

Concurrence of Intraoperative Hypotension, Low Minimum Alveolar Concentration, and Low Bispectral Index Is Associated with Postoperative Death

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ABSTRACT

Background: An intraoperative concurrence of mean arterial pressure less than 75 mmHg, minimum alveolar concentration less than 0.8, and bispectral index less than 45 has been termed a “triple low” state. An association between triple low and postoperative mortality has been reported but was not replicated in a subsequent study. The authors pooled existing data from clinical trials to further evaluate the purported association in an observational study.

Methods: This retrospective observational study included 13,198 patients from three clinical trials: B-Unaware, BAG-RECALL, and Michigan Awareness Control Study. Patients with greater than 15 not necessarily consecutive minutes of triple low were propensity matched to controls with similar characteristics and comorbidities. A multivariable Cox proportional hazards model was used to evaluate the association between triple low duration and postoperative mortality.

Results: Thirty-day mortality was 0.8% overall, 1.9% in the triple low cohort, and 0.4% in the nontriple low cohort (odds ratio, 5.16; 95% CI, 4.21 to 6.34). After matching and adjusting for comorbidities, cumulative duration of triple low was significantly associated with an increased risk of mortality at 30 days (hazard ratio, 1.09; 95% CI, 1.07 to 1.11, per 15 min) and 90 days (hazard ratio, 1.09; 95% CI, 1.08 to 1.11, per 15 min).

Conclusion: There is a weak independent association between the triple low state and postoperative mortality, and the propensity-matched analysis does not suggest that this is an epiphenomenon. (**ANESTHESIOLOGY 2015; 123:775-85**)

POSTOPERATIVE mortality is not that uncommon.¹ Many studies have found associations between perioperative factors and postoperative mortality, including intraoperative hypotension, low bispectral index (BIS) values, and low volatile anesthetic concentrations.²⁻⁶ However, the strength of these associations has varied with patient populations, statistical methods, and inclusion of covariables. Given the conceptual relation between anesthetic concentration and hypotension, it has been hypothesized that the occurrence of hypotension and deep hypnosis, suggested by low BIS values, despite a low volatile anesthetic concentration might represent an unusual sensitivity to volatile anesthetics. In 2012, Sessler *et al.*⁷ reported that the intraoperative concurrence of mean arterial pressure (MAP) less than 75 mmHg, BIS less than 45, and minimum alveolar concentration (MAC) less than 0.8 was associated with an increased risk of postoperative mortality. Concurrently, low values of these three parameters were called the “triple low” state. Mortality was substantially increased when patients experienced more than 15 min of triple low. However, these striking findings were not replicated in a subsequent study.⁸

What We Already Know about This Topic

- An association between time spent in a “triple low” state of low blood pressure, low delivered anesthetic concentration, and low bispectral index has been associated with perioperative mortality, but this association was not replicated in another study

What This Article Tells Us That Is New

- In a retrospective study of nearly 14,000 patients from three clinical trials, the likelihood of 30- and 90-day mortality was increased approximately 10% for every 15 cumulative minutes in the triple low state, after controlling for known confounders for perioperative death

The primary aim of the current study is to explore the independent relation between the triple low state and 30- and 90-day postoperative mortality in a multicenter population. We hypothesized that there would be a significant relation between the triple low state and postoperative mortality. We further hypothesized that the association was likely to be epiphenomenal rather than causal, and that after propensity matching patients according to their

This article is featured in “This Month in Anesthesiology,” page 1A.

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theoretical likelihood of experiencing a triple low state (based on their characteristics and comorbidities), there would no longer be a significant relation between triple low state and postoperative death.

Materials and Methods

Study Population

The study population in this retrospective observational study included patients from three clinical trials. The B-Unaware Trial and BAG-RECALL trials were prospective, randomized, controlled studies that sought to evaluate the superiority of a BIS-guided protocol compared with a protocol based on volatile anesthetic concentration alerts in preventing intraoperative awareness with recall (AWR) in patients at high risk for this complication.⁹ The Michigan Awareness Control Study evaluated the role of BIS in preventing AWR in an unselected surgical population.^{10,11} The details of these trials have been reported extensively.^{9–11} The three parent studies received institutional review board committee approval from the Washington University Human Research Protection Office (St. Louis, Missouri), the University of Manitoba Research Ethics Board (Winnipeg, Manitoba, Canada), and the institutional review boards of University of Chicago (Chicago, Illinois), and University of Michigan (Ann Arbor, Michigan). All patients provided written or electronic informed consent. All three studies specified in their protocols and on the ClinicalTrials.gov registration site that the association between intraoperative factors and postoperative mortality would be explored although evaluating the association between the triple low state and mortality was not prespecified (NCT00281489, NCT00682825, and NCT00689091). This reporting of this study is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.¹²

In all three trials, patients were included for analysis if they were older than 18 yr and were undergoing a surgical procedure at one of the institutions participating in the study: Washington University in St. Louis, University of Michigan Health System in Ann Arbor, and University of Chicago and University of Manitoba in Winnipeg. As B-UNAWARE and BAG-RECALL were explicitly assessing AWR in a population of patients deemed to be at high risk for this complication, patients enrolled in these studies were also required to have specified characteristics that qualified them as high risk.^{9,10} The Michigan Awareness Control Study included all surgical patients undergoing general anesthesia.¹¹ Anesthetics provided in the B-Unaware and BAG-RECALL studies were inhaled general anesthetics. Nitrous oxide was also permitted. In the Michigan Awareness Control Study, both inhaled volatile and intravenous anesthetic agents were used although the vast majority of anesthetics were based on potent inhaled agents.

Exclusion criteria were similar for all three trials. Patients were excluded if their surgical procedure precluded BIS monitoring (either secondary to surgical site requirements or

an adhesive allergy) if the surgery required a wake-up test, if they had a previous history of dementia or stroke with residual neurological deficits or previous traumatic brain injury, or if they were unable to provide informed consent.^{9–11}

Study Design

A retrospective analysis of data from all three clinical trials was undertaken in the current study. All three trials had a primary endpoint of AWR in surgical patients. In all studies, patients underwent randomization to a BIS-guided protocol or an anesthetic concentration-guided protocol. All patients received a BIS Quatro sensor (Covidien, USA), which was applied to their foreheads, and BIS, hemodynamic, and anesthetic parameters were recorded for each patient using an anesthesia information system. The current study analyzed perioperative data from patients enrolled in any of the three clinical trials. Analysis included data from patients whose surgeries lasted at least 30 min and whose BIS, MAP, and MAC values were all available for at least half of the case's duration. BIS values were excluded from the analysis if the electrode's signal quality index was less than 50. If a patient had multiple operations, we included intraoperative data from the most recent surgery.

Data Processing

A standard electronic data form was used to collect perioperative data for patients in BAG-RECALL and B-UNAWARE using data from medical files, surgical reports, anesthetic and postoperative charts, discharge letters, and records of outpatient clinic visits. All data for patients enrolled in the Michigan Awareness Control Study were electronically captured by an anesthesia information system. Data for these patients were prospectively collected with the exception of malignancy (BAG-RECALL and B-UNAWARE) and mortality status (all three studies). History of malignancy was obtained by retrospectively reviewing medical charts (BAG-RECALL and B-UNAWARE) and from specific provider entry into the anesthesia information system preoperative history and physical (Michigan Awareness Control Study). Postoperative mortality dates were ascertained from the U.S. Social Security Death Index and by contacting patients and their families in Canada. All patients were recruited while the Social Security Death Index was still available.

Data from the three trials were combined and processed using MATLAB[®] 7.14 R2012a (The MathWorks Inc., USA). Intraoperative measurements collected before the induction of anesthesia or after the emergence were excluded by removing measurements collected at BIS greater than 80. Periods of cardiopulmonary bypass were removed from the patients' intraoperative records because volatile anesthetic concentration could not be reliably ascertained during cardiopulmonary bypass and because MAP is generated by the cardiopulmonary bypass roller pump rather than by the heart. End-tidal anesthetic concentration, BIS, and MAP measurements were resampled to one measurement per minute by retaining the first value of every minute.

End-tidal anesthetic concentration values were converted to non-age-adjusted MAC equivalents.^{7,13} Arterial MAP values were included in preference to noninvasive MAP measures where available. MAP values less than 30 and greater than 180 were considered outliers and were excluded. In addition, MAP values were excluded when their corresponding systolic blood pressures (SBPs) and diastolic blood pressures (DBP) were considered to be artifacts. Blood pressure artifacts were defined by the following algorithm: (1) SBP-DBP is less than 30 when SBP is greater than 150, (2) SBP-DBP is less than 20 when 100 is less than SBP is less than 150, and (3) SBP-DBP is less than 10 when SBP is less than 100. Artifacts were further reduced by dividing the anesthetic period into 5-min epochs and retaining only the median BIS, MAC, and MAP values from each epoch. Discrepancies in the numbers of BIS, MAC, and MAP epochs arose due to data from some variables being available for a greater portion of the case than other variables. Cases with more than a four-epoch difference between any of the three variables were excluded, as this analysis is principally interested in the concurrence of these factors. The cumulative duration of triple low was determined by summing the number of 5-min epochs (regardless of whether or not these were consecutive) during which the median BIS was less than 45, median MAC less than 0.8, and median MAP less than 75. Temperature data were collected, where available, and recorded as the median temperature per 5-min epoch. We could not include the temperature for all patients as one of the trials (B-Unaware) was conducted before implementation of the electronic medical record and one of the trials (BAG-RECALL) was half completed before implementation of the electronic medical record. Temperatures above 50°C or below 10°C were excluded as artifacts. The manufacturer of the BIS™ monitor (Covidien, USA) had no role in study design, data collection, data analysis, or manuscript preparation. No study monitors or means of support of any kind were provided by the manufacturer of the BIS monitor.

Statistical Analysis

Differences in categorical patient characteristics between the patients with greater than 15 cumulative but not necessarily contiguous minutes of triple low and those without were evaluated with Pearson chi-square test. Baseline differences in age, body mass index (BMI), and case duration were compared with Mann-Whitney U test as they were determined to follow nonnormal distributions by one-sample Kolmogorov-Smirnov tests. Survival differences for cohorts with and without greater than 15 min of triple low were visualized using Kaplan-Meier methods, and statistical differences were determined using log-rank tests. Similar to the study by Sessler *et al.*,⁷ participants were partitioned into groups by the duration of their triple low state: 0 to 15, 16 to 30, 31 to 45, 46 to 60, and greater than 60 min. Differences in mortality rate between groups was determined by Pearson chi-square tests. Differences were considered significant if their *P* values were

less than 0.008 (per Bonferroni correction). We evaluated the association between minutes of triple low with 30- and 90-day mortality using both univariable and multivariable Cox proportional hazards regression, including adjustment for age, sex, American Society of Anesthesiologists (ASA) physical status score (classified as 1 or 2, 3, and 4 or 5), patient comorbidities, and intraoperative factors, including case time, nitrous oxide exposure, and use of intraoperative cardiopulmonary bypass. Univariable associations with a *P* value less than 0.05 were included in the initial construction of the multivariable Cox proportional hazards model. In addition, to evaluate for a potential confounding role that low blood pressure may have on triple low, duration of time spent in single low (MAP < 75 mmHg) was force entered into the model as well. To avoid bias secondary to overfitting of the data, backward deletion of least significant predictors was used to form a final model. Discriminatory power of this model was calculated by use of the *C*-index, which ranges from 0.5 (outcomes described by chance alone) to 1.0 (outcomes completely explained by model). The degree of overoptimism was found by bootstrapping 100 samples into the original model. Optimism was estimated as the difference in the *C*-index between the original model and bootstrapped model. The proportional hazards assumption was tested by evaluating the scaled Schoenfeld residuals across all time points, and any covariables found to violate this assumption were removed from the model.

To better account for the differences in baseline characteristics in patients with and without triple low, we matched patients with greater than 15 min of triple low to those without, based on their demographic characteristics and comorbidities *via* a propensity score.¹⁴ This technique balances the demographic variables and patient comorbidities between both the exposed and unexposed cohorts.¹⁵ We performed a 1:1 nearest neighbor match with replacement and a caliper allowing matches up to 0.20 SDs of the predicted propensity score.^{14,16} Weights were computed to account for controls matched to multiple cases without expanding the sample size. Success of the match was evaluated by the propensity scores' standardized mean difference and variance ratios and by ensuring the standardized mean difference for any variable did not exceeded 0.25.¹⁷ Weighted paired *t* test and Pearson chi-square test were used to evaluate the differences after matching. Cox proportional hazards models were used to evaluate the association between duration of triple low and 30- and 90-day mortality in the matched sample. All remaining covariables from the backwards elimination unmatched regressions were included in these matched analyses.

The effect of temperature on the relation between triple low and mortality was tested in a secondary analysis. Only patients who had temperature data available for at least half of their surgery were included. Cox proportional hazards models were used to evaluate the association between duration of triple low and 30- and 90-day mortality in the unmatched sample. Duration of temperature below the 25th percentile was included as a covariate, in addition to covariables remaining in the final

unmatched 30- and 90-day regressions from the complete sample. A mixed-effects model was created to evaluate the relation between BIS and temperature after adjusting for several covariables, including MAC, administration of nitrous oxide, age, sex, ASA physical status score, cardiopulmonary bypass, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, cancer, pulmonary hypertension, cardiac valvular disease, and a history of substance use including γ -aminobutyric acidergic drugs (alcohol, benzodiazepines, and barbiturates), anticonvulsants, and opioids. A random intercept was added to account for between-patient differences. Statistical analyses were performed in R version 3.0.2 (The R Foundation for Statistical Computing, Austria).

Results

The three clinical trials included 26,586 patients. In our analysis, 13,388 patients were excluded due to lack of adequate

intraoperative data, case duration less than 30 min, duplicate procedures, epoch length discrepancies, lack of data on vital status, or lack of other intraoperative variables (fig. 1). The final sample included 13,198 unique patients with 43,929 h of intraoperative recordings. Temperature data were available for 9,202 of these patients.

Approximately 30% of patients included in this analysis experienced greater than 15 cumulative minutes of triple low during their surgery ($n = 3,950$). Patients who experienced greater than 15 min of triple low were generally older and male, with lower BMI, higher ASA scores, a higher prevalence of comorbidities (coronary artery disease, prior strokes, congestive heart failure, dysrhythmias, valve disease, hypertension, diabetes, peripheral vascular disease, pulmonary hypertension, chronic obstructive pulmonary disease, and chronic anticonvulsant use), a lower prevalence of cancer, and less preoperative barbiturate, benzodiazepine, alcohol,

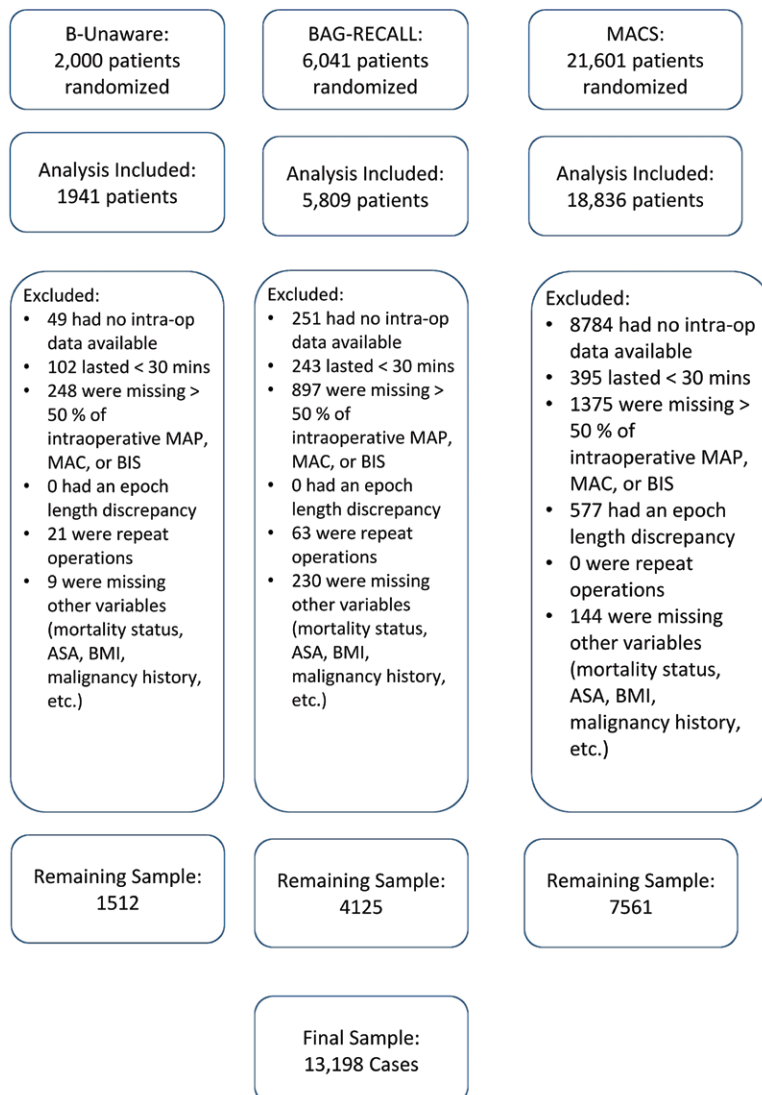


Fig. 1. Flow chart of patient selection. ASA = American Society of Anesthesiologists; BIS = bispectral index; BMI = body mass index; MAC = minimum alveolar concentration; MAP = mean arterial pressure.

Table 1. Characteristics between TL and non-TL Groups on All Baseline Characteristics before and after Propensity Score Matching

Characteristics	All (n = 13,198)	TL (n = 3,950)	Unmatched Non-TL (n = 9,248)	Matched Non-TL (n = 2,497)
Age, yr	56 (44, 66)	61 (51, 70)	54 (42, 64)*	59.6 ± 15.3
Body mass index, kg/m ²	28.2 (24.8, 33.0)	28.0 (24.1, 32.6)	28.5 (24.9, 33.0)*	29.1 ± 7.2
Site			Overall <i>P</i> < 0.001	Overall <i>P</i> = 0.483
Chicago, Illinois	170 (1.3)	43 (1.1)	127 (1.4)	30 (1.1)
Ann Arbor, Michigan	7,561 (57.3)	1,295 (32.8)	6,266 (67.8)	837 (31.3)
St. Louis, Missouri	4,823 (36.5)	2,216 (56.1)	2,607 (28.2)	1,518 (56.7)
Winnipeg, Manitoba	644 (4.9)	396 (10.0)	248 (2.7)	292 (10.9)
Male sex	6,952 (52.7)	2,193 (55.5)	4,759 (51.5)*	1,470 (54.9)
ASA physical status score			Overall <i>P</i> < 0.001	Overall <i>P</i> = 0.610
I	1,179 (8.9)	157 (4.0)	1,022 (11.1)	118 (4.4)
II	5,223 (39.4)	874 (22.1)	4,349 (47.0)	583 (21.8)
III	4,669 (35.4)	1,521 (38.5)	3,148 (34.0)	1,058 (39.5)
IV	2,126 (16.1)	1,397 (35.4)	729 (7.9)	917 (36.3)
V	1 (0)	1 (0)	0 (0)	0 (0)
Medical history				
Coronary artery disease	2,641 (20.0)	1,366 (34.6)	1,275 (13.8)*	943 (35.2)
Cerebrovascular accident	450 (3.4)	187 (4.7)	263 (2.8)*	115 (4.3)
Congestive heart failure	913 (6.9)	563 (14.3)	350 (3.8)*	337 (12.6)
Hypertension	6,348 (48.1)	2,303 (58.3)	4,045 (43.7)*	1,518 (56.7)
COPD	1,130 (8.6)	463 (11.7)	667 (7.2)*	323 (12.1)
Cancer	3,295 (25.0)	795 (20.1)	2,500 (27.0)*	614 (22.9)*
Dysrhythmia	1,130 (8.6)	560 (14.2)	570 (6.2)*	352 (13.2)
Diabetes mellitus	2,190 (16.6)	905 (22.9)	1,285 (13.9)*	591 (22.1)
Peripheral vascular disease	788 (6.0)	415 (10.5)	373 (4.0)*	276 (10.3)
Pulmonary hypertension	286 (2.2)	180 (4.6)	106 (1.1)*	101 (3.8)
Valvular disease	1,276 (9.7)	803 (20.3)	473 (5.1)*	495 (18.5)
Preoperative anticonvulsant use	539 (4.1)	205 (5.2)	334 (3.6)*	165 (6.2)
Preoperative barbiturate, benzodiazepine, and alcohol	4,326 (32.8)	1,170 (29.6)	3,156 (34.1)*	782 (29.2)
Preoperative opioid use	3,037 (23.0)	783 (19.8)	2,254 (24.4)*	505 (18.9)
Intraoperative factors				
Case length, min	178 (115, 259)	248 (168, 333)	158 (103, 222)*	191 ± 105*
Intraoperative nitrous oxide	6,678 (50.6)	1,046 (26.5)	5,632 (60.9)*	884 (33.0)*
Intraoperative CPB	2,059 (15.6)	1,542 (39.0)	514 (5.6)*	600 (22.4)*

Values presented as counts (percentages), mean ± SD, or median (25th percentile, 75th percentile).

* *P* < 0.05 compared with patients who experienced at least 15 min of TL.

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; TL = triple low.

and opioid use (table 1). Furthermore, patients with greater than 15 min of triple low were more likely to have longer case times, less nitrous oxide exposure, and undergo intraoperative cardiopulmonary bypass.

The overall 30-day mortality rate was 0.8% (n = 111; 95% CI, 0.69 to 1.00%) and the overall 90-day mortality rate was 1.9% (n = 247; 95% CI, 1.64 to 2.10%). Mortality at 30 and at 90 days was increased in patients who experienced greater than 15 min of triple low (1.9% [1.50 to 2.35%] and 3.7% [3.15 to 4.34%], respectively) compared with those who did not (0.4% [0.25 to 0.50%] and 1.1% [0.86 to 1.28%], *P* < 0.001 for both). Relative risk of mortality was also increased among patients with greater than 15 cumulative minutes of low MAP and all double low categories in the unmatched population (fig. 2). The number of patients experiencing a particular triple low duration was as follows: 6,002 (0 min), 3,246 (1 to 15 min), 1,275 (16 to 30 min), 762 (31 to 45 min), 494 (46 to 60 min), and 1,419

(> 60 min). Postoperative mortality tended to increase with increasing triple low duration (fig. 3). Survival up to 90 days was lower in patients with greater than 15 min of triple low (log-rank *P* < 0.001; fig. 4). Thirty-day mortality tended to increase for all combinations of MAC and MAP when BIS values were less than 45 (fig. 5). Despite these associations, triple low was a moderate discriminator of postoperative mortality with areas under receiver-operator characteristics curves of 0.764 and 0.713 at 30 and 90 days, respectively, in the unmatched sample (fig. 6).

Unadjusted associations with postoperative mortality are provided in the appendix. After correcting for baseline differences, cumulative duration of the triple low state was significantly associated with an increased risk of postoperative mortality at 30 days (hazard ratio [HR], 1.08 per 15 min; 95% CI, 1.03 to 1.13) and 90 days (HR, 1.10; 95% CI, 1.07 to 1.13; *P* < 0.001) (table 2). Increased 30-day mortality was also independently associated with certain demographic

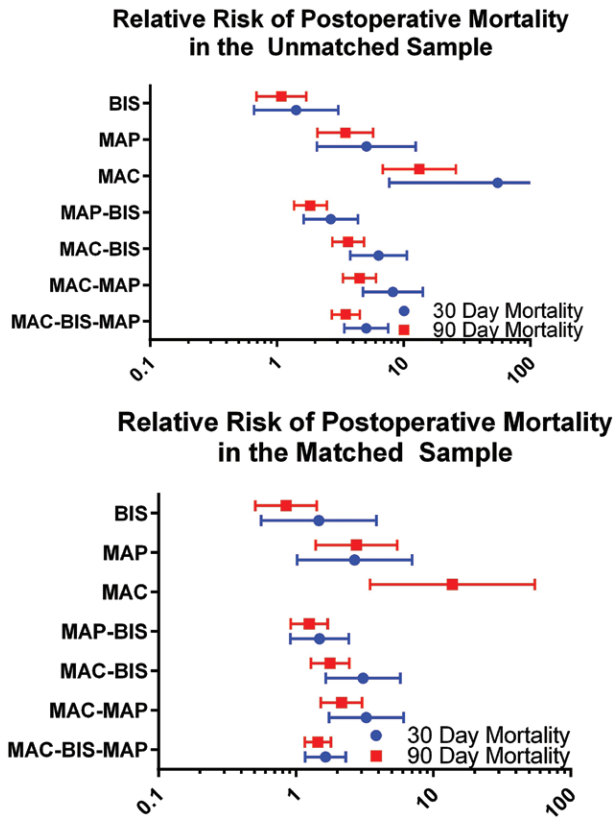


Fig. 2. Relative risk of postoperative mortality among patients having greater than 15 min of low bispectral index (BIS), mean arterial pressure (MAP), minimum alveolar concentration (MAC), or combinations thereof. Risk of mortality was increased for all categories except for low BIS in the unmatched sample. Low MAP-BIS was no longer associated with mortality after matching. The risk for low MAC is unstable because only 1 and 0 patient(s) with ≤ 15 min of low MAC died within 30 days in the unmatched and matched samples, respectively. Error bars represent 95% CIs.

characteristics (increasing age and increasing ASA physical status) and patient comorbidities (chronic obstructive pulmonary disease, malignancy, cardiac dysrhythmia, and peripheral vascular disease). Nitrous oxide exposure was associated with a lower risk of mortality. At 90 days, similar demographic characteristics and patient comorbidities (with the addition of BMI and history of stroke) were independently associated with postoperative mortality. These models had good discrimination (C -index = 0.89 and 0.86, respectively, for 30- and 90-day mortality), with minimal overoptimization (0.03, 0.02), resulting in adjusted C -indices of 0.87 and 0.85, respectively. Similar regressions including only patients with temperature data available found no difference in the association between triple low and mortality when duration of temperature below 35.7°C (the 25th percentile) was included as a covariable (30-day HR 1.09 per 15 min; 95% CI, 1.05 to 1.12, and 90-day HR, 1.09 per 15 min; 95% CI, 1.07 to 1.11). Temperature below 35.7°C was not significantly associated with mortality. The mixed-effects model found that the temperature was significantly associated with BIS, even after accounting for several covariables including MAC, administration of nitrous oxide, and several patient characteristics and comorbidities ($\beta = 1.0$, standard error = 0.02, $P < 0.001$).

There were no significant differences in patient characteristics or prevalence of comorbidities between the two propensity-matched groups, except for a higher rate of cancer among patients without triple low (table 1). The absolute value of the standardized mean difference of the propensity scores was 0.23, and the propensity score's standardized variance ratio was 1.18. Ultimately, 2,676 controls were matched to 3,950 cases of individuals with triple low greater than 15 min. Combined, this group experienced 100 deaths at 30 days and 214 deaths at 90 days. Triple low's discriminative ability fell after matching, with areas under receiver-operator

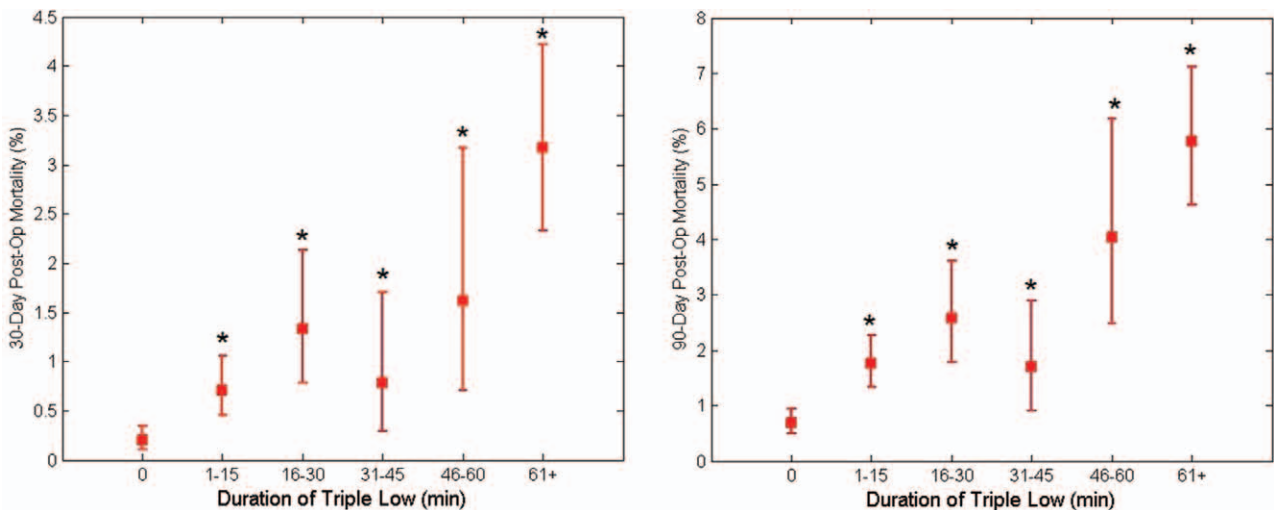


Fig. 3. Thirty- and 90-day mortality as a function of the number of cumulative (although not necessarily contiguous) minutes of triple low. *Thirty- and 90-day mortality was increased from baseline for all durations of triple low, after Bonferroni correction for multiple comparisons. Error bars represent 95% CIs.

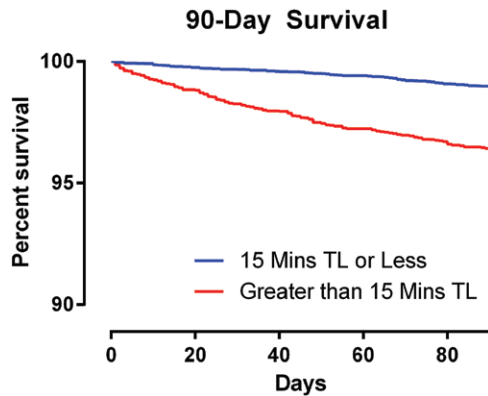


Fig. 4. Percent of the study population surviving up to 90 days after surgery. Patients who experienced greater than 15 cumulative minutes of concurrently low mean arterial pressure, minimum alveolar concentration, and bispectral index values had decreased postoperative survival to 90 days. TL = triple low.

characteristics curve values of 0.658 and 0.633 for 30- and 90-day mortality, respectively (fig. 6). After propensity score matching and adjusting for comorbidities, cumulative duration of the triple low state was significantly associated with an increased risk of mortality at 30 days (HR, 1.09 per 15 min; 95% CI, 1.07 to 1.11; $P < 0.001$) and 90 days (HR, 1.09 per 15 min; 95% CI, 1.08 to 1.11; $P < 0.001$).

Discussion

For patients enrolled in the B-Unaware and BAG-RECALL trials, and in the Michigan Awareness Control Study, cumulative concurrent duration of MAC less than 0.8, MAP less than 75 mmHg, and BIS less than 45 was independently associated with an increased risk of 30- and 90-day postoperative mortality. Furthermore, this association remained even after attempting to control for patient comorbidity through propensity matching. These findings are generally consistent with those previously reported by Sessler *et al.*⁷ and are in contrast to the findings by Kertai *et al.*⁸

This study found a much higher rate of triple low than that reported by Sessler *et al.* (6% experienced > 15 min) or Kertai *et al.* (20% experienced > 18 min). The patients in this study tended to have higher ASA scores than those in the study by Kertai *et al.* Many underwent cardiac surgeries, which was a population excluded from the analysis by Sessler *et al.* Our propensity match regression found that triple low was associated with several comorbidities, which may partially explain the higher rate. The B-UNAWARE and BAG-RECALL studies included only patients at high risk for awareness during anesthesia, who often had many comorbidities. As patients with several comorbidities appear to have higher rates of both triple low and mortality, there is possible residual confounding of the relation between triple low and mortality.

Individuals who experienced greater than 15 min of triple low were more likely to have a number of cardiovascular

comorbidities, including previous myocardial infarctions, previous strokes, congestive heart failure, cardiac dysrhythmias, valvular heart disease, hypertension, diabetes, peripheral vascular disease, and pulmonary hypertension. Volatile anesthetics produce dose-responsive hypotension by lowering systemic vascular resistance and also by decreasing myocardial contractility. These findings are accentuated in hearts with left or right ventricular dysfunction. In addition, patients with cardiovascular conditions are more likely to be on medications that lower intrinsic myocardial contractility, that is, calcium channel blockers or β_1 -adrenergic blockers. Thus, for patients with cardiovascular disease, it is not surprising that hypotension can occur even with modest exposure to volatile anesthetic agents. However, it is unclear how cardiovascular disease would increase the likelihood of low BIS values at low MAC values. It is also perhaps unsurprising that patients with increased triple low states tended to have a decreased prevalence of preoperative benzodiazepine, barbiturate, alcohol, or opioid use. Chronic alcohol use may increase anesthetic requirements in patients undergoing general anesthesia.^{18–20} Alternatively, patients in the triple low group tended to be older and have more comorbidities and may have been less likely to routinely use these medications.

Longer case times were associated with a higher rate of triple low and 30-day mortality. This could be interpreted as increased duration of triple low being merely a reflection of longer case times. However, triple low was consistently associated with 30- and 90-day mortality before and after matching, whereas case duration was only associated with 30-day mortality in the unmatched sample. This finding suggests that duration of triple low adds additional information regarding future mortality risk that is not found in case duration alone. Patients with increased triple low had less exposure to nitrous oxide, and nitrous oxide was associated with a lower 30-day mortality. Nitrous oxide has previously been associated with a lower postoperative mortality.²¹ However, the recently published ENIGMA II trial powerfully established that, in general, nitrous oxide use does not impact postoperative mortality or major morbidity.²² This provides a sober reminder of the potential of published research, especially with subgroups or small studies, to produce misleading findings.^{23–25} With any regression analysis where multiple statistical associations are tested, there is potential for spurious results or confounding. The decrease in mortality associated with nitrous oxide use in the current regression analysis is a probable example, especially given that there was an apparent five-fold reduction with nitrous oxide in 30-day mortality, whereas it was excluded from the 90-day mortality regression as a poor predictor. When controlling for nitrous oxide exposure in the current study, cumulative time spent in the triple low state was still associated with an increased risk of mortality.

In the current study, both cumulative time with MAP less than 75 mmHg and average case MAP less than 75 mmHg were eliminated from the Cox multivariable hazard model. In

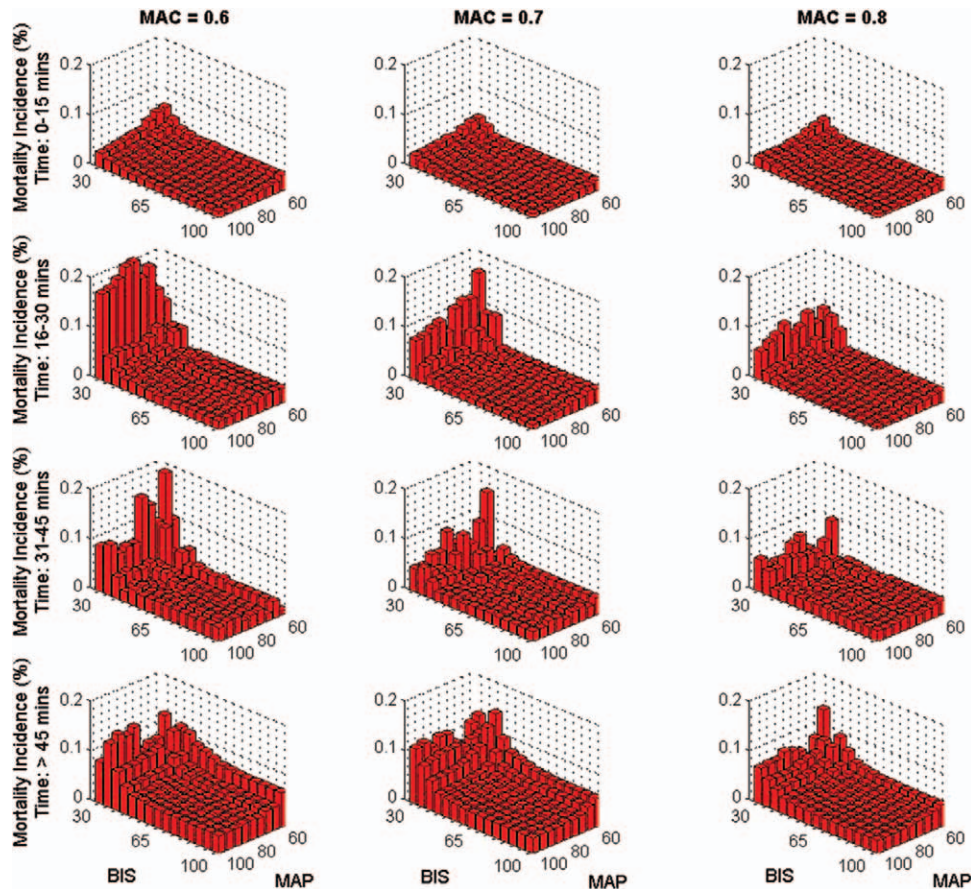


Fig. 5. Thirty-day mortality as a function of cumulative (not necessarily contiguous) minutes at various thresholds of low mean arterial pressure (MAP), bispectral index (BIS), and minimum alveolar concentration (MAC). Mortality tends to increase with extended duration of low BIS, MAP, and MAC at all thresholds. There was a sharper increase in mortality at low BIS values than low MAP or MAC values.

other words, we did not find that MAP less than 75 mmHg in isolation was independently associated with postoperative death. A lower blood pressure might be more strongly linked (causally) to adverse outcomes. For example, a study examining the risk of postoperative renal failure has suggested that intraoperative MAP less than 55 mmHg might be a contributory factor.²⁶ Part of the intriguing nature of the triple low state is that isolated intraoperative occurrences of MAP less than 75 mmHg, MAC less than 0.8, or BIS less than 45 may not be considered clinically significant. However, their concurrence might be predictive of adverse outcomes.

The relation between triple low and mortality was found to be independent of low body temperatures. Perioperative hypothermia may be a confounder as it is associated with decreased BIS values during cardiopulmonary bypass and increased cardiac morbidity, coagulation dysfunction, and mortality.²⁷⁻³¹ This study identified a positive association between temperatures and BIS values while patients were not on cardiopulmonary bypass. However, the lack of association between temperature and postoperative mortality may be due to the fact that there were relatively few epochs of severe hypothermia.

It has been suggested that the link between triple low and death is epiphenomenal, with triple low merely reflecting

patient comorbidities.³² We attempted to control for these comorbid conditions with propensity matching. By creating two cohorts with similar comorbid conditions, the associations of intraoperative variables with postoperative mortality might be more clearly identified. Even after propensity score matching, triple low remained an independent predictor of postoperative mortality at both 30 and 90 days. Although this propensity matching accounts for many comorbid conditions, neither does it fully account for the severity of these conditions nor does it account for the overall frailty or functional status of the patient.

This study's primary strengths are its multicenter population, use of propensity score matching to balance covariables, and inclusion of rigorously and prospectively collected data. The most important limitation is that an observational study, no matter how sophisticated its methods, cannot exclude hidden confounding and typically cannot establish causality. This limitation must be strongly emphasized with the current study. A further consideration is that if triple low has deleterious consequences, it is likely that contiguous periods of triple low are more concerning than sporadic episodes. Our analysis did not distinguish whether the triple low episodes were contiguous or dispersed. Another

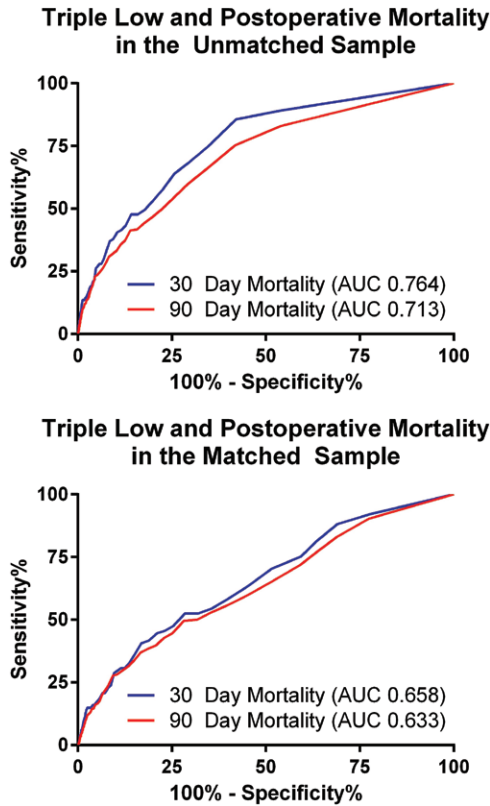


Fig. 6. Receiver-operator characteristics curve displaying the sensitivity and specificity of duration of mean arterial pressure less than 75 mmHg, minimum alveolar concentration less than 0.8, and bispectral index less than 45 as a predictor of 30- and 90-day mortality. AUC = area under the curve.

potential constraint is that unlike MAP and MAC, the BIS number is calculated *via* a proprietary algorithm and has no units of measurement. It cannot be assumed that a BIS value of 44 in one individual indicates an equivalent depth

of anesthesia to a BIS value of 44 in another individual. Furthermore, BIS values cannot be translated to other processed electroencephalograph devices, limiting the generalizability of findings based on BIS or any other processed electroencephalograph monitor. In contrast, burst suppression is an electroencephalograph feature that is nonproprietary, is indicative of excessive anesthetic depth, and might be associated with increased postoperative mortality.³³ Future studies, in testing candidate relations between electroencephalograph features and postoperative outcomes, should seek to include electroencephalograph features that are not restricted to particular devices. A further limitation of the current study is that intraoperative data on anesthetic adjuvants (*e.g.*, intraoperative use of opioids, *N*-methyl-D-aspartate antagonists, α_2 -agonists, neuraxial anesthesia, and peripheral nerve blocks) were not routinely collected for many patients. Adjuvant agents are commonly administered as part of a balanced anesthesia regimen. Many such agents are MAC sparing, have hemodynamic effects, and are associated with alterations in the electroencephalograph. Theoretically, these adjuvant drugs could be important confounders in a triple low analysis. Finally, our models were deficient based on important missing patient characteristics (*e.g.*, markers of frailty) and excluded incomplete intraoperative variables (*e.g.*, end-tidal carbon dioxide).

In summary, this is the second large observational trial that has found that cumulative duration of MAP less than 75 mmHg and BIS less than 45 in the setting of MAC less than 0.8 is independently associated with postoperative mortality. The replication of the findings by Sessler *et al.* increases the interest in the ongoing clinical trial (NCT00998894) that is attempting to resolve the question whether alerting clinicians about a triple low state will change anesthetic management (*e.g.*, through increasing MAP or decreasing MAC) and result in decreased postoperative mortality.

Table 2. Multivariable Predictors of 30- and 90-day Mortality before Matching

Factors	30-day Conditional Hazard Ratio (95% CI)	P Value	90-day Conditional Hazard Ratio (95% CI)	P Value
Age (/yr)	1.04 (1.02–1.05)	<0.001	1.02 (1.01–1.03)	<0.001
ASA physical status score 3 (vs. 1–2)	—	—	4.25 (2.41–7.48)	<0.001
ASA physical status score 4 or 5 (vs. 1–2)	2.64 (1.63–4.26)	<0.001	9.45 (5.13–17.41)	<0.001
Body mass index (kg/m ²)	—	—	0.97 (0.95–0.99)	<0.001
Cancer	2.77 (1.61–4.75)	<0.001	3.15 (2.31–4.30)	<0.001
Case duration (/15 min)	1.03 (1.01–1.06)	0.010	—	—
Cerebrovascular accident	—	—	1.62 (1.07–2.45)	0.002
COPD	2.01 (1.32–3.06)	0.001	2.04 (1.54–2.70)	<0.001
Dysrhythmia	2.17 (1.43–3.29)	<0.001	2.05 (1.53–2.74)	<0.001
Nitrous oxide use	0.16 (0.07–0.36)	<0.001	0.55 (0.38–0.80)	0.002
Peripheral vascular disease	1.96 (1.24–3.10)	0.004	1.56 (1.12–2.18)	0.009
Triple low (/15 min)	1.08 (1.03–1.13)	0.001	1.10 (1.07–1.13)	<0.001

Data are presented as hazard ratios followed by 95% CIs. Factors entered in the regression included duration of MAP < 75 mmHg, having > 50% of MAP values < 75 mmHg, age, sex, ASA = 3, ASA ≥4, coronary artery disease, cerebrovascular accident, hypertension, COPD, cancer, dysrhythmias, diabetes mellitus, peripheral arterial disease, pulmonary hypertension, valvular heart disease, a history of using barbiturates, benzodiazepines, or alcohol, use of nitrous oxide during surgery, use of cardiopulmonary bypass during surgery, and case duration.

ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; MAP = mean arterial pressure.

Acknowledgments

Parent studies received funding from the National Institutes of Health (Bethesda, Maryland; grant no. KL2 RR024987-01 to Dr. Mashour), grants from the Foundation for Anesthesia Education and Research (Schaumburg, Illinois; to Drs. Avidan and Mashour), a grant from the Barnes Jewish Hospital Foundation (St. Louis, Missouri; to Dr. Avidan), a grant from Winnipeg Regional Health Authority and University of Manitoba, Department of Anesthesia (Winnipeg, Manitoba, Canada; to Dr. Jacobsohn), and departmental support from the Department of Anesthesiology at Washington University in St. Louis (St. Louis, Missouri), the Department of Anesthesiology at the University of Chicago (Chicago, Illinois), and the Department of Anesthesiology at the University of Michigan (Ann Arbor, Michigan). This publication was made possible by grant nos. ULI TR000448 and TL1 TR000449 from the National Center for Advancing Translational Sciences, National Institutes of Health to Washington University School of Medicine. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing Interests

The authors declare no competing interests.

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Appendix: Univariable Associations with 30- and 90-day Mortality

Factors	30-day Mortality		90-day Mortality	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Low MAP (/15 min)	1.11 (1.08–1.14)	<0.001	1.10 (1.08–1.12)	<0.001
Low MAC (/15 min)	1.13 (1.11–1.14)	<0.001	1.11 (1.10–1.12)	<0.001
Low BIS (/15 min)	1.10 (1.08–1.12)	<0.001	1.07 (1.06–1.09)	<0.001
Low MAP and MAC (/15 min)	1.16 (1.13–1.19)	<0.001	1.14 (1.12–1.17)	<0.001
Low MAC and BIS (/15 min)	1.14 (1.12–1.16)	<0.001	1.12 (1.11–1.14)	<0.001
Low MAP and BIS (/15 min)	1.13 (1.10–1.16)	<0.001	1.11 (1.09–1.13)	<0.001
Triple low (/15 min)	1.19 (1.15–1.22)	<0.001	1.17 (1.14–1.19)	<0.001
Case average MAP <75	1.24 (0.86–1.81)	0.249	1.43 (1.11–1.83)	0.005
Age (/yr)	1.07 (1.05–1.08)	<0.001	1.06 (1.05–1.07)	<0.001
BMI (kg/m ²)	0.97 (0.94–1.00)	0.051	0.96 (0.94–0.98)	<0.001
Male sex	1.88 (1.26–2.79)	0.002	1.52 (1.18–1.97)	0.001
ASA physical status score 3 (vs. 1 to 2)	10.45 (4.11–26.56)	<0.001	9.69 (5.64–16.64)	<0.001
ASA physical status score 4 to 5 (vs. 1 to 2)	41.67 (16.80–103.33)	<0.001	26.34 (15.42–44.97)	<0.001
Coronary artery disease	5.93 (4.06–8.66)	<0.001	3.99 (3.11–5.12)	<0.001
Cerebrovascular accident	4.14 (2.37–7.26)	<0.001	3.43 (2.29–5.14)	<0.001
Congestive heart failure	5.79 (3.86–8.70)	<0.001	4.56 (3.42–6.09)	<0.001
Hypertension	2.45 (1.64–3.67)	<0.001	2.36 (1.80–3.08)	<0.001
COPD	4.57 (3.04–6.86)	<0.001	17.68 (13.68–22.85)	<0.001
Current malignancy	1.16 (0.77–1.76)	0.473	1.73 (1.33–2.24)	<0.001
Dysrhythmia	4.99 (3.35–7.45)	<0.001	4.35 (3.29–5.73)	<0.001
Diabetes	2.23 (1.49–3.34)	<0.001	1.96 (1.49–2.59)	<0.001
Peripheral vascular disease	5.14 (3.33–7.92)	<0.001	3.80 (2.77–5.23)	<0.001
Pulmonary hypertension	4.57 (2.39–8.74)	<0.001	4.79 (3.12–7.36)	<0.001
Valvular disease	2.45 (1.55–3.89)	<0.001	2.46 (1.81–3.35)	<0.001
Anticonvulsant use	1.59 (0.74–3.42)	0.233	1.22 (0.69–2.18)	0.492
Regular barbiturate, benzodiazepine, or alcohol use	0.57 (0.36–0.89)	0.013	0.81 (0.61–1.07)	0.131
Regular opioid use	0.60 (0.36–1.01)	0.056	0.83 (0.60–1.13)	0.229
Case duration (/15 min)	1.08 (1.06–1.10)	<0.001	1.07 (1.05–1.08)	<0.001
Intraoperative nitrous oxide	0.06 (0.02–0.13)	<0.001	0.17 (0.12–0.25)	<0.001
Intraoperative CPB	5.38 (3.71–7.81)	<0.001	3.70 (2.87–4.78)	<0.001

ASA = American Society of Anesthesiologists; BIS = bispectral index; BMI = body mass index; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; MAC = minimum alveolar concentration; MAP = mean arterial pressure.