-term mortality in cardiac surgical patients, but this does not seem to be reflective of a cumulative increase in anesthetic dose

PATIENTS with multiple comorbidities undergoing cardiac surgery can be at substantial risk for perioperative and late mortality.[1] Clinical factors that may affect hospital and long-term survival have been identified over the last several decades and can be grouped into patient-related and surgery-related variables. The associations between anesthesia-related factors and short- and long-term survival after cardiac surgery remain unclear. In recent years, research has emerged suggesting that cumulative duration of a low proprietary processed electroencephalogram index called the bispectral index (BIS®; Aspect Medical System, Norwood, MA) may be associated with increased intermediate-term

◇ This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 9A.

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postoperative death after noncardiac surgery.[2,3] These data suggest the possibility that there may be a link between cumulative anesthesia dose and intermediate-term mortality. Biologic mechanisms advanced for such a relationship include the notion that exposure to increased concentrations of potent inhalation anesthetics may lead to immunosuppression or cerebral hypoxia or that some individuals may have increased cerebral susceptibility to the effects of anesthetics.[2] The interpretation of these intriguing findings has been hampered by lack of quantitative information on the concentrations of inhalation anesthetics administered. A study in intensive care patients, also using the BIS® monitor, showed that the incidence of electroencephalogram burst suppression was associated with statistically significant higher 6-month mortality.[4] The investigators speculated that this association could potentially be related to increased administration of anesthetic or sedative medications.[4] To date, no studies have been performed on the possible association between cumulative duration of a low processed electroencephalogram index and intermediate-term mortality in patients undergoing cardiac surgery. Therefore, we undertook a predetermined substudy of the B-Unaware Trial[5] to investigate which perioperative factors were independently associated with postoperative mortality in patients undergoing cardiac surgery. In addition to factors that have been examined previously, we planned to incorporate volatile anesthetic concentration and BIS in the risk model.

Materials and Methods

Study Population

Between September 2005 and October 2006, 1,941 patients, 18 yr and older, undergoing surgery were screened and prospectively enrolled to the B-Unaware randomized clinical trial at Department of Anesthesiology, Washington University School of Medicine, St Louis, Missouri.[5] The Human Research Protection Office at Washington University School of Medicine approved the study, and the written informed consent was obtained from all patients participating in the study. In brief, the purpose of the B-Unaware clinical trial was to test the hypothesis that in patients at high risk, the incidence of anesthesia awareness was reduced when clinicians followed a BIS®-guided protocol rather than an end-tidal anesthetic gas concentration-guided protocol. The study protocol had several predetermined secondary outcomes including the aim to study the association between perioperative factors and intermediate-term mortality after surgery.[5] Patients at high risk for anesthesia awareness were identified based on the presence of one major criterion or on the presence of two minor criteria. The major criteria were preoperative long-term use of anticonvulsant agents, opiates, benzodiazepines, or cocaine; a cardiac ejection fraction less than 40%; a history of anesthesia awareness; a history of difficult intubation or anticipated difficult intubation; American Society of Anesthesiologists physical status class 4 (those who have systemic disease that is a constant threat to life) or class 5 (those who are not expected to survive without the operation); aortic stenosis; end-stage lung disease; marginal exercise tolerance not resulting from musculoskeletal dysfunction; pulmonary hypertension; planned open heart surgery; and daily alcohol consumption. The minor criteria were as follows: preoperative use of β-blockers, chronic obstructive pulmonary disease, moderate exercise tolerance not resulting from musculoskeletal dysfunction, smoking two or more packs of cigarettes per day, and obesity—defined as a body mass index (the weight in kilograms divided by the square of the height in meters) of more than 30 kg/m^2. Of the 1,941 patients, 460 underwent open cardiac surgery and were included in these analyses.

Conduct of the Trial

Per study design of the B-Unaware trial, there were no protocol-based restrictions of anesthetic technique; except that, for the maintenance of general anesthesia one of the potent volatile anesthetic agents—desflurane, sevoflurane, or isoflurane—had to be used. Radial artery, central venous, and, if indicated on clinical grounds, pulmonary artery catheters were inserted for hemodynamic monitoring and blood sampling. All patients had tracheal intubation, and the lungs were ventilated (volume or pressure controlled) using an oxygen–air mixture, with an inspiratory oxygen concentration of at least 50%. A positive end-expiratory pressure of 5 cm H_2O was applied. End-tidal anesthesia gas concentration was monitored throughout the case. During cardiopulmonary bypass, anesthesia was maintained using isoflurane or desflurane administered from vaporizers incorporated in the cardiopulmonary bypass machine. The anesthetic-gas concentration was measured from the exhaust gas of the bypass machine.[6] Age-adjusted minimum alveolar concentration (MAC) values were calculated according to the charts published by Nickalls and Mapleson, which were based on the following equation: age adjusted MAC = ([MAC at age 40] $\times$ $10^{[age\ -\ 40]\ \times\ -0.00269}$), where MAC at age 40 yr is 6.6% for desflurane, 1.17% for isoflurane, 1.8% for sevoflurane, and 104% for nitrous oxide.[7] All patients were admitted to the Cardiothoracic Intensive Care Unit for postoperative management.

A BIS Quatro Sensor® (Aspect Medical Systems) was applied to the forehead of each patient. The BIS is a proprietary index derived from a single frontal electroencephalogram channel that has been described to have the ability to measure the hypnotic component of the anesthetic state.[8] The index is dimensionless with a number from 0 to 100, with decreasing numbers intending to indicate progressively deeper sedation and hypnosis. During the B-Unaware trial, among other parameters, the BIS was recorded at 1-s intervals and downloaded to a computer database for subsequent analysis with TrendFace Solo software (ixellence GmbH, Wildau, Germany). Manual records of anesthesia and digital photographs of monitor trends were used as alternatives in the event that the computer data were incomplete.

Data Collection

A standard set of perioperative data were collected using data from medical files, surgical reports, anesthetic and postoperative charts, discharge letters, and records of the outpatient clinic visit. These data were recorded using a standard electronic data collection form. Quality of data collection was ascertained by two of the investigators (M.D.K and N.P.) using regular checks for completeness of the collected data and crosschecking for inconsistencies or missing information between the collected database and the medical records. The manufacturer of the BIS® monitor had no role in the study design, data collection, data analysis, or manuscript preparation. No study monitors or other means of support were provided by Aspect Medical System.

Follow-up

Patients were prospectively followed up after surgery; telephone interviews were conducted at 30 days and at 1 yr. The Social Security Database was checked for living status. This follow-up was further extended and in May 2009, the final follow-up was performed. In addition, in order not to miss any patient who died after surgery, we used a variety of approaches. To ascertain 30-day mortality and cause of death, hospital records, discharge letters, and (whenever available) autopsy results were screened. For those who survived beyond the 30 days after surgery, information about the vital status was ascertained by a multistep approach. First, patients were checked for subsequent hospital admissions, treatments, and follow-up visits, using the hospital electronic database. After that a Social Security Database†† was accessed to check for vital status up to April 28, 2009. Finally, a structured telephone interview was conducted by a trained research person to verify the time and cause of death.

Potential clinical determinants of intermediate-term mortality, collected for this study, included the following: patient characteristics, chronic medication use, preoperative laboratory values (hemoglobin, leukocyte count, and serum creatinine), and risk factors that are determinants of the European System for Cardiac Operative Risk Evaluation score (EuroScore).[1] The EuroScore is a method of calculating predicted operative mortality for patients undergoing cardiac surgery. It has also been used and validated for predicting intermediate-term mortality after cardiac surgery.[9,10] The determinants of EuroScore are patient-, cardiac-, and surgery-related factors. For the purposes of this study, we also collected information on potential intraoperative determinants of outcome, including type and dose of intravenous anesthetic drugs; durations of general anesthesia, cardiopulmonary bypass, and aortic cross clamping; baseline body temperature; durations of mild (32°–34°C) and moderate hypothermia (20° to 32°C) during cardiopulmonary bypass; and the duration of low or high mean arterial blood pressure. Mean arterial pressure was classified as low (mean arterial pressure lower than 55 mmHg) or high (mean arterial pressure higher than 100 mmHg), according to the methodology of Reich *et al.*[11] Also noted were the number of erythrocytes, fresh frozen plasma, and platelet units transfused intraoperatively. The intraoperative use of inotropes, vasopressors, vasodilators, and antifibrinolytics, and the end-tidal anesthetic gas concentrations were recorded. In addition, the hospital electronic database was reviewed for the length of intensive care unit stay.

To avoid misclassification of the cause of death, all-cause mortality was chosen as the outcome of the study. Nevertheless, we made every effort to ascertain the cause of death through medical records, death certificates, and information provided by the relatives of the deceased using structured telephone interviews.

Statistical Analysis

Continuous variables are presented as means (±SD) or medians (interquartile range), and categorical variables are presented as percent frequencies. Comparisons were made using the *t* test, ANOVA, Kruskal-Wallis test, or chi-square test, as appropriate. We also assessed the relationship between the BIS and the end-tidal anesthetic gas concentrations for patients who died and for those who survived. The median BIS for a wide range of age-adjusted MAC[7,12] was determined. To study the strength and direction of the association between the BIS and end-tidal anesthetic gas concentrations for patients who died and for those who survived, first patients with the most complete BIS and anesthetic gas data during the whole maintenance phase and during cardiopulmonary bypass were chosen. Second, only periods where the anesthetic gas concentration had not changed by greater than 0.05 MAC in either direction for the preceding 10 min were included. This stipulation was to decrease pharmacokinetic confounding on the relationship between the anesthetic gas concentrations and the BIS. Third, only subjects who did not have constant anesthetic gas concentrations during the entire maintenance phase were included in the model. This provision was to avoid singularity in the design matrix when fitting a linear model with effects indexed by the individual subject. Of the 82 patients who died and the 378 patients who survived, 49 and 175, respectively, met all three of these criteria and were included. The scattergram showing the relationship between individual BIS values and anesthetic gas concentrations was generated using MATLAB statistical software version 7.8 (The MathWorks Inc., Natick, MA). Because BIS and anesthetic gas concentrations were repeatedly measured for each individual, a linear mixed effects model for repeated measures was used to analyze the relationship between BIS and anesthetic gas concentrations using PROC MIXED program of SAS statistical software version 9.1.3 (SAS Institute Inc., Cary, NC). Several models were considered for studying the relationship between BIS and anesthetic gas concentrations, and the best result was given

†† Social Security Death Index. Rootsweb.com. Available at: http://ssdi.rootsweb.ancestry.com/cgi-bin/ssdi.cgi. Accessed April 28, 2009.

by a model that used square-root transformed BIS values with random intercept and random slope.

Recently, two studies in noncardiac surgical patients showed that patients with increased cumulative duration of BIS less than 45 (in hours) had an increased risk of intermediate-term mortality.[2,3] Therefore, in the current study, this definition was specified *a priori* to study the association between cumulative duration of low BIS and intermediate-term mortality after cardiac surgery. The number of patients who died during follow-up was relatively limited. Therefore, to avoid overfitting and to enable assessment of the relationship between clinical risk factors and mortality during follow-up, we used the additive EuroScore.[1] The Kaplan-Meier method was applied to evaluate the prognostic importance of the duration of cumulative BIS less than 45 with respect to event-free survival. Differences among survival curves were compared using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were applied to evaluate the relations among preoperative, intraoperative, and postoperative clinical variables, cumulative duration of BIS less than 45, and all-cause mortality. Univariable associations with $P < 0.25$ were considered in the initial construction of the mortality model, and the final model was then selected according to the backward deletion of the least significant predictors. The discriminatory power of the final multivariable model was quantified by the c-index, which corresponds to the area under the receiver operating characteristics curve, ranging from 0.5 (performance at chance) to 1.0 (optimal performance). To further evaluate the discriminatory power of the final multivariable model, the bootstrap method was used to assess the degree of overoptimism. Overoptimization occurs when application of statistical modeling techniques results in models that inaccurately predict the outcomes on subsequent datasets. A bootstrapping procedure is one method that can be used to try to correct for this "overoptimism."[13] Hazard ratios and corresponding 95% CIs are reported. These analyses were performed using SPSS statistical software version 16.0 (SPSS Inc., Chicago, IL) and R statistical environment (libraries: survival and design; The R Foundation for Statistical Computing, version 2.9.1; R Development Team, Vienna, Austria).

Results

Patient Characteristics

The mean (±SD) age of the 460 patients who underwent cardiac surgery was 63.0 ± 13.1 yr, and 287 (62.4%) of the patients were men. A total of 75.2% of patients had a history of hypertension, 61.1% had a history of ischemic heart disease, 22% had a history of significant extracardiac artheriopathy, and 18.3% had a history of chronic pulmonary disease. Nineteen percent of the patients had a history of previous cardiac surgery, 13% had a history of cereberovascular disease, and 12.8% had a history of chronic renal disease. Seventy-two percentage of the cohort had moderate left ventricular function (ejection fraction, 30–50%), and 5.4% had poor left ventricular function (ejection fraction, < 30%). The majority of patients underwent an operation other than an isolated coronary artery bypass surgery (67.6%). Ten patients (2.2%) had surgery of the thoracic aorta, 9 (2%) had emergency cardiac surgery procedure, and 6 (1.3%) patients had surgery of the ascending aorta with repair of the aortic arch with circulatory arrest and isolated cerebral perfusion. The average duration of general anesthesia was 6.1 h (interquartile range, 5.2–7.1 h), the average intraoperative BIS was 40 ± 7.23, and the average cumulative duration of BIS less than 45 was 3.27 h (interquartile range, 2.25–4.25 h). Baseline and clinical characteristics of the patients stratified according to the tertials of the cumulative duration of BIS less than 45 are presented in tables 1 and 2. Patients with longer cumulative duration of BIS less than 45 had moderate or poor left ventricular function more often. Furthermore, a longer cumulative duration of BIS less than 45 was associated with higher frequency of β-blocker use, with longer durations of cardiopulmonary bypass, aortic cross clamping, general anesthesia, intraoperative low mean arterial pressure (< 55 mmHg), and mild hypothermia (32° to 34°C) during cardiopulmonary bypass; with the use of donor blood and fresh frozen plasma transfusion; with the intraoperative use of tranexamic acid; and with length of intensive care unit stay.

There was no significant association between the cumulative duration of BIS less than 45 and the concentration of end-tidal anesthetic gas concentration in relation to intermediate-term mortality (table 2). We did find a significant, weak inverse correlation between end-tidal anesthetic gas concentrations, expressed as age-adjusted MAC equivalents, and BIS values ($P = 0.02$), which is demonstrated graphically in figure 1. This association was not significantly different between patients who died and those who survived during intermediate-term follow-up (P value for testing the difference on the intercept, 0.48; and the P value for testing the difference on the slope, 0.66). The likelihood ratio test for overall difference in the relationship of BIS values and anesthetic gas concentrations also did not show a significant difference between those who died and those who survived ($P = 0.07$).

The median follow-up was 3 yr (interquartile range, 2.7–3.3 yr). The mortality rate was 3.5% (16 of 460) at 30 days and 14.3% (66 of 460) on average 3 yr after cardiac surgery. We found no significant difference in mortality rates between patients whose general anesthesia was managed according to the BIS protocol compared with patients who were managed according to the end-tidal anesthetic gas concentration protocol (19.7% [47 of 239] *vs.* 15.8% [35 of 221]; $P = 0.33$). The causes of death are shown in table 3.

Table 4 shows univariable predictors of intermediate-term mortality that were significant at a nominal two-tailed $P < 0.25$. Many of the preoperative, intraoperative, and postoperative predictors were associated with an increased risk of intermediate-term mortality (table 4; fig. 2), except for hemoglobin concentration, which showed that increasing

Table 1. Demographic, Chronic Medication Use, and Patient and Cardiac-related Characteristics (n = 460)

Characteristics	Cumulative Duration of Bispectral Index < 45			*P* Value
	≤ 2 h 50 min (n = 155; 33.7%)	2 h 51 min to 4 h 10 min (n = 164; 35.7%)	> 4 h 10 min (n = 141; 30.6%)	
Demographics				
Age, yr	62.0 ± 14.0	63.0 ± 14.0	64.0 ± 12.0	0.60
Female gender	69 (44.5)	51 (31.1)	53 (37.6)	0.20
Race				0.71
White	35 (87.1)	148 (90.3)	123 (87.2)	
Black	18 (11.6)	15 (9.1)	18 (12.8)	
Other	2 (1.3)	1 (0.6)	0	
Body mass index, kg/m^2	30.0 ± 7.0	29.0 ± 7.0	29.0 ± 6.0	0.49
Current smoker or previous smoking history	101 (65.2)	101 (61.6)	96 (68.1)	0.62
Chronic medication use				
Aspirin	93 (60.0)	101 (61.6)	94 (66.7)	0.24
Angiotensin converting enzyme inhibitors	85 (54.8)	76 (46.3)	74 (52.5)	0.66
α-receptor blockers	5 (3.2)	9 (5.5)	6 (4.3)	0.65
β-receptor blockers	82 (52.9)	100 (61.0)	95 (67.4)	0.01
Calcium channel blockers				0.80
No use	128 (82.6)	131 (79.9)	117 (83.0)	
Dihydropyridine	18 (11.6)	22 (13.4)	13 (9.2)	
Nondihydropyridine	9 (5.8)	11 (6.7)	11 (7.8)	
Clopidogrel	22 (14.2)	20 (12.2)	16 (11.3)	0.46
Coumadin	20 (12.9)	26 (15.9)	24 (17.0)	0.32
Diuretics	68 (43.9)	61 (37.2)	60 (42.6)	0.79
Nitrates	31 (20.0)	33 (20.1)	34 (24.1)	0.40
Statins	73 (47.1)	97 (59.1)	74 (52.5)	0.33
Euroscore-related variables				
Patient-related variables				
Chronic pulmonary disease	33 (21.3)	30 (18.3)	21 (14.9)	0.16
Extracardiac artheriopathy	31 (20.0)	35 (21.3)	35 (24.8)	0.32
Cerebrovascular disease	18 (11.6)	21 (12.8)	21 (14.9)	0.41
Previous cardiac surgery	31 (20.0)	32 (19.5)	25 (17.7)	0.62
Chronic renal disease or elevated preoperative serum creatinine > 2 mg/dl	15 (9.7)	23 (14.0)	21 (14.9)	0.18
Active endocarditis	3 (1.9)	7 (4.3)	3 (2.1)	0.89
Critical preoperative state	2 (1.3)	2 (1.2)	2 (1.4)	0.93
Cardiac-related variables				
Unstable angina	4 (2.6)	5 (3.0)	2 (1.4)	0.53
Left ventricular dysfunction				< 0.0001
Normal > 50%	94 (60.6)	44 (26.8)	23 (16.3)	
Moderate or LVEF 30–50%	54 (34.8)	112 (68.3)	108 (76.6)	
Poor or LVEF < 30%	7 (4.5)	8 (4.9)	10 (7.1)	
Recent myocardial infarction (< 90 d)	3 (1.9)	4 (2.4)	4 (2.8)	0.61
Pulmonary hypertension (systolic PASP > 60 mmHg)	2 (1.3)	5 (3.0)	5 (3.5)	0.22
Operation-related variables				
Emergency	2 (1.3)	2 (1.2)	5 (3.5)	0.17
Other than isolated CABG	105 (67.7)	113 (68.9)	93 (66.0)	0.75
Surgery on thoracic aorta	3 (1.9)	4 (2.4)	3 (2.1)	0.90
Postinfarct septal rupture	0	0	0	—

Values are expressed as mean ± SD, median (interquartile range), or n (%).

CABG = coronary artery bypass surgery; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure.

hemoglobin concentration was associated with a significant reduction in the risk of intermediate-term mortality. In addition, cumulative duration of BIS less than 45 showed a strong association with intermediate-term mortality (table 4), which was also reflected by the event-free survival curves (fig. 3). We also studied the relation between mean end-tidal volatile anesthetic gas concentration of different volatile anesthetics and mortality. The results of the univari-

Table 2. Intraoperative and Postoperative Characteristics (n = 460)

Characteristics	Cumulative Duration of Bispectral Index < 45			*P* Value
	≤ 2 h 50 min (n = 155; 33.7%)	2 h 51 min to 4 h 10 min (n = 164; 35.7%)	> 4 h 10 min (n = 141; 30.6%)	
Preoperative laboratory values				
Hemoglobin, g/dl	13.1 ± 1.9	13.1 ± 1.9	12.8 ± 1.8	0.51
Leukocyte count, 10^3/mm^3	7.6 ± 3.0	7.3 ± 2.5	7.6 ± 2.8	0.55
Serum creatinine, mg/dl	1.0 (0.8–1.10)	1.0 (0.8–1.2)	1.0 (0.9–1.3)	
Intraoperative variables				
Surgery related				0.27
Coronary artery bypass surgery	50 (32.3)	51 (31.1)	55 (39.0)	
Heart valve surgery	55 (35.5)	53 (32.3)	43 (30.5)	
Coronary artery bypass with valve surgery	24 (15.5)	34 (20.7)	27 (19.1)	
Other	26 (16.8)	26 (15.9)	16 (11.3)	
Average duration of cardiopulmonary bypass, min	106.0 (77.0–136.0)	119.5 (96.0–151.8)	147.0 (122.5–198.0)	< 0.0001
Average duration of aortic cross clamping, min	63.0 (36.0–89.0)	70.0 (44.8–95.0)	93.0 (70.0–112.5)	< 0.0001
Anesthesia related				
Average propofol dose, mg	120.0 (75.0–180.0)	120.0 (70.0–200.0)	110.0 (80.0–190.0)	0.94
Average fentanyl dose, mcg	750.0 (500.0–1000.0)	750.0 (500.0–1000.0)	750.0 (600.0–1000.0)	0.19
Average methadone dose, mg	0 (0–10.0)	0 (0–10.0)	0 (0–10.0)	0.43
Average midazolam dose, mg	5.0 (2.0–6.0)	5.0 (3.0–5.0)	5.0 (3.0–5.5)	0.31
Average vecuronium dose, mg	10.0 (8.0–12.0)	10.0 (10.0–10.0)	10.0 (10.0–11.5)	0.34
Average baseline body temperature, °C	35.8 ± 0.6	35.8 ± 0.5	35.8 ± 0.5	0.56
Average duration of mild hypothermia, 32°C–34°C	40.0 (20.0–80.0)	60.0 (40.0–80.0)	80.0 (60.0–100.0)	< 0.0001
Average duration of anesthesia, min	344.8 ± 86.8	364.4 ± 81.3	431.3 ± 88.4	< 0.0001
Average duration of mean arterial pressure < 55 mmHg, min	9.9 (3.0–20.0)	10.0 (5.0–30.0)	16.0 (7.0–29.0)	0.004
Average duration of mean arterial pressure > 100 mmHg, min	15.0 (5.1–30.0)	17.5 (8.0–32.0)	15.0 (6.0–34.5)	0.37
Average unit of erythrocyte transfusion	1 (0–3)	2 (0–3)	2 (0–4)	0.003
Average unit of fresh frozen plasma	0 (0–1)	0 (0–3)	0 (0–4)	0.002
Average unit of platelets	0 (0–1)	0 (0–1)	0 (0–1)	0.24
Aprotinin	39 (25.2)	26 (15.9)	28 (19.9)	0.24
Dexmedetomidine	4 (2.6)	4 (2.4)	6 (4.3)	0.41
Dobutamine	97.0 (62.6)	111 (67.6)	102 (72.3)	0.07
Epinephrine	9 (5.8)	10 (6.1)	13 (9.2)	0.26
Norepinephrine	68 (43.9)	81 (49.4)	72 (51.1)	0.21
Milrinone	17 (11.0)	18 (11.0)	23 (16.3)	0.17
Nitroglycerin	18 (11.6)	22 (13.4)	16 (11.3)	0.96
Tranexamic acid	75 (48.4)	103 (62.8)	88 (62.4)	0.01
Vasopressin	27 (17.4)	23 (14.0)	28 (19.9)	0.60
Average end-tidal isoflurane concentration*	0.81 (0.73–0.89)	0.81 (0.72–0.91)	0.80 (0.71–0.92)	0.88
Average end-tidal desflurane concentration†	4.4 ± 0.7	4.7 ± 0.8	4.7 ± 1.0	0.18
Average days spent on intensive care unit	2 (1–4)	2 (1–5)	3 (1–5)	0.03

Values are mean ± SD, median (interquartile range), or n (%).
* n = 406. † n = 95.

able analysis showed that higher mean end-tidal isoflurane concentration was not associated with a decreased risk of mortality (univariable hazard ratio, 0.30; 95% CI, 0.1–1.1; $P = 0.07$), and desflurane (univariable hazard ratio, 0.8; 95% CI, 0.4–1.5; $P = 0.55$) concentration also showed no significant association with intermediate-term mortality. Finally, there was no significant association between the duration of mild hypothermia during cardiopulmonary bypass and mortality (univariable hazard ratio, 1.0; 95% CI, 0.9–1.0; $P = 0.69$).

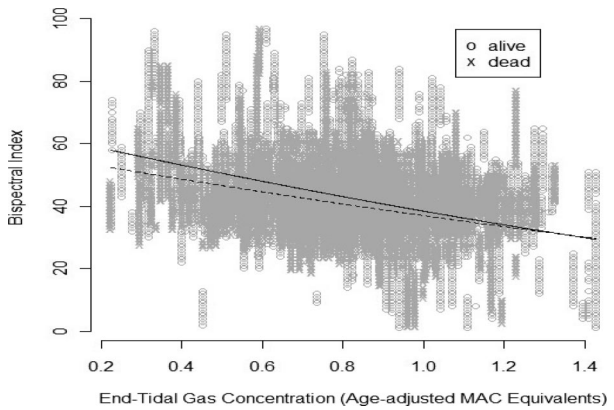


Fig. 1. A scattergram of bispectral index (BIS) plotted against contemporaneous end-tidal anesthetic gas (ETAG) concentrations during the anesthetic maintenance phase for 49 of the patients who died (*crosses*, 119, 107 data points) and for 175 of those who survived (*open circles*, 328, 325 data points). Data for this analysis were included first from patients whose complete BIS and ETAG data were available at 1-s intervals for the whole case, second, when the ETAG concentrations had been stable for the preceding 10-min period, and third, when there was variation in anesthetic gas concentration during the maintenance phase (for further details see Materials and Methods). Regression lines across the data points for patients who died (*dotted line*) and for those who survived (*solid line*) were fitted based on the following estimated models: dead patients: square root (BIS) = 7.5725 − 1.4871 × ETAG; alive patients: square root (BIS) = 8.0201 − 1.8187 × ETAG. MAC = minimum alveolar concentration.

In a multivariable analysis, higher additive EuroScore, erythrocyte transfusion, intraoperative infusion of norepinephrine, and increased duration of intensive care unit stay remained significant predictors of intermediate-term mortality (table 5). A higher preoperative hemoglobin concentration and intraoperative administration of tranexamic acid were associated with decreased intermediate-term mortality (table 5). After correcting for differences in preoperative, intraoperative, and postoperative characteristics, patients with an increasing cumulative duration of BIS less than 45 remained at increased risk of mortality. The hazard ratio for intermediate-term mortality was 1.29 per h, which translated into a 29% increased risk of intermediate-term mortality for every cumulative hour spent with BIS less than 45 (table 5). We observed a good c-index of 0.78 for the final model, and the degree of overoptimism was minimal at 0.0124 (resulted in an adjusted c-index of 0.77). The increasing mean end-tidal isoflurane concentrations were not significantly associated with intermediate-term mortality after multivariable adjustment. Although duration of anesthesia was not found to be independently associated with mortality in the final model, we decided to further test whether the relationship between BIS less than 45 and mortality was independent of duration of anesthesia. We repeated the multivariable analysis, incorporating a ratio of cumulative duration of BIS less than 45 to length of anesthesia as a variable. With this approach, there remained a robust independent association between this ratio and intermediate-term mortality, suggesting that the association was not reliant on duration of anesthesia.

Table 3. Cause of Intermediate-term Mortality (n = 82)

Cardiac	45 (55)
Cerebrovascular	7 (8.5)
Sepsis	7 (8.5)
Cancer	6 (7)
Multiorgan failure	5 (6)
Renal failure	4 (5)
Respiratory failure	4 (5)
Other	4 (5)

Values are expressed as number of patients (percentage).

Discussion

This study suggests that in patients undergoing cardiac surgery, similar to those undergoing noncardiac surgery,[2,3] cumulative duration of low BIS was independently associated with intermediate-term mortality. Importantly, however, this association was independent of total anesthetic dose.

The cumulative duration of BIS less than 45 has been identified as a predictor of poor intermediate-term outcome in patients undergoing noncardiac surgery.[2,3] The study of Monk *et al.*[2] was the first to report that cumulative duration of low BIS was a significant independent predictor of 1-yr mortality. However, the authors did not determine whether the relationship between the cumulative duration of BIS less than 45 and increased mortality was causal or coincidental. Furthermore, despite the fact that the most common cause of death was malignancy (52%), no stratified analysis was performed for preexisting malignant disease. In a subsequent study, Lindholm *et al.*[3] questioned these findings in their study linking perioperative risk factors with mortality in 5,056 noncardiac surgical patients. Multivariable analyses showed that the preexisting malignancy status and the American Society of Anesthesiologist physical status were the most important determinants of survival 2 yr after surgery. When the prognostic value of the cumulative duration of BIS less than 45 was studied, it showed a weak but significant association with intermediate-term mortality. However, after preexisting malignancy status was taken into consideration, the previously significant relation between cumulative duration of BIS less than 45 and 2-yr mortality was no longer significant. These two studies concluded that some selected clinical risk factors may have had the potential to influence the association between the cumulative duration of low BIS and intermediate-term mortality. Nevertheless, these studies did not collect information on many of the perioperative risk factors, including chronic cardiac medication use, preoperative laboratory values, intraoperative use of inotropes and vasopressors, and intensive care unit length of stay.

In this study, we, therefore, attempted to clarify the association between clinical variables and the cumulative duration of BIS less than 45. Patients with moderate to poor left ventricular function; patients with longer durations of cardiopulmonary bypass time, aortic cross clamp time, anesthe-

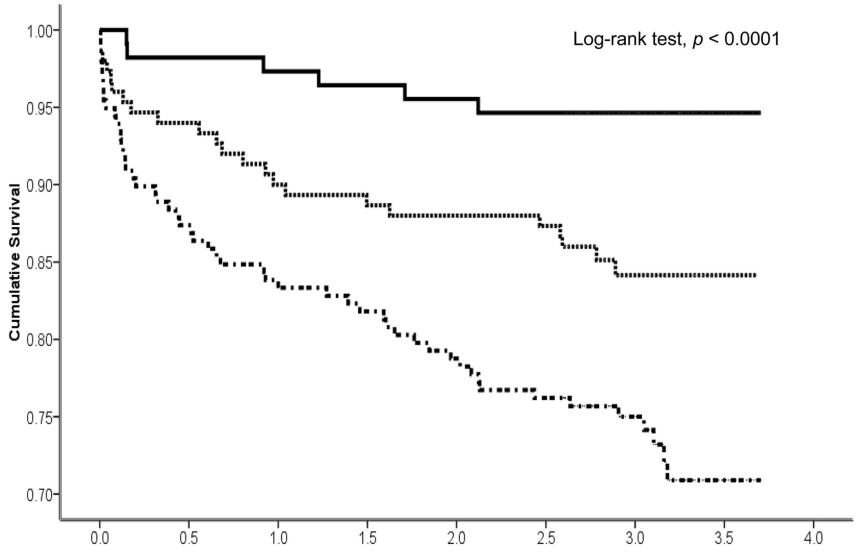
Table 4. Univariable Predictors of Intermediate-term Mortality

Predictors	Hazard Ratio (95% Confidence Interval)	*P* Value
Demographics		
Current smoker or previous smoking history	2.20 (1.29–3.75)	< 0.0001
Chronic medication use		
α-receptor blockers	2.35 (1.09–5.12)	0.004
Clopidogrel	1.43 (0.80–2.53)	0.22
Coumadin	1.74 (1.04–2.91)	0.03
Diuretics	2.20 (1.42–3.43)	0.03
Nitrates	1.40 (0.86–2.28)	0.18
Additive Euroscore per 1 point increase	1.21 (1.13–1.28)	< 0.0001
Preoperative laboratory values		
Hemoglobin, per 1 g/dl increase	0.77 (0.68–0.86)	< 0.0001
Anesthesia related		
Duration of anesthesia, per 10 min	1.04 (1.02–1.06)	< 0.0001
Duration of cardiopulmonary bypass, per 10 min	1.03 (0.99–1.07)	0.09
Duration of mean arterial pressure < 55 mmHg, per 10 min	1.13 (1.05–1.22)	0.001
Erythrocyte transfusion per unit increase	1.23 (1.17–1.30)	< 0.0001
Fresh frozen plasma per unit increase	1.18 (1.12–1.25)	< 0.0001
Platelets per unit increase	1.27 (1.11–1.46)	0.001
Cumulative duration of bispectral index < 45, per hour	1.30 (1.13–1.49)	< 0.0001
Anesthesia-related intraoperative infusion/administration of		
Aprotinin	1.40 (0.90–2.29)	0.18
Epinephrine	2.85 (1.55–5.27)	0.001
Norepinephrine	2.71 (1.70–4.35)	< 0.0001
Milrinone	3.35 (2.10–5.42)	< 0.0001
Anesthesia-related intraoperative infusion/administration of		
Tranexamic acid	0.75 (0.48–1.16)	0.19
Vasopressin	2.61 (1.64–4.13)	< 0.0001
Postoperative variable		
Intensive care unit stay, per day increase	1.07 (1.06–1.09)	< 0.0001

sia time, and hypothermic cardiopulmonary bypass; and patients with increased cumulative duration of intraoperative low mean arterial pressure, all more frequently had increased cumulative duration of BIS less than 45. In addition, patients with increased cumulative duration of BIS less than 45 were also more likely to receive intraoperative transfusions of blood products and remain in the intensive care unit longer. In contrast, no association was observed between cumulative duration of BIS less than 45 and other comorbidities, type of surgery, or mean end-tidal anesthetic gas concentration. Hence, it seems that the cumulative duration of BIS less than 45, which showed no association with volatile anesthetic concentrations or with the average total dose of intravenous anesthetic drugs, is likely to be a marker of factors such as systemic illness, poor cardiac function, and a complicated intraoperative course. These factors likely place patients at higher risk for intermediate-term mortality after cardiac surgery. A complicated intraoperative course is also often associated with a longer duration of hypothermic cardiopulmonary bypass time, which may influence the cumulative duration of BIS less than 45. It has been shown that during hypothermic cardiopulmonary bypass, BIS decreases along with body temperature. A study in a group of 100 cardiac surgery patients found that for each degree of Celsius decrease in body temperature, the BIS decreased by 1.12.[14] However, this observation was not replicated in another study.[15]

Consistent with the hypothesis that mortality risk was not causally related to volatile anesthetic dosing or depth, we found, similar to studies in noncardiac surgery patients,[16,17] that the BIS was relatively invariant to alterations in anesthetic dose beyond loss of responsiveness in individual cardiac surgery patients. Evidence indicates that there is a nonlinear model for the dose-response of electroencephalogram parameters to increasing concentrations of anesthetic agents with a dosing plateau response over a clinically relevant dose range.[18] We have, therefore, used the description, cumulative duration of low processed electroencephalogram index, or cumulative duration of low BIS, in preference to the previously coined term—cumulative deep hypnotic time.[2] Some patients, possibly those with underlying brain dysfunction or other comorbidities, may have more profound electroencephalogram changes with relatively light anesthesia. It does not necessarily follow that subjecting these patients to even less anesthesia would decrease either their cumulative duration of low processed electroencephalogram index or their chance of mortality after surgery.

The efficacy of processed electroencephalogram in preventing unintended intraoperative awareness with postoperative explicit recall remains unresolved and is currently the focus of two ongoing, large clinical trials.[19,20] Similarly,

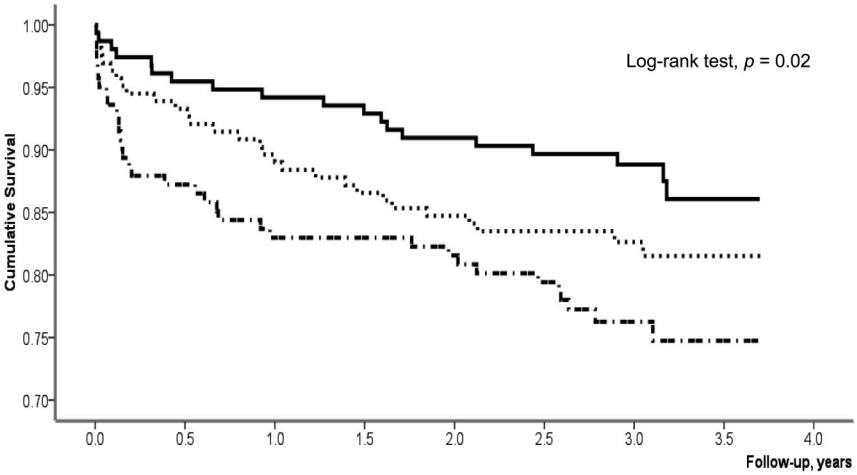


Risk categories by EuroScore	No. at risk							
Low-risk	112	110	109	108	107	106	67	15
Intermediate-risk	150	141	135	133	132	131	71	17
High-risk	198	173	165	161	155	150	94	24

Fig. 2. Kaplan-Meier estimates of all-cause mortality, according to the risk categories of the additive EuroScore (0–2, low-risk group; 3–5, intermediate-risk group; and >6, high-risk group). *P* value (log-rank test) indicates the differences in survival.

the efficacy of processed electroencephalogram in guiding the safe reduction in anesthetic dosing has not been demonstrated consistently. If minor increases in anesthetic dosing are found not to be associated with adverse outcomes in patients undergoing cardiac surgery, then minimizing anesthetic dose may have no benefit and may lead to resurgence in the incidence of unintended intraoperative awareness.

The optimal treatment strategies to prevent intermediate- and long-term mortality in high-risk patients after successful cardiac surgery are controversial. We confirmed the predic-



Cumulative duration of bispectral index <45	No. at risk							
≤ 2 hrs 50 min	155	148	146	144	141	139	91	23
2 hrs 51 min to 4 hrs 10 min	164	153	147	141	138	136	83	18
> 4 hrs 10 min	141	123	117	117	115	112	58	15

Fig. 3. Kaplan-Meier estimates of all-cause mortality, according to the tertials of duration of cumulative bispectral index suppression. *P* value (log-rank test) indicates the differences in survival.

Table 5. Multivariable Predictors of Intermediate-term Mortality

Predictors	Hazard Ratio (95% Confidence Interval)	*P* Value
Additive Euroscore per 1 point increase	1.13 (1.10–1.22)	0.001
Preoperative hemoglobin, per 1 g/dl increase	0.84 (0.74–0.95)	0.007
Erythrocyte transfusion per unit increase	1.10 (1.02–1.18)	0.01
Cumulative duration of bispectral index < 45, per hour	1.29 (1.12–1.49)	< 0.0001
Intraoperative infusion of norepinephrine	1.89 (1.15–3.10)	0.01
Intraoperative administration of tranexamic acid	0.56 (0.36–0.88)	0.01
Intensive care unit stay, per day increase	1.05 (1.04–1.07)	< 0.0001

tive value of many previously described risk factors for intermediate-term mortality after cardiac surgery.[21,22] Some of these strong risk factors also showed association in the current study with cumulative duration of BIS less than 45. The roles of perioperative anemia and blood transfusion have been extensively debated as risk factors for mortality.[23–25] Recently, anemia has been shown to increase the risk of acute kidney injury after coronary artery bypass surgery.[26] Anemia has also been shown to increase the risk of early and late mortality after coronary artery bypass surgery, and a combination of low hemoglobin concentrations and blood transfusions has been associated with increased morbidity and mortality after cardiac surgery.[27] Our findings are consistent with a similar study showing that lower preoperative hemoglobin level was an independent predictor of late mortality.[28] Preoperative correction of anemia, successful surgical control of hemostasis, restrictive blood transfusion policies, and the use of antifibrinolytics such as tranexamic acid may all have a potential role in reducing perioperative and long-term mortality after cardiac surgery. In addition, in our study, we observed that the Euroscore reinforced its utility as an independent predictor of intermediate-term mortality after cardiac surgery. Many components of the Euroscore, including poor left ventricular function and renal dysfunction, have been identified as modifiable predictors of long-term outcome after cardiac surgery.[29–31] Optimum perioperative management of preexisting or developing organ dysfunctions, such as left ventricular failure and renal dysfunction, may improve the intermediate and long-term survival of these patients.

Study Limitations

The patients in this study were screened for risk factors and selected according to the predefined criteria of the B-Unaware clinical trial, but information on some important predictors of postoperative mortality was not prospectively collected. Therefore, we had to collect additional data on clinical risk factors using administrative data and medical records, based on physician documentation of significant clinical risk factors. Thus, the effect of some of the risk factors may be biased. Nevertheless, the predictive values of these risk factors were similar to those described by others and by current guidelines.[32]

Furthermore, the patients of the current study were considered high risk per study protocol of the original B-Unaware trial and frequently underwent complex cardiac surgery at a major tertiary academic center. Therefore, the observed mortality rates may seem higher than those reported from other studies after similar cardiac surgery.[33] However, these studies with lower mortality rates used strict inclusion criteria or selected patients at low risk for perioperative and late mortality. Furthermore, the cutoff BIS number of 45 for low BIS is arbitrary and is higher than the more generally accepted arbitrary number of 40.[34] Therefore, we repeated our multivariable analysis and found that cumulative duration of BIS less than 40 had the same predictive value as BIS less than 45 for intermediate-term mortality. Finally, the BIS is a processed proprietary index, which is derived from several electroencephalogram elements, such as the ratio of higher to lower frequency beta waves (BetaRatio), synchronization or phase coherence between high frequency and low frequency waves (SynchFastSlow), and burst suppression ratio.[35] It is unclear which, if any, electroencephalogram features during anesthesia might be associated with increased intermediate-term mortality, although burst suppression has been identified as a potential candidate in intensive care patients.[4] It is notable that, unlike several other electroencephalogram features seen during general anesthesia,[36] burst suppression does not occur during physiologic sleep states and has been associated with poor prognosis in brain injury.[37]

Conclusions

The findings suggest that the relationship between a low processed electroencephalogram index and death is likely epiphenomenal rather than causal. As an analogy, consider a patient who has electrocardiographic ST segment depression with treadmill testing. If this patient dies a year thereafter, this is more likely attributable to underlying heart disease than to treadmill test-induced cardiac damage. Similarly, consider a patient who has a low processed electroencephalogram index with exposure to potent anesthetic agents and dies 1 yr thereafter. It is possible that the anesthesia exposure contributed to the patient's late demise. A more parsimonious, albeit mundane, explanation is that the low processed electroencephalogram index is a marker of underlying illness or vulnerability.

This study found that several previously identified perioperative factors, such as the Euroscore, anemia, and transfusion,

were independently associated with mortality after cardiac surgery. Although cumulative duration of low BIS was associated with intermediate-term all-cause mortality, anesthetic dose was not implicated. Previous studies have suggested that the choice of anesthetic technique, drugs, or dosages during cardiac surgery is not strongly implicated in adverse patient outcomes.[38] The results of this substudy of the B-Unaware Trial similarly suggest that, although several candidate changes in perioperative care may be beneficial, no change in anesthetic drugs or dosages for cardiac surgery is currently warranted.

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Appendix 1. B-Unaware Study Group

The participants of the B-Unaware Study Group are as follows: Michael S. Avidan, M.B.B.Ch., F.C.A.S.A. (Associate Professor of Anesthesiology, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Michael Bottros, M.D. (Resident, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Beth A. Burnside, B.A. (Research Assistant, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Alex S. Evers, M.D. (Henry E. Mallinckrodt Professor, Anesthesiology Head, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Kevin J. Finkel, M.D. (Resident, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Charles B. Hantler, M.D. (Professor of Anesthesiology, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Bernadette Henrichs, Ph.D., C.R.N.A., C.C.R.N. (Director, Nurse Anesthesia Program, Goldfarb School of Nursing at Barnes-Jewish College, St. Louis, Missouri); Eric Jacobsohn, M.B.Ch.B., M.H.P.E., F.R.C.P.C. (Professor and Chair Department of Anesthesia, Department of Anesthesia and Perioperative Medicine, University of Manitoba, Winnipeg, Manitoba, Canada); Heiko Kaiser, M.D. (Research Fellow, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Miklos D. Kertai, M.D., Ph.D. (Instructor in Anesthesiology, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Andrew Leitner, B.S. (Medical Student, Washington University School of Medicine, St. Louis, Missouri); Nirvik Pal, M.D. (Instructor in Anesthesiology, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Srikar Rao, B.S. (Medical Student, Washington University School of Medicine, St. Louis, Missouri); Clare Ridley, M.D. (Resident, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Leif Saager, M.D. (Instructor in Anesthesiology, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Furqaan Sadiq, B.J. (Research Assistant, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Elika Safarzadeh, M.D. (Research Assistant, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Adam C. Searleman, B.S. (Medical Student, Washington University School of Medicine, St. Louis, Missouri); Sylvia A. Searleman, B.S. (Research Assistant, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri); Jacqueline A. Selvidge, M.S. (Research Assistant, Washington University School of Medicine, St. Louis, Missouri); Brian Torres, B.S.N., R.N., C.C.R.N. (Research Assistant, Washington University School of Medicine, St. Louis, Missouri); Michelle S. Turner, M.S. (Research Assistant, Washington University School of Medicine, St. Louis, Missouri); Heidi Tymkew, M.H.S. (Research Coordinator, Washington University School of Medicine, St. Louis, Missouri); Anna Woodbury, B.S. (Medical Student, Washington University, School of Medicine, St. Louis, Missouri); Lini Zhang, M.D. (Research Assistant, Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri).