Triple-low Alerts Do Not Reduce Mortality

A Real-time Randomized Trial

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ABSTRACT

Background: Triple-low events (mean arterial pressure less than 75 mmHg, Bispectral Index less than 45, and minimum alveolar fraction less than 0.8) are associated with mortality but may not be causal. This study tested the hypothesis that providing triple-low alerts to clinicians reduces 90-day mortality.

Methods: Adults having noncardiac surgery with volatile anesthesia and Bispectral Index monitoring were electronically screened for triple-low events. Patients having triple-low events were randomized in real time, with clinicians either receiving an alert, "consider hemodynamic support," or not. Patients were blinded to treatment. Helpful responses to triple-low events were defined by administration of a vasopressor within 5 min or a 20% reduction in end-tidal volatile anesthetic concentration within 15 min.

Results: Of the qualifying patients, 7,569 of 36,670 (20%) had triple-low events and were randomized. All 7,569 were included in the primary analysis. Ninety-day mortality was 8.3% in the alert group and 7.3% in the nonalert group. The hazard ratio (95% CI) for alert *versus* nonalert was 1.14 (0.96, 1.35); $P = 0.12$, crossing a prespecified futility boundary. Clinical responses were helpful in about half the patients in each group, with 51% of alert patients and 47% of nonalert patients receiving vasopressors or having anesthetics lowered after start of triple low ($P < 0.001$). There was no relationship between the response to triple-low events and adjusted 90-day mortality.

Conclusions: Real-time alerts to triple-low events did not lead to a reduction in 90-day mortality, and there were fewer responses to alerts than expected. However, similar mortality with and without responses suggests that there is no strong relationship between responses to triple-low events and mortality. (ANESTHESIOLOGY 2018; XXX:00-00)

INTRAOPERATIVE hypotension,[1,2] low Bispectral Index (BIS),[3–5] and low minimum alveolar concentration (MAC) fractions[6] have each been associated with mortality. Perhaps unsurprisingly, the combination of any two low values,[7,8] and especially the combination of all three, a "triple low,"[8,9] are strong predictors of postoperative mortality as summarized in a recent meta-analysis.[10] A remarkable aspect of triple-low events is that they are defined by thresholds that are individually unremarkable, specifically mean arterial pressure (MAP) of less than 75 mmHg, BIS less than 45, and MAC fraction of less than 0.8.

The potential importance of the individual triple-low components is that they distinguish between the normal physiologic response to volatile anesthetics and patients at risk. For example, low MAC fractions normally provoke high BIS and high MAP. The opposite response (low MAP

Editor's Perspective

What We Already Know about This Topic

- Intraoperative triple-low events (mean arterial pressure less than 75 mmHg, Bispectral Index less than 45, and minimum alveolar fraction of anesthetic less than 0.8) have been found to be associated with increased risk of mortality

What This Article Tells Us That Is New

- A randomized electronic alert of triple-low events to treating clinicians did not reduce 90-day mortality
- The alerts minimally influenced clinician responses, assessed as vasopressor administration or reduction in end-tidal volatile anesthetic partial pressure, and there was no association between response to alerts and mortality
- Triple-low events predict mortality but do not appear to be causally related

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and low BIS) is unexpected and thus identifies patients who could be described as sensitive to anesthesia—possibly because of underlying fragility or illness.

Mild hypotension (*i.e.*, MAP ≈ 75 mmHg) is usually considered to be harmless in most patients,[1,2] and few anesthesiologists would consider such pressures to be alarming. However, just as otherwise-healthy patients can hypoperfuse their brains in the beach-chair position,[11] relatively sick patients who are mildly hypotensive may have inadequate cerebral perfusion while supine. Even mildly low MAP may thus be associated with inadequate brain and organ perfusion in some patients. In theory, low MAC should be associated with high BIS. When it is not, brain hypoperfusion is one potential explanation—especially when hypotension is observed—and possibly explains why triple-low states are stronger predictors of death than mild hypotension alone.

As suggestive as the observational results are, causal conclusions regarding the impact of early intervention for triple-low events require a randomized trial design. A challenge is that only about one in five adults having noncardiac surgery experiences a triple-low event. A conventional randomized trial would thus need to enroll many patients for each who experiences a triple-low event, making the study impractical. We thus conducted an innovative comparative-effectiveness trial using real-time randomization based on decision-support technology.

We tested the theory that smart alarms for the triple-low state incorporated into a decision-support system prompts clinicians to intervene earlier in situations that would otherwise provoke little concern and that the alerts reduce 90-day mortality. Specifically, we tested the hypothesis that providing triple-low alerts reduces 90-day mortality. Secondary outcomes included the effects of alerts on 30-day and 1-yr mortality and the duration of hospitalization. We also evaluated the fraction of alerts that generated early clinician responses and consequent resolution of triple-low conditions. Finally, we evaluated the fraction of triple-low events that generated helpful clinician responses, independent of group status, and the relationship between helpful responses and mortality.

Materials and Methods

The trial was registered in October 2009 at ClinicalTrials.gov: NCT00998894. The protocol is available from the investigators. With institutional review board approval and waiver of informed consent, we considered consecutive adults having noncardiac surgery with volatile general anesthesia and BIS monitoring that started within 30 min of induction. There were no restrictions on the type of volatile anesthetic used; concomitant neuraxial anesthesia and nerve blocks were permitted. Patients were enrolled from July 16, 2010, to October 5, 2016, at the Cleveland Clinic Main Campus (Cleveland, Ohio).

Protocol

Patients meeting these requirements were screened throughout anesthesia at 1-min intervals, with oscillometric pressures carried forward when no new value was available. Triple-low events were identified when MAP was less than 75 mmHg, BIS was less than 45, and MAC fraction was less than 0.80. MAC fractions were calculated based on MAC values of 6.6% for desflurane, 1.17% for isoflurane, and 1.8% for sevoflurane. MAC values were not adjusted for age because a previous unpublished analysis indicated that adjustment did not substantively improve mortality prediction.

Patients who experienced triple-low events were randomized without stratification in real time using computer-generated codes generated by the statistical team using the PLAN procedure in SAS 9.2 (SAS Institute, USA) that were not available to investigators. Allocation was thus completely concealed. In the control group, triple-low events were electronically recorded, but no alert was given; in the remaining 50% of patients, clinician alerts were generated through our clinical decision-support system. Alert conditions were indicated by flashing a "DSS" button on the electronic anesthesia display, with the specific alert being identified when clinicians touched the button. An electronic pager alert was also generated that was sent to the in-room clinician and to the attending anesthesiologist. The text of the alerts read: "A triple-low (MAP, MAC, and BIS) condition has been detected. Consider hemodynamic support."

If a triple-low event remained uncorrected, an additional alert was generated 10 min after the initial alert was acknowledged. Randomization was on a per-patient basis rather than by event. Consequently, subsequent triple-low events in a given patient were assigned the same randomization.

Implementation of the study was preceded by meetings and discussion within the Department of General Anesthesiology, so faculty, residents, and certified registered nurse anesthetists were well aware of the study, its basis, and its purpose. Clinicians were entirely free to act on the alert, ignore the alert, or consider the provided information without acting on it. Furthermore, the suggestion to consider raising MAP did not specify how pressure might be treated; clinicians accepting the suggestion might thus do so by giving a vasopressor, reducing anesthetic administration, augmenting vascular volume, putting the patient into the Trendelenburg position, or using a combination of approaches. Availability of alerts and clinicians' responses to them therefore reflected real-world conditions rather than being guided by a strict efficacy-type protocol.

Measurements

Randomization, the anesthesia record, a detailed record of triple-low events, alerts provided, clinician responses, MAP response, and in-hospital mortality were captured in our electronic record and decision-support system. When the study started, mortality (our primary outcome) was readily available from the Social Security Death Index. During the study, access was restricted, so we developed a two-pronged approach to obtaining vital status. First, we searched the Cleveland Clinic electronic records to find evidence of

appointments and procedures subsequent to the index surgery, which indicated that the subject remained alive. Second, we queried the Centers for Disease Control National Death Index.

Data Analysis

The randomized groups (alert *vs*. no alert) were descriptively compared for balance on baseline risk variables (demographics, past medical history/comorbidities, surgery type, *etc.*) using absolute standardized difference, defined as the absolute difference in means, mean ranks, or proportions divided by the pooled SD. Any variable with an absolute standardized difference of at least 0.045 (*i.e.*, $1.96\times\sqrt{\frac{(n1+n2)}{n1\times n2}}=0.045$) was considered imbalanced and adjusted for in all analyses.

Primary Analysis. Randomized groups (alert *vs*. no alert) were compared on the primary outcome, 90-day mortality, using Kaplan–Meier analysis with a log-rank test. The primary analysis included a Cox proportional hazards model to adjust for any imbalanced baseline variables which were also associated with outcome. Patients who were still alive at 90 days were censored at that time in the analysis.

We further assessed whether the treatment effect depended on key baseline variables including sex, age (greater than 60 yr *vs*. less than or equal to 60 yr), American Society of Anesthesiologists (ASA) status of I or II *versus* III or higher, and duration of case (more than 2 h *vs*. at most 2 h) by assessing the treatment-by-covariate interactions in separate Cox proportional hazards models and displaying a hazards ratio (97.5% CI) for each subgroup in a forest plot. We conducted sensitivity analyses using mortality data only from our hospital *versus* the primary analysis of also incorporating death information from the Centers for Disease Control National Death Index and found the estimate hazard ratios to be very similar for each interim analysis.

Secondary Outcomes. Secondary analyses assessed the effects of the alert on 30-day and 1-yr mortality and the duration of hospitalization using Cox proportional hazards regressions. For patients who died in the hospital (n = 277), duration was designated to be the longest observed hospital stay plus 1 day.

Helpful responses to triple-low events were defined by administration of a vasopressor within 5 min of the triple-low onset or a 20% reduction in end-tidal volatile anesthetic concentration within 15 min. The relationship between a helpful response to triple-low events and 30- or 90-day mortality was evaluated using a multivariable Cox proportional hazard model, adjusting for randomized group and unbalanced baseline variables. A Cox proportional hazards model was used to evaluate the time that elapsed between the initial episode alert until the triple-low condition resolved. We did not use Bonferroni correction for the analyses of the secondary outcomes: response to triple-low events and effect of responses.

Interim Analyses. This trial followed a group sequential design in which eight analyses (seven interims and a final) were planned, using the gamma error spending function.[12] During the study, three of the interim analyses were inadvertently omitted because of a combination of the speed of enrollment and the "hidden" nature of the database alerts. Results for the final analysis presented here used interim-adjusted CIs incorporating the Z-statistic efficacy boundary of 2.077 (corresponding to *P*-value criterion of 0.038) for the n = 7,584 patients included. Throughout we refer to them as "adjusted 95% CIs" to indicate that the significance level was controlled at 5% for the primary outcome over the entire study (*i.e.*, across the interim analyses).

Sample Size Considerations. In our preliminary analysis from an observational study, risk-adjusted 90-day mortality in patients who experienced a triple low without clinician responses was 2.97%. We thus expect about ≈3% (3.2%) mortality without responses (no response or late response) in both randomized groups (alert and no alert). In contrast, 90-day risk-adjusted mortality was 1.97% in patients who experienced a triple low and were given vasopressors within 5 min. We thus expected a 90-day mortality rate of about 1.8% in patients in whom clinicians responded quickly to the triple low in either randomized group.

On the basis of other (nonrandomized) alerts currently in our system, we expected a large proportion of clinicians would respond effectively to the alert (*i.e.*, increase MAP to at least 75 mmHg). In general, we expected 80% response to the triple low in the alert group and 20% in the nonalert group and 80% of responses to be effective in each group. The aforementioned assumptions implied that 90-day mortality would be 2.1% in patients with alerts and 2.9% in those without alerts, for a relative risk of 0.71. The maximum (across eight potential interim analyses) sample size of 14,443 was therefore based on having 80% power at the 0.05 significance level to detect a difference of 2.9% *versus* 2.1% in 90-day mortality for the alert and no-alert groups, respectively, for a relative 28% reduction. The incidence estimates were based on retrospective analyses and thus subject to various reporting and confounding biases.

Interim analyses were evaluated on a group A *versus* group B basis and were thus blinded to outcome direction. Clinicians participating in the study were not privy to interim results. At the second interim analysis (in August 2013), the maximum sample size was reassessed based on the observed incidence of 90-day mortality of 7.9% in the worst group. We thus resized the study using an internal pilot study design in which the incidence in the control group, which might be considered a "nuisance parameter," was updated using the observed study data to that point.[13] To combine our initial estimates with the observed incidence at the second interim, we assumed that the true baseline incidence in the worst group had a β distribution. Using that structure, we estimated the true incidence as a function of our original estimate (3%) and the observed 8%, giving 90% weight to

the 8% and 10% weight to the initial estimate. This resulted in an estimate incidence of 7.6% for the worst group. To be conservative, we based the new sample size on 7% in the worst group, which also corresponds to the lower limit on a 95% CI on the observed 8%.

In the reassessment, assuming an incidence of 7%, a maximum of 7,060 patients were needed to have 80% power to detect a 25% reduction in 90-day mortality at the 0.05 significance level assuming eight interim analyses (as in original plan) and a gamma spending spending function with γ parameters of −4 for efficacy and −1 for futility (also as in original plan). We also redefined our sample size to be 7,060 patients in whom we could determine 90-day vital status, which represents our original intent. Because it was unclear in how many patients vital status would be available and because the Center for Disease Control National Death Index releases data on a yearly basis, we stopped enrollment at the end of 2016. This approach provided a cushion of about 500 extra patients under the assumption that vital status would not be available for some. Statistical analyses were conducted with SAS 9.2 and East 5 (Cytel, Inc., USA) software.

Results

Figure 1 shows the enrollment, exclusions, and patients available for analysis. of qualifying patients, 21% (7,569 of 36,670) experienced at least one triple-low event and were thus randomized. Of 7,569 randomized patients, 3,764 (49.7%) were assigned to alerts and 3,805 (50.3%) to the nonalert group. In total, 95% (7,215 of 7,569) of patients had an arterial catheter.

Table 1 shows that baseline variables were well balanced between two groups except for drug abuse (absolute standardized difference = 0.048, which is higher than the criteria of 0.045) and type of surgery (0.094). However, the differences were tiny and not clinically meaningful (for example, the differences in each level of the surgical types was less than 1%). We therefore did not adjust for any baseline characteristics in our analyses.

More than 96% of triple-low alerts (or triple-low measurements in the nonalert group) were accurate. For technical reasons, about 11% of the alerts took more than 2 min to be generated and displayed or not per randomization. The averages of MAP, BIS, and MAC at the first alert (or would-be alert) did not differ in the two groups, with mean ± SD of 66 ± 7 mmHg for MAP, 38 ± 6 for BIS, and 0.65 ± 0.14 for MAC in the alert group.

Primary Outcome

The observed incidence of 90-day mortality was 8.3% in the alert group and 7.3% in the nonalert group, a difference that was not statistically significant with a hazard ratio (95% CI) of 1.14 (0.96, 1.35); $P = 0.12$ (table 2; fig. 2). The boundaries for futility were crossed with the prespecified P-value boundaries for futility of $P > 0.038$ (fig. 3). The treatment effect of the alert on the primary outcome of 90-day mortality did not depend on sex (interaction $P = 0.46$), age more

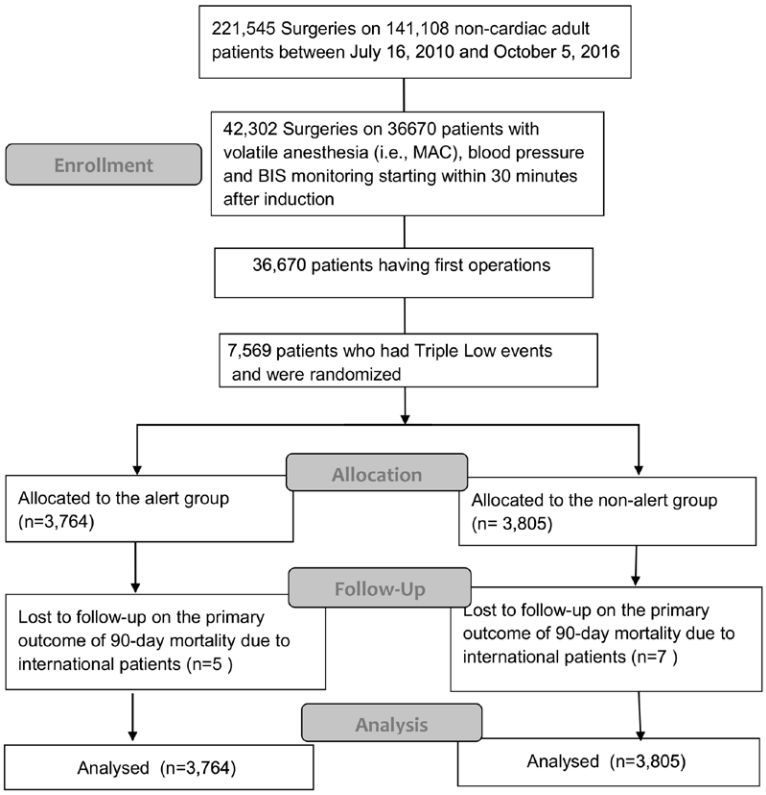

Fig. 1. Trial diagram. BIS, Bispectral Index; MAC, minimum alveolar concentration.

Table 1. Baseline Characteristics by the Triple-low Alert and Nonalert Groups

Factor	Alert Group (n = 3,764)	Nonalert Group (n = 3,805)	Absolute Standardized Difference
Female, n (%)	1,723 (46)	1,797 (47)	0.029
Age, yr	63 ± 14	63 ± 14	0.038
Body mass index, kg/m^2	29 ± 7.7†	29 ± 7.7‡	0.018
ASA status, n (%)			0.033
1	18 (0)	19 (1)	
2	353 (9)	399 (10)	
3	2,202 (59)	2,224 (58)	
4	1,160 (31)	1,122 (29)	
5	31 (1)	41 (1)	
Emergency, n (%)	428 (11)	404 (11)	0.024
Surgical time, h	5.8 ± 3.0	5.8 ± 3.3	0.001
Comorbidity, n (%)*			
Congestive heart failure	473 (13)	515 (14)	0.029
Valvular disease	275 (7)	303 (8)	0.025
Pulmonary circulation disease	177 (5)	191 (5)	0.015
Peripheral vascular disease	592 (16)	611 (16)	0.009
Hypertension	2,406 (64)	2,476 (65)	0.024
Paralysis	92 (2)	93 (2)	0.001
Other neurologic disorders	273 (7)	271 (7)	0.005
Chronic pulmonary disease	691 (18)	664 (17)	0.024
Diabetes without chronic complications	1,068 (28)	1,067 (28)	0.008
Hypothyroidism	582 (15)	567 (15)	0.016
Renal failure	631 (17)	650 (17)	0.009
Liver disease	368 (10)	359 (9)	0.012
Peptic ulcer disease with bleeding	6 (0)	4 (0)	0.014
Acquired immune deficiency syndrome	6 (0)	4 (0)	0.014
Lymphoma	53 (1)	52 (1)	0.003
Metastatic cancer	510 (14)	469 (12)	0.037
Solid tumor without metastasis	735 (20)	751 (20)	0.005
Rheumatoid arthritis/collagen vas	151 (4)	136 (4)	0.022
Coagulopathy	668 (18)	707 (19)	0.022
Obesity	696 (19)	699 (18)	0.003
Weight loss	818 (22)	787 (21)	0.026
Fluid and electrolyte disorders	1,600 (43)	1,561 (41)	0.030
Chronic blood loss anemia	43 (1)	59 (2)	0.036
Deficiency anemias	556 (15)	595 (16)	0.024
Alcohol abuse	110 (3)	113 (3)	0.003
Drug abuse	51 (1)	75 (2)	0.048
Psychoses	228 (6)	218 (6)	0.014
Depression	492 (13)	495 (13)	0.002
Principal procedure, n (%)			0.094
Nervous system	164 (4)	163 (4)	
Endocrine system	72 (2)	74 (2)	
Eye	2 (0)	0 (0)	
Ear	8 (0)	8 (0)	
Nose, mouth, and pharynx	38 (1)	47 (1)	
Respiratory system	64 (2)	50 (1)	
Vascular	404 (11)	473 (12)	
Hemic and lymphatic system	52 (1)	48 (1)	
Digestive system	1,434 (38)	1,393 (37)	
Urinary system	474 (13)	509 (13)	
Male genital organs	83 (2)	71 (2)	
Female genital organs	140 (4)	128 (3)	
Obstetrical procedures	1 (0)	0 (0)	
Musculoskeletal system	480 (13)	492 (13)	
Integumentary system	154 (4)	174 (5)	
Other diagnostic and therapeutic procedures	194 (5)	175 (5)	

The data are presented as means ± SD or number (%); absolute standardized difference: difference in means or proportions divided by standard deviation, with a value ≥0.045 considered as imbalanced ($1.96\times\sqrt{\frac{(n1+n2)}{n1\times n2}} = 0.045$).

*n = 2 missing data points in the alert group. †n = 111 missing body mass index data points. ‡n = 119 missing body mass index data points.

ASA, American Society of Anesthesiologists.

Table 2. Comparing Alert and Nonalert Randomized Groups on 30-day, 90-day, and 1-yr Mortality

Mortality	No. of Event (%) Alert Group (n = 3,764)	Nonalert Group (n = 3,805)	Hazard Ratio (95% CI)	*P* Value
Primary: 90-day	313 (8.3)	279 (7.3)	1.14 (0.96, 1.35)†	0.12‡
30-day	180 (4.8)	165 (4.3)	1.10 (0.89, 1.36)	0.36
1-yr	562 (14.9)	579 (15.2)	0.98 (0.87, 1.10)	0.71

†CIs at the final analysis are interim adjusted, with a critical Z statistic of 2.07 (corresponding to significance criterion of $P < 0.038$) to maintain an overall 0.05 significance level for the trial. ‡The boundary for futility was crossed with the prespecified *P*-value boundaries for futility of $P > 0.0378$.

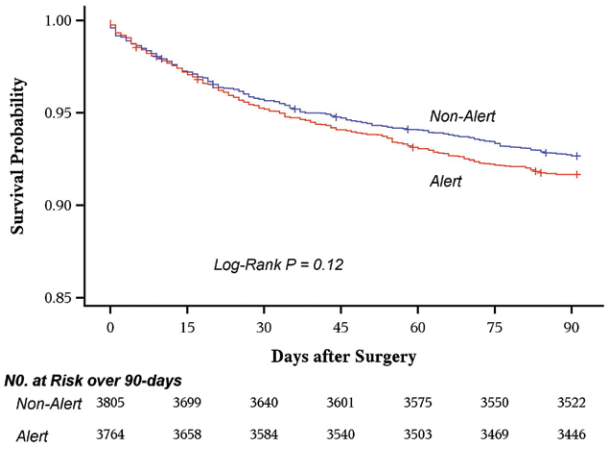

Fig. 2. Kaplan–Meier estimates of 90-day survival among patients who gave triple-low alerts *versus* without giving alerts. *Cross marks* indicate censored data.

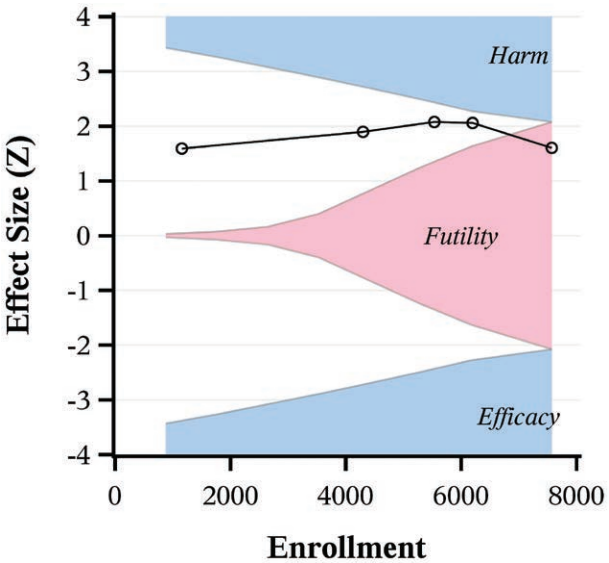

Fig. 3. Interim monitoring results for the primary outcome of 90-day mortality at total n = 7,569. The group sequential futility boundary (*pink region*) was crossed. The *vertical axis* is the Z statistic corresponding to the standardized treatment effect estimated at each interim analysis; negative values indicate efficacy (significant if reaching *lower blue region*), whereas positive values indicate harm (significant if reaching *upper blue region*).

than 60 yr ($P = 0.31$), ASA status of I or II *versus* III or higher ($P = 0.17$), or duration of case more than 2 h *versus* 2 h or less ($P = 0.49$; fig. 4).

Secondary Outcomes

No difference was found between the groups on 30-day or 1-yr mortality. The observed incidences of 30-day mortality were 4.8% in the alert group and 4.3% in the nonalert group with a hazard ratio (95% CI) of 1.10 (0.88, 1.38); $P = 0.36$. The observed incidences of 1-yr mortality were 14.9% in the alert group and 15.2% in the nonalert group with a hazard ratio (95% CI) of 0.98 (0.86, 1.10); $P = 0.70$ (table 2).

The length of hospital stay (discharge alive) did not differ significantly in the alert and no-alert groups, with a hazard ratio (95% CI) of 0.98 (0.94, 1.03); $P = 0.50$. The observed median (Q1, Q3) length of hospital stay was 7 (4, 11) days in each group (table 3).

Response to Triple-low Events

Helpful response to triple-low events, defined as vasopressor use within 5 min of the alert and/or a 20% decrease in end-tidal volatile anesthetic concentration any time during in the 15 min after alert, was 51% in the alert group and 47% in the nonalert group, for a relative risk (95% CI) of 1.08 (1.03, 1.14); $P < 0.001$ (table 3). Although highly statistically significant, the difference between 47 and 51% is not clinically important. The median (25^{th}, 75^{th} quartiles) number of minutes from the first alert to termination of the triple-low event did not differ between groups, with a hazard ratio (95% CI) of 1.04 (0.99, 1.09); $P = 0.09$.

Further, the alert did not change the proportion of patients with a 20% increase in MAP after either 5 min ($P = 0.44$) or 15 min ($P = 0.40$; table 4). In addition, the mean maximum change in MAP within 5 min after alert was not different between the alert and no-alert groups (12 ± 14 *vs.* 12 ± 14 mmHg), with a mean difference (95% CI) of 0 (–0.2, 1.1); $P = 0.17$. A sensitivity analysis using a 15-min interval gave similar results.

Relationship between Response to Triple-low Events and Outcomes

No relationship was observed between helpful responses to triple-low events (defined as vasopressor use in 5 min or 20% decrease in anesthetics by 15 min) and 90-day mortality

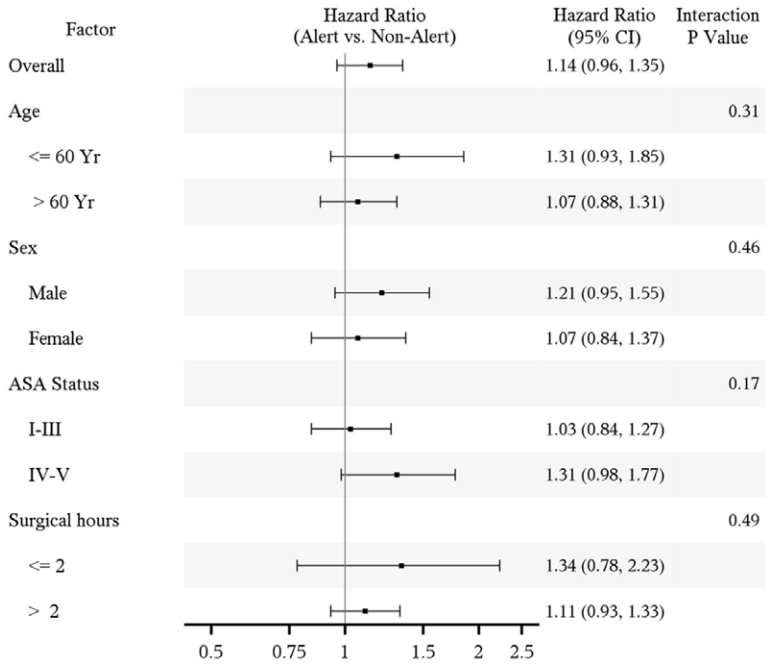

Fig. 4. Subgroup analyses. We assessed the treatment-by-covariate interaction on the primary outcome of 90-day mortality for several baseline factors and report the interaction *P* value, as well as the estimated treatment effect. None of the interactions were significant at the 0.05 significance level. ASA, American Society of Anesthesiologists.

Table 3. Effect of Alert on Secondary Outcomes

Response to Triple-low Alert	Alert	Nonalert	Relative Risk (95% CI)	*P* Value
Vasopressor use (5 min) or 20% decrease in anesthetics (15 min)*	1,844/3,631 (51%)	1,715/3,659 (47%)	1.08 (1.03, 1.14)	< 0.001
Vasopressor use in 5 min†	1,248/3,631 (34%)	1,093/3,665 (30%)	1.15 (1.08, 1.23)	< 0.001
20% decrease in expired anesthetics concentration in 15 min†	931/3,631 (25.6%)	913/3,658 (24.9%)	1.03 (0.95, 1.11)	0.52
	Median (Q1, Q3)	Median (Q1, Q3)	Hazard Ratio (95% CI)	*P* Value
Time from the first alert to above any of three thresholds (MAP <75, BIS <45, and MAC <0.8), min	3 (1, 6)	3 (1, 6)	1.04 (0.99, 1.09)	0.09
Length of hospital stay, days	7 (5, 11)	7 (5, 11)	0.98 (0.94, 1.03)	0.37
Additional response to triple-low outcome	Alert	Nonalert	Relative Risk (95% CI)	*P* Value
20% increase in MAP after first triple low				
20% MAP increase in 5 min	1,268/3,627 (35.0%)	1,249/3,663 (34.1%)	1.03 (0.96, 1.09)	0.44
20% MAP increase in 15 min	2,417/3,630 (66.5%)	2,402 /3,665 (65.5%)	1.02 (0.98, 1.05)	0.35
Maximum change in MAP after first triple low	Mean ± SD	Mean ± SD	Mean Difference (95% CI)	*P* Value
Baseline MAP at alert time	67 ± 6	67 ± 6		0.97
Maximum change in MAP within 5 min	12 ± 14	12 ± 14	0 (–0.2, 1.1)	0.18
Maximum change in MAP within 15 min	23 ± 17	23 ± 18	0 (–0.8, 0.8)	0.91

*Primary assessment of response. †Secondary assessments of response.BIS, Bispectral Index; MAC, minimum alveolar concentration; MAP, mean arterial pressure.

Table 4. Relationship between Helpful Responses to Triple-low Events and 30- and 90-day Mortality

Outcome Variable	No. of Events (%)	Adjusted Hazard Ratio (95% CI)*	*P* Value*
30-day mortality			
Response	173/3,555 (4.9%)	1.08 (0.87, 1.34)	0.45
No response	163/3,732 (4.4%)	Reference = 1	
90-day Mortality			
Response	292/3,555 (8.2%)	1.06 (0.90, 1.25)	0.52
No response	287/3,732 (7.6%)	Reference = 1	

Helpful responses to triple-low events were defined as vasopressor use within 5 min of the alert and/or a 20% decrease in end-tidal volatile anesthetic concentration any time during the 15 min after alert. *Multivariable Cox proportional hazard model adjusting for confounding variables listed in table 1. There was no interaction between the effect of responding to the alert and the randomized alert group for either 30-day mortality ($P = 0.83$) or 90-day mortality ($P = 0.75$); 3% missing body mass index points were replaced by the median.

adjusting for randomized group and covariates in the table 1. There was also no interaction between the response to triple-low and alert group on 30-day mortality ($P = 0.83$). The overall response rate was 49%. The observed 30-day mortality was 4.9% in the response group and 4.4% in the nonresponse group, with a covariable-adjusted hazard ratio (95% CI) of 1.08 (0.87, 1.34); $P = 0.45$. Similarly, we did not find a relationship between the response to triple low and 90-day mortality (hazard ratio = 1.06, 95% CI, 0.90 to 1.25, $P = 0.52$). Finally, there was no interaction between helpful responses and randomized group on 90-day mortality ($P = 0.75$). For patients who received an alert, the hazard ratio of 90-day mortality for the response group compared with nonresponse was 1.03 (95% CI, 0.81 to 1.31); for patients who did not give an alert, the hazard ratio of 90-day mortality for response compared with nonresponse was 1.08 (95% CI, 0.86 to 1.36).

Discussion

Observational studies indicate that double-[7] and triple-low[8–10] events are strong predictors of postoperative mortality (with one exception[14]). Despite adjustment for known confounding factors, much of this association presumably results from selection of high-risk patients. Frailty, for example, is an important predictor of death[15] but is not generally formally evaluated or recorded in electronic records. We could not directly assess whether triple-low events cause mortality because all enrolled patients had triple-low events. Instead, our major clinical question was the extent to which alerts and consequent interventions in *response* to triple-low events might be causally related to mortality; that is, whether intervening to limit mild hypotension, low MAC fraction, and low BIS might reduce mortality. Causality can only be established with reasonable certainty from an interventional trial such as ours.

Broadly speaking, all major outcomes were negative. Electronic alerts for triple-low events did not reduce 90-day mortality (our primary outcome), nor did they reduce 30-day or 1-yr mortality, which were our secondary outcomes. Nonetheless, interpreting our trial results requires some nuance because clinicians largely ignored the alerts. Clinicians responded helpfully (defined as vasopressor use in 5 min or 20% decrease in anesthetics by 15 min) to about half of the triple-low events, with or without alerts, and the duration of triple-low events did not differ in the alert and no-alert groups. The results were similar in a previous trial of alerts for double-low events, in which clinicians also largely ignored the alerts.[16]

In many respects, our trial therefore failed to adequately test whether helpful interventions for triple-low events improve outcomes. There was no apparent relationship between helpful responses to triple-low events in either group and adjusted 90-day mortality. Overall, our results do not support for the hypothesis that alerts for triple-low events reduce mortality.

Normally protocols are fairly tightly controlled in clinical trials to reduce response variability and thereby enhance internal reliability. A reasonable question is thus why the protocols for our current and previous trials of alerts for double- and triple-low events did not mandate specific responses such as vasopressor administration and reducing volatile anesthetic administration (which normally increases blood pressure and the BIS)? The answer comes from the trials' unique designs, both of which used electronic systems to randomize qualifying patients in real time. Triple-low events are relatively rare, occurring in only about one of five surgical patients at the Cleveland Clinic Main Campus. Using a conventional approach, we would thus have had to consent more than 36,000 patients to accrue the 7,569 who were actually randomized, an obviously impractical number. Furthermore, efficacy trials, with their highly selected patients and rigid protocols, generalize poorly to routine clinical practice in broad populations. They are also limited in that mortality and many other serious complications are too rare to study except in the largest conventional randomized trials.

We therefore requested and obtained approval for waived consent from our Institutional Review Board based on national guidelines because (1) obtaining individual consent would be nearly impossible; (2) the provided alert was not currently the standard of care; (3) the recommended intervention (consider hemodynamic support) was low risk and likely to prove beneficial; (4) there was no prohibition against intervention in the control group nor a requirement to respond in the treatment group; and (5) part of the research

was to determine acceptance of the decision-support recommendation, which would be impossible if only selected clinicians participated. A consequence of this approach was that we were unable to mandate specific responses in patients randomized to alerts, nor to prohibit responses in the no-alert control group. We expected clinicians to respond more aggressively to alerts than they did; we also expected fewer responses in the no-alert group. In fact, response rates were similar in each group. Being unable to control responses therefore turned out to be the trial's major limitation.

The randomized patients were relatively sick. About 90% had ASA status of III to IV, and 95% had arterial catheters. Furthermore, 30-day mortality exceeded 4%, which is about twice the national average for noncardiac surgical inpatients. It is thus apparent that patients who experienced triple-low events were especially sick, which is perfectly consistent with such events being strong predictors of postoperative death. That triple-low events are associated with mortality is now well established[10] but could not be confirmed in our present study because enrollment and our analysis were restricted to patients who had triple-low events. A limitation of our electronic records is that total fluids are tracked for each case, but timing of administration is not. It is thus possible that some clinicians responded to triple-low events, with or without alerts, by giving fluid boluses.

Our statistical methods were robust, including a group sequential design that controlled the overall type I error at 5% and power at 80% while conducting several interim analyses. A further strength was the inclusion of an internal pilot study at the second interim analysis, in which we reassessed the incidence of the primary outcome in the control group and then resized the maximum sample size for the study. This technique, in which either the planned SD for a continuous outcome or the proportion with the event in one of the groups for a binary outcome (because the variance of a proportion is a function of that proportion) is re-assessed during a trial, is a statistically sound and judicious method to adjust an initial sample size calculation.[13] It is particularly helpful when, as often is the case, initial estimates of variability are only rough estimates based on existing data. As appropriate, our reassessment was done without observing or taking into account the estimated treatment effect, with only the variability estimate.

Decision-support alerts, even those that might seem obviously beneficial, may not trigger the expected behaviors and may not improve outcomes even when they do. For example, alerts for severe hypotension are not helpful because clinicians respond equally quickly and effectively without alerts.[17] Similarly, a recently developed sophisticated decision-support system that provides substantial guidance to clinicians provoked less response than might have been expected and did not significantly improve outcomes.[18] In our present study, clinicians largely ignored the alerts; that is, the expected response to the alert was only observed about half the time. These are just three of many reasons why alerts can fail to ultimately provide patient benefit. A corollary is that decision-support systems should be treated just like other devices and be formally validated.[19] Failure to require adequate validation of electronic guidance and alerts will surely result in a proliferation of such systems that might actual worsen patient care by distracting clinicians.

In summary, real-time alerts to triple-low events did not reduce 90-day mortality, although there were fewer responses to the alerts than expected. However, similar mortality with and without helpful responses, independent of randomized group, suggests that there is little or no relationship between responses to triple-low events and mortality. Decision-support alerts, even those that might seem obviously beneficial, may not trigger the expected behaviors and may not improve outcomes even when they do.

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Competing Interests

Dr. Sessler is a consultant for Medtronic. All other authors declare no competing interests.

Reproducible Science

Full protocol available at: DS@OR.org. Raw data available at: DS@OR.org.

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Untangling the Triple Low

Causal Inference in Anesthesia Research

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IN 1965, Sir Austin Bradford Hill[1] published a landmark article in which he considered under what circumstances could a clinician convert an observed association into a verdict of causation. In other words, if there is a link between a risk factor and an adverse outcome, does it hold true that removing or reducing this risk factor will reduce the risk of that adverse outcome occurring? He outlined nine criteria to support causal inference (table 1). Bradford Hill emphasized that clinicians should not solely rely upon these as hard and fast rules for evidence—he reminded readers that, "*None of my nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis …. What they can do, with greater or less strength, is to help answer the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?*"[1] He went on to remind readers that statistical tests of significance can not (and do not) answer this question.

"… at this point in time, there is no justification in avoiding the triple low state or a low BIS on the basis of current evidence."

It is with this background that readers should consider the evidence addressing the "triple low" hypothesis first outlined by Sessler *et al.* in ANESTHESIOLOGY in 2012.[2] In brief, the triple low refers to an intraoperative state in which there is hypotension during the delivery of low alveolar concentration of volatile anesthesia, combined with a low bispectral index (BIS), a state presumed to reflect anesthetic hypersensitivity. Sessler *et al.*[2] found that the triple low state was associated with a higher risk of 30-day mortality. This line of research first began with Monk *et al.*,[3] who in 2005 reported an intriguing relation between cumulative deep hypnotic time as indicated by a low BIS and 1-yr mortality. Many other studies have since found similar associations.[4]

In this issue of ANESTHESIOLOGY, Kertai *et al.*[5] attempted to reproduce Sessler *et al.*'s original findings in an observational study of an electronic perioperative database that included 16,263 patients undergoing noncardiac surgery. They did identify an association between the cumulative duration of the triple low state and 30-day mortality, but this association disappeared *after* adjusting for specific patient- and procedure-related characteristics. In other words, the triple low state was not independently associated with 30-day mortality.

There are several reasons why this study may have missed a true association—similar to many large-scale observational studies, the data were derived from an electronic perioperative medical record linked to administrative databases whose prime purposes are not research; the latter is more likely to have inaccurate and incomplete data and a greater risk of residual confounding compared with prospectively collected data in a clinical trial.[6] On the contrary, such datasets are large and so provide statistical power, are readily available, and offer greater generalizability because they reflect routine practice.

With multivariable testing, Kertai *et al.*[5] found a possible relation between low blood pressure alone (P = 0.0197), and intriguingly, a low BIS seemed to be associated with a lower risk of mortality (but P = 0.0683). These findings could indicate true associations or they could be false because of residual confounding or collinearity.[7,8] Great caution is needed when interpreting multivariable

Image: ©Thinkstock.

Corresponding article on page 18.

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Table 1. An Outline of the Bradford Hill Criteria[1]

Criteria	Explanation
1. Strength of association	The stronger the relation between a risk factor and the effect (outcome), the less likely it is that the relation is due to a third or extraneous factor.
2. Consistency	Multiple studies in a range of settings report similar results.
3. Specificity	Ideally, the effect has only one cause.
4. Temporality	The purported cause should be present before the effect occurs.
5. Biological gradient	A dose–response relation between the risk factor and the effect.
6. Biological plausibility	There should be a rational and theoretical basis explaining how or why the risk factor led to the effect.
7. Coherence	The association should not conflict with known facts.
8. Experimental evidence	Is there any supportive research based on experiment; if preventive action is taken, does the effect dissipate?
9. Analogy	A previously accepted phenomenon in one area can be applied to another.

analysis of nonrandomized data. Spurious associations can appear because one variable is associated with a third, perhaps unmeasured, variable that is truly linked in a causal pathway. Reliable multivariable analysis should also consider interaction terms and avoid overfitting of data and model instability.[8] Most of these concerns were admirably addressed by Kertai *et al.* in their analyses. Their findings are robust and believable.

A most obvious explanation for the original triple low-mortality association is that frail and/or elderly patients are both more likely to enter a triple low state during anesthesia and are more likely to die after surgery—that is, some aspect(s) of a patient's health status is likely to be the true causal factor. In their analysis, Kertai *et al.* found that older age, poorer physical status, emergency surgery, and a surgical risk index score remained significant predictors of 30-day mortality. Once these confounding factors were accounted for in the multivariable model, the triple low state was found to be unrelated to mortality.

If we apply the Bradford Hill criteria (table 1), the association between the triple low state and mortality is weak, inconsistent, could be explained by other factors that are supported by stronger evidence (*e.g.*, patient frailty), and is only based on nonrandomized data from one study. On the contrary, the hypothesis has some plausibility in that the larger doses of some anesthetic drugs might be immunosuppressive or neurotoxic, the triple low state incorporates hypotension which we know can impair vital organ perfusion, it is temporally related, and there is a demonstrable biological gradient. So, if we take up Bradford Hill's challenge and ask ourselves, *is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect*? The answer is clearly yes, it is most likely an epiphenomenon. The weight of evidence supporting a causal relation between triple low, or a low BIS, and excess mortality is unconvincing, but the concept is not yet ready to be dismissed because the triple low state, unlike the other factors identified by Kertai *et al.*,[5] is potentially modifiable such that it could change how we practice anesthesia around the world.

How should anesthesiologists respond to the disparate results from the "triple low" and "low BIS" observational studies? The underlying hypotheses deserve our ongoing attention and need testing with definitive randomized trials. At least two such related trials are underway—see www.clinicaltrials.gov (NCT00998894) and www.anzctr.org.au (ACTRN12612000632897). But at this point in time, there is no justification in avoiding the triple low state or a low BIS on the basis of current evidence. As stated by Bradford Hill,[1] "*All scientific work is incomplete—whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore knowledge we already have, or to postpone the action that it appears to demand at a given time*." We have a moral and ethical duty to our patients and society to pursue knowledge that informs our practice to make anesthesia safer and more cost-effective.

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Competing Interests

Dr. Myles is a coauthor on postoperative nausea and vomiting guidelines led by Tong J. Gan, M.D., M.H.S., F.R.C.A., the senior author of the accompanying article, and is a chief investigator on the BALANCED trial (www.anzctr.org.au, ACTRN12612000632897), a large clinical trial comparing two levels of anesthetic depth on 1-yr mortality after major surgery.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Guaranteed by Gas: Neiman's Advertising Bookmark

An 1883 graduate of the "Dental Department of the University of Maryland," Eli H. Neiman, D.D.S., returned home to Pennsylvania to set up practice on York's West Market Street. From there, Dr. Neiman attracted patients using advertisements, such as this floral bookmark (*left*), which touted that teeth were "extracted by the use of Nitrous Oxide Gas…." The reverse side of each bookmark notified potential patients that Dr. Neiman's "ALL WORK GUARANTEED" slogan was backed by his promise that he would extract teeth "Without Pain, or no charge [would be] made." Apparently nobody counseled Dr. Neiman against using a frightening image of a dental extraction (*upper right*) as part of his advertising campaign. This bookmark is part of the Wood Library-Museum's Ben Z. Swanson Collection.

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

Cumulative Duration of "Triple Low" State of Low Blood Pressure, Low Bispectral Index, and Low Minimum Alveolar Concentration of Volatile Anesthesia Is Not Associated with Increased Mortality

Miklos D. Kertai, M.D., Ph.D., William D. White, M.S., M.P.H., Tong J. Gan, M.D., M.H.S., F.R.C.A.

ABSTRACT

Background: Mortality after noncardiac surgery has been associated with the "triple low state," a combination of low mean arterial blood pressure (<75 mmHg), low bispectral index (<45), and low minimum alveolar concentration of volatile anesthesia (<0.70). The authors set out to determine whether duration of a triple low state and aggregate risk associated with individual diagnostic and procedure codes are independently associated with perioperative and intermediate-term mortality.

Methods: The authors studied 16,263 patients (53 ± 16 yr) who underwent noncardiac surgery at Duke University Medical Center between January 2006 and December 2009. Multivariable logistic and Cox regression analyses were used to determine whether perioperative factors were independently associated with perioperative and intermediate-term all-cause mortality.

Results: The 30-day mortality rate was 0.8%. There were statistically significant associations between 30-day mortality and various perioperative risk factors including age, American Society of Anesthesiologists Physical Status, emergency surgery, higher Cleveland Clinic Risk Index score, and year of surgery. Cumulative duration of triple low state was not associated with 30-day mortality (multivariable odds ratio, 0.99; 95% CI, 0.92 to 1.07). The clinical risk factors for 30-day mortality remained predictors of intermediate-term mortality, whereas cumulative duration of triple low was not associated with intermediate-term mortality (multivariable hazard ratio, 0.98; 95% CI, 0.97 to 1.01). The multivariable logistic regression (c-index = 0.932) and Cox regression (c-index = 0.860) models showed excellent discriminative abilities.

Conclusion: The authors found no association between cumulative duration of triple low state and perioperative or intermediate-term mortality in noncardiac surgery patients. **(ANESTHESIOLOGY 2014; 121:18-28)**

PATIENTS undergoing noncardiac surgery can be at substantial risk for perioperative and intermediate-term mortality.[1] Patient- and surgery-related factors have been linked to perioperative and late survival. However, the association between anesthesia-related factors and perioperative and intermediate-term survival after noncardiac surgery remains unclear.[2,3] Recent studies have found that when a processed electroencephalographic index is used during general anesthesia, patients generally receive lower doses of hypnotic drugs emerge faster from anesthesia with less postoperative nausea and vomiting.[4,5] It has also been proposed that intraoperative hypotension and organ toxicity may be avoided if lower doses of anesthetics are administered, which would potentially translate into a reduction in serious morbidity or mortality.[3,6]

The bispectral index (BIS) monitor (BIS® monitor; Covidien, Boulder, CO) is one of several candidate depth-of-anesthesia monitors that are based on processed electroencephalography. Studies have shown that cumulative duration of BIS below certain arbitrary thresholds is associated with an increased morbidity and intermediate-term postoperative mortality.[7–10] These findings may suggest a mortality–hypnosis association, which could be reflective of a relative overdose of anesthetic agents in patients who have anesthetic hypersensitivity.[3] In support of this mortality–hypnosis association, it was recently observed that the occurrence of intraoperative hypotension, expressed as low mean arterial

What We Already Know about This Topic

- The so-called triple low state of low mean arterial pressure, low bispectral index, and low minimum alveolar concentration of anesthesia has been associated with perioperative mortality
- Whether duration of time in the triple low state imparts risk of mortality is not known

What This Article Tells Us That Is New

- In a review of over 16,000 patients, there was no association between duration of triple low state intraoperatively and either perioperative or intermediate-term mortality

This article is featured in "This Month in Anesthesiology," page 3A. Corresponding article on page 1.

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pressure (MAP) during low minimum alveolar concentration (MAC) fraction of volatile anesthetics, combined with low BIS was a significant predictor of perioperative mortality, indicating anesthetic hypersensitivity.[11]

Thus, the results of this study indicate that the combination of low MAP, low MAC, and low BIS—a triple low state—could be a predictor of poor outcome. This association is especially concerning because the threshold and average low values for each state are well within the range that is routinely tolerated.[11] However, a recent mortality substudy of the B-Unaware Trial[12] found no evidence that cumulative BIS values below a threshold of 45, or cumulative inhalational anesthetic dose, or low intraoperative MAP was associated with increased risk for intermediate-term mortality. Therefore, using comprehensive, multivariable models of a large dataset of patients who underwent noncardiac surgery, we sought to determine whether a combination of cumulative duration of low MAP, BIS, and MAC (a triple low state), comorbidities, and type of surgery are independently associated with increased perioperative and intermediate-term mortality.

Materials and Methods

Study Population

A dataset of patients who underwent noncardiac surgery at Duke University Medical Center (Durham, North Carolina) between January 1, 2006 and December 31, 2009 was constructed from the Duke Perioperative Electronic Database (Innovian® Anesthesia; Draeger Medical Inc., Telford, PA). The Institutional Review Board for Clinical Investigations at Duke University Medical Center approved the study and waived the requirement for informed consent.

On the basis of Duke Perioperative Electronic Database, we identified a set of 72,236 records of cases with intraoperative BIS monitoring. We included only the first surgery for any patient, excluding 15,882 cases in which the same patient had additional surgeries. We further excluded 12,592 cases with no record of intraoperative monitoring of MAP and end-tidal MAC; 21,727 cases that met any of the following criteria: less than 18 yr old, cardiac surgical procedure, primary anesthetic was not a single volatile agent, or intraoperative BIS monitoring was not available for at least 55% of the case time; 4,679 that lacked essential clinical information needed for the estimation of the Cleveland Clinic Risk Index score[13]; and 1,093 in which duration of MAP, BIS, and end-tidal MAC monitoring was less than 10 min, or all three parameters were simultaneously monitored for less than 75% of the case time. Consequently, 16,263 cases were included in the current analyses.

At Duke University Medical Center, general anesthesia for adult noncardiac surgery is usually induced with a small amount of propofol (1 to 1.5 mg/kg) and fentanyl (100 to 150 μg). One of the potent volatile anesthetic agents—desflurane, sevoflurane, or isoflurane—in an oxygen–nitrous oxide or oxygen–air mixture, with an inspiratory oxygen concentration of at least 50%, is used to maintain general anesthesia. In addition, as part of routine anesthesia care, patients undergo tracheal intubation; the lungs are ventilated volume or pressure controlled, with a positive end-expiratory pressure of 5 cm H_2O; and end-tidal anesthetic gas concentration is monitored throughout the case. After adult noncardiac surgery, patients are routinely admitted to the postoperative anesthesia recovery unit or intensive care unit as indicated.

Data Extraction and Analysis

We extracted data on BIS, MAP, and end-tidal volatile anesthetic concentration. Data were also extracted on age at surgery, sex, race, American Society of Anesthesiologists (ASA) Physical Status Classification System scores, duration of operating room time, and International Classification of Diseases and Procedures, version 9, billing codes,* which are determinants of the Cleveland Clinic Risk Stratification Index.[13] The Cleveland Clinic Risk Stratification Index is a method of predicting 30-day and late mortality in patients undergoing noncardiac surgery. The Risk Stratification Index value† was calculated for each patient according to published methodology validated with published example standards.

Bispectral index values and end-tidal anesthesia gas concentration values were recorded at 1-min intervals. As part of routine intraoperative care, a BIS Quatro Sensor® (Covidien) was applied to the forehead of each patient. Age-adjusted MAC values were calculated according to the charts published by Nickalls and Mapleson,[14] which include adjustment for nitrous oxide. In the final sample of 16,263 patients, all but 21 patients had some nonzero expired concentration of nitrous oxide recorded.

Mean arterial pressure values were also recorded at 1-min intervals when an arterial catheter was used or at 2- to 5-min intervals when blood pressure was measured oscillometrically. Similar to the definition used by Sessler *et al.*,[11] MAP values were considered to be artifactual and were excluded when the recorded value was less than 30 mmHg or greater than 250 mmHg. The BIS, the end-tidal anesthesia gas concentration, and MAP values assigned to a given minute, if missing, were interpolated linearly between the preceding and following values. No case was included with more than 15 consecutive minutes missing.

Classification of Outcomes

The outcomes chosen for the current study were all-cause mortality occurring within 30 days after surgery and intermediate-term all-cause mortality for patients who survived

* International Classification of Diseases and Procedures version 9. Available at: http://www.cdc.gov/nchs/icd/icd9cm.htm. Accessed August 12, 2013.

† Cleveland Clinic Risk Stratification Index. Available at: http://my.clevelandclinic.org/anesthesiology/outcomes-research/risk-stratification-index.aspx. Accessed August 12, 2013.

beyond 30 days. Survival information was obtained from return hospital encounters, the National Cancer Registry,‡ the National Death Index,§ and the Social Security Death Index,‖ all accessed to verify vital status as of March 22, 2011.

Statistical Analysis

Continuous variables are presented as means (±SD) or medians (interquartile range), and categorical variables are presented as group frequencies and percentages. Descriptive comparisons were made by using Kruskal–Wallis test, or chi-square test, as appropriate.

A recent study reported that patients with the triple low state—a combination of MAP less than 75 mmHg, BIS values less than 45, and MAC less than 0.70 of volatile anesthesia—had an increased risk for 30-day all-cause mortality.[11] Therefore, in the current study, this definition was specified *a priori* and calculated for each patient as cumulative, but not necessarily consecutive, minutes in a triple low state to study the association between cumulative duration of triple low state and 30-day and intermediate-term all-cause mortality.

Univariable and multivariable logistic regression models were applied to evaluate the association between all-cause mortality at 30 days and cumulative duration of triple low state and baseline and clinical characteristics. In addition to the Risk Stratification Index, age, sex, race, ASA Physical Status Classification System, emergency status, duration of surgery, and year of surgery were prespecified for inclusion as covariates in the multivariable models. Logistic regression diagnostic tests and plots for goodness-of-fit and influence were inspected.

To study the association between the cumulative duration of triple low state and intermediate-term mortality, we first applied the Kaplan–Meier method to evaluate the prognostic importance of the cumulative duration of triple low state with respect to survival. Differences among survival curves for quartiles of cumulative duration of triple low state were compared using the log-rank test. Subsequently, univariable and multivariable Cox proportional hazard regression models were applied to assess the association of cumulative duration of triple low state and intermediate-term all-cause mortality, adjusting for the same set of baseline and clinical variables used in the 30-day analysis.

Furthermore, we quantified the discriminatory power of the final multivariable models for logistic and Cox regression analyses 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).[15] To further evaluate the performance of the final multivariable models for logistic and Cox regression analyses, the bootstrap method was used to assess the degree of overoptimism. Overoptimism occurs when statistical models fitted on one set of data inaccurately predict the outcomes on subsequent datasets.[12]

A bootstrapping procedure is one method that can be used to try to correct for this "overoptimism."[16] First, the covariates in the final regression models were fitted for each bootstrap sample. The original dataset was then fitted using the coefficients of the bootstrap sample model, and thus, a c-index statistic was generated from this fit on the original dataset. The degree of overoptimism was then estimated as the difference in the c-index statistic from the bootstrap sample and that from the bootstrap model fit on the original sample. These differences were averaged across 1,000 bootstrapped samples, and the difference in the original model c-index statistic and the average optimism provided the model c-index corrected for overoptimism.

The model fit of the final multivariable logistic regression model was further assessed using the Hosmer–Lemeshow goodness-of-fit test,[17] and for the Cox regression by comparing the average model prediction to the observed mortality rate across deciles of predicted risk.[18,19] Odds ratios or hazard ratios and the corresponding 95% confidence limits are reported. The analyses were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patient Characteristics

The mean age (±SD) of the 16,263 patients was 53 ± 16 yr, and 7,595 patients (46.7%) were men. Seventy percent of the study population were whites; 6.6% of the cohort were classified as category P1 using the ASA Physical Status Classification System; 46%, P2; 43.4%, P3; 3.7%, P4; and 0.03%, P5. Ten percent of the patients underwent emergency surgery.

The median Cleveland Clinic Risk Index score was −0.42 (interquartile range, −1.37 to 0.08); the median cumulative duration of MAP of less than 75 mmHg was 34 min (interquartile range, 14 to 70); the median cumulative duration of BIS value of less than 45 was 70 min (interquartile range, 31 to 122); the median cumulative duration of MAC value of less than 0.70 was 65 min (interquartile range, 27 to 127); and the median cumulative duration of triple low state was 3 min (interquartile range, 0 to 13).

The most common International Classification of Diseases and Procedures, version 9, diagnosis category was cancer (44.2% of patients); 20.3% had genitourinary diseases, and 17.5% had diseases in the digestive system. The most frequently performed procedures in the International Classification of Diseases and Procedures, version 9, procedure category involved the digestive system (23.2%), the musculoskeletal system (20.4%), and the female genital organs (15%). Demographic and clinical characteristics of the patients stratified according to the quartiles of the cumulative duration of triple low state are presented in table 1.

‡ National Cancer Registry. Available at: http://www.cdc.gov/cancer/npcr/. Accessed March 22, 2011.

§ National Death Index. Available at: www.cdc.gov/nchs/ndi.htm. Accessed March 22, 2011.

‖ Social Security Death Index. Available at: http://www.ntis.gov/products/ssa-dmf.aspx. Accessed March 22, 2011.

Table 1. Baseline Clinical Characteristics (n = 16,263)

Characteristics	Cumulative Duration of Triple Low								
	None (n = 6,240; 38.4%)		1 to 5 min (n = 3,513; 21.6%)		6 to 17 min (n = 3,232; 19.9%)		>18 min (n = 3,278; 20.1%)		*P* Value*
Age, yr	6,240	49 ± 16	3,513	54 ± 16	3,232	56 ± 15	3,278	58 ± 14	<0.0001
Male sex	6,240	2,911 (46.7)	3,513	1,611 (45.9)	3,232	1,491 (46.1)	3,278	1,582 (48.3)	0.20
Race	6,237		3,513		3,230		3,275		<0.0001
White		3,917 (62.8)		2,485 (70.7)		2,375 (73.5)		2,595 (79.2)	
Black		1,878 (30.1)		847 (24.1)		670 (20.7)		514 (15.7)	
Asian		75 (1.2)		35 (1.0)		43 (1.3)		28 (0.9)	
Native American		79 (1.3)		30 (0.9)		33 (1)		35 (1.1)	
All Other		288 (4.6)		116 (3.3)		109 (3.4)		103 (3.1)	
ASA category	6,031		3,390		3,122		3,165		<0.0001
P1		515 (8.5)		241 (7.1)		175 (5.6)		120 (3.8)	
P2		3,121 (51.7)		1,553 (45.8)		1,378 (44.1)		1,177 (37.2)	
P3		2,254 (37.4)		1,491 (44.0)		1,434 (45.9)		1,651 (52.2)	
P4		141 (2.3)		103 (3.0)		135 (4.3)		213 (6.7)	
P5		0		2 (0.1)		0		4 (0.1)	
Emergency surgery	6,031	616 (10.2)	3,390	292 (8.6)	3,122	309 (9.9)	3,165	370 (11.7)	0.0006
Cleveland Clinic Risk Index	6,240	−0.48 [−1.35; −0.10]	3,513	−0.47 [−1.44; 0.04]	3,232	−0.47 [−1.41; 0.14]	3,278	−0.26 [−1.34; 0.64]	<0.0001
Surgery date, mm/dd/yy median (min, max)		2/8/08 (1/9/06, 12/31/09)		5/7/08 (1/8/06, 12/30/09)		5/22/08 (3/21/06, 12/31/09)		5/30/08 (1/13/06, 12/31/09)	<0.0001
Minutes MAP <75 mmHg	6,240	17 [3; 44]	3,513	28 [13; 56]	3,232	34 [20; 62]	3,278	78 [50; 124]	<0.0001
Minutes BIS <45	6,240	49 [16; 96]	3,513	56 [23; 103]	3,232	75 [39; 123]	3,278	117 [73; 177]	<0.0001
Minutes MAC <0.70	6,240	30 [13; 70]	3,513	59 [28; 110]	3,232	84 [46; 136]	3,278	142 [92; 214]	<0.0001
									P Value†
ICD-9 diagnosis category†	9,454		5,367		4,991		5,290		
Infectious and parasitic		34 (0.4)		26 (0.5)		28 (0.6)		46 (0.9)	
Neoplasm		2,570 (27.2)		1,625 (30.3)		1,504 (30.1)		1,497 (28.3)	
Endocrine, nutritional, metabolic, and immunity disorders		253 (2.7)		173 (3.2)		183 (3.7)		262 (5.0)	
Blood and blood-forming organs		50 (0.5)		38 (0.7)		33 (0.7)		53 (1.0)	
Mental		12 (0.1)		11 (0.2)		12 (0.2)		18 (0.3)	
Nervous systems and sense organs		100 (1.1)		70 (1.3)		49 (1.0)		83 (1.6)	
Circulatory system		259 (2.7)		161 (3.0)		191 (3.8)		322 (6.1)	
Respiratory system		128 (1.4)		112 (2.1)		119 (2.4)		143 (2.7)	
Digestive system		1,439 (15.2)		754 (14.0)		656 (13.1)		475 (9.0)	
Genitourinary system		1,344 (14.2)		751 (14.0)		642 (12.9)		564 (10.7)	
Pregnancy, childbirth, puerperium		167 (1.8)		77 (1.4)		48 (1.0)		17 (0.3)	

(*Continued*)

Table 1. (*Continued*)

Characteristics	Cumulative Duration of Triple Low: None (n = 6,240; 38.4%)	1 to 5 min (n = 3,513; 21.6%)	6 to 17 min (n = 3,232; 19.9%)	>18 min (n = 3,278; 20.1%)	*P* Value*
Skin and subcutaneous tissue	93 (1.0)	39 (0.7)	33 (0.7)	32 (0.6)	
Musculoskeletal system	1,030 (10.9)	542 (10.1)	573 (11.5)	717 (13.6)	
Congenital anomalies	92 (1.0)	45 (0.8)	40 (0.8)	54 (1.0)	
Conditions originating in the perinatal period	0	1 (0)	1 (0)	0	
Symptoms, signs, ill-defined	364 (3.9)	217 (4.0)	182 (3.6)	156 (2.9)	
Injury and poisoning	1,245 (13.2)	583 (10.9)	534 (10.7)	675 (12.8)	
External causes	33 (0.3)	8 (0.1)	6 (0.1)	5 (0.1)	
Supplementary factors	241 (2.5)	134 (2.5)	157 (3.1)	171 (3.2)	
					P Value*
ICD-9 primary procedure category	6,240	3,513	3,232	3,276	<0.0001
Miscellaneous diagnostic and therapeutic	36 (0.6)	20 (0.6)	12 (0.4)	12 (0.4)	
Obstetrical	17 (0.3)	3 (0.1)	0	1 (0)	
Cardiovascular system	157 (2.5)	103 (2.9)	97 (3.0)	165 (5.0)	
Digestive system	1,518 (24.3)	834 (23.7)	763 (23.6)	664 (20.3)	
Ear	54 (0.9)	34 (1)	38 (1.2)	28 (0.9)	
Endocrine	172 (2.8)	104 (3)	116 (3.6)	153 (4.7)	
Eye	2 (0)	2 (0.1)	3 (0.1)	2 (0.1)	
Female genital organs	1,078 (17.3)	576 (16.4)	469 (14.5)	319 (9.7)	
Hemic and lymphatic system	149 (2.4)	98 (2.8)	79 (2.4)	73 (2.2)	
Integumentary system	332 (5.3)	182 (5.2)	161 (5)	223 (6.8)	
Male genital organs	471 (7.5)	308 (8.8)	234 (7.2)	207 (6.3)	
Musculoskeletal system	1,280 (20.5)	630 (17.9)	631 (19.5)	787 (24)	
Nervous system	149 (2.4)	76 (2.2)	84 (2.6)	118 (3.6)	
Nose, mouth, and pharynx	51 (0.8)	27 (0.8)	34 (1.1)	28 (0.9)	
Respiratory system	154 (2.5)	173 (4.9)	148 (4.6)	169 (5.2)	
Urinary system	593 (9.5)	330 (9.4)	348 (10.8)	301 (9.2)	
Other procedures and interventions	27 (0.4)	13 (0.4)	15 (0.5)	26 (0.8)	

Values are mean ± SD, median [25th percentile; 75th percentile], or numbers (percentages).

* Descriptive comparisons were made using Kruskal–Wallis test or chi-square tests, as appropriate. *P* values presented in the table are for overall comparisons among all groups and do not reflect comparisons between specific groups. † All diagnoses per patient were counted, resulting in a higher number of diagnoses than patients. Hence, no *P* value was calculated for diagnoses.

ASA = American Society of Anesthesiologists; BIS = bispectral index; ICD-9 = International Classification of Diseases and Procedures, version 9; MAC = minimum alveolar concentration; MAP = mean arterial pressure; P = Physical Status Classification.

Perioperative Mortality

The 30-day mortality rate was 0.8% (130 of 16,263). Univariable predictors of 30-day mortality are shown in table 2. Many of the baseline and clinical characteristics were associated with an increased risk for 30-day mortality. However, female sex was associated with a significant reduction in the risk for 30-day mortality. In addition, cumulative duration of the triple low state showed a strong association with 30-day mortality before accounting for other covariates. The result of the univariable analysis showed that year of surgery was not associated with a decreased risk of 30-day mortality. Finally, there was no significant association between the duration of operating room time and 30-day mortality.

Of the 16,263 patients, 555 case records were missing information on the ASA Physical Status Classification System category and 8 were missing information on the race designation; thus, these patients were excluded from multivariable analysis. Based on mortality, Cleveland Clinic Risk Index score, and cumulative duration of triple low, we compared cases dropped from the final analyses to those included. Although the 30-day mortality appeared higher in patients with missing data (1.6 *vs.* 0.8%; $P = 0.0302$), there was no difference in the Cleveland Clinic Risk Index score (mean of −0.474 *vs.* −0.564; $P = 0.3854$) and cumulative duration of triple low (mean of 13.2 *vs.* 12.3 min; $P = 0.5635$) between cases dropped from the final analyses compared with those included.

In the multivariable analysis, higher mean age at surgery, higher ASA Physical Status Classification System category, emergency surgery, and higher Cleveland Clinic Risk Index score remained significant predictors of 30-day mortality (table 2). A more recent year of surgery was associated with decreased 30-day mortality. After adjusting for differences in baseline and clinical characteristics, the association between the cumulative duration of triple low state and the risk for 30-day mortality was not significant ($P = 0.85$).

Because it has been recently suggested that frail patients may be prone to entering a triple low state, and the low blood pressure component of the triple low state may lead to poor outcome, we repeated our multivariable analysis by adding, in a stepwise manner, the cumulative duration of low MAP followed by the cumulative duration of low BIS. We found that cumulative duration of low MAP alone did not add significantly to the predictive value of the logistic regression model of 30-day mortality, which included the Cleveland Clinic Risk Index score and age ($P = 0.0929$). However, when cumulative duration of low MAP and cumulative duration of low BIS were both added into the logistic regression model after Cleveland Clinic Risk Index score and age, low MAP showed a significant association with risk for 30-day mortality (odds ratio, 1.04 per 15 min; 95% CI, 1.006 to 1.076; $P = 0.0197$), whereas low BIS did not (odds ratio, 0.967 per 15 min; 95% CI, 0.933 to 1.003; $P = 0.0683$).

The final multivariable model for 30-day mortality showed good discriminative ability and good fit (c-index = 0.926; overall goodness-of-fit Hosmer–Lemeshow test, chi-square test = 5.71; $P = 0.6795$). The degree of overoptimism was minimal (0.0071), which resulted in an adjusted c-index of 0.919.

Intermediate-term Mortality

The 16,133 patients who survived surgery for at least 30 days were followed until March 22, 2011. The follow-up duration was 2.6 ± 1.2 yr, and the overall mortality rate was 9.5% (1,535 of 16,133).

Table 3 shows univariable predictors of intermediate-term mortality. Again, many baseline and clinical characteristics were associated with intermediate-term mortality. There was a significant association between the quartiles of cumulative duration of triple low state and event-free survival, reflected by the event-free survival curves (fig. 1).

Table 2. Univariable and Multivariable Predictors of 30-day Mortality

	Univariable		Multivariable*	
Predictors	Odds Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Age at surgery, per year increase	1.05 (1.04–1.06)	<0.0001	1.03 (1.02–1.04)	<0.0001
Female sex	0.70 (0.50–0.96)	0.047	0.98 (0.66–1.45)	0.91
Race		0.09		0.09
White	1.0		1.0	
African-American	0.88 (0.58–1.31)		0.71 (0.44–1.15)	
All other	0.12 (0.01–0.53)		0.16 (0.01–0.79)	
ASA Physical Status, per category increase	9.02 (6.74–12.15)	<0.0001	2.96 (2.09–4.22)	<0.0001
Emergency surgery	2.97 (1.93–4.45)	<0.0001	1.65 (1.02–2.62)	0.03
Year of surgery, per year increase	0.88 (0.76–1.02)	0.08	0.82 (0.69–0.98)	0.03
Duration of operating room time, per 30 min	1. 0 (0.96–1.01)	0.97	0.99 (0.93–1.01)	0.61
Cleveland Clinic Risk Index, per 1 point increase	1.99 (1.87–2.14)	<0.0001	1.71 (1.57–1.86)	<0.0001
Cumulative duration of triple low, per 15 min	1.15 (1.09–1.20)	<0.0001	0.99 (0.92–1.07)	0.85

* The final multivariable logistic regression analysis was based on n = 15,700 due to missing ASA class (n = 555) and race (n = 8).
ASA = American Society of Anesthesiologists.

Table 3. Univariable and Multivariable Predictors of Intermediate-term Mortality

	Univariable		Multivariable*	
Predictors	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value
Age at surgery, per year increase	1.046 (1.043–1.05)	<0.0001	1.036 (1.032–1.04)	<0.0001
Female sex	0.82 (0.74–0.67)	<0.0001	0.90 (0.81–0.99)	0.03
Race		<0.0001		0.16
White	1.0		1.0	
African-American	0.99 (0.89–1.12)		0.94 (0.83–1.06)	
All other	0.51 (0.39–0.68)		0.77 (0.58–1.04)	
ASA Physical Status, per category increase	3.65 (3.37–3.96)	<0.0001	1.55 (1.42–1.70)	<0.0001
Emergency surgery	1.02 (0.86–1.21)	0.82	0.78 (0.66–0.93)	0.005
Year of surgery, per year increase	0.86 (0.83–0.90)	<0.0001	0.82 (0.78–0.86)	<0.0001
Duration of operating room time, per 30 min	0.99 (0.98–1.01)	0.68	0.98 (0.96–0.99)	0.0009
Cleveland Clinic Risk Index, per 1 point increase	1.73 (1.70–1.76)	<0.0001	1.66 (1.62–1.70)	<0.0001
Cumulative duration of triple low, per 15 min	1.09 (1.07–1.11)	<0.0001	0.98 (0.97–1.01)	0.37

* The final multivariable Cox proportional hazard regression analysis was based on n = 15,579 due to missing ASA class (n = 546) and race (n = 8).
ASA = American Society of Anesthesiologists.

Of the 16,133 patients, 546 case records were missing information on the ASA Physical Status Classification System category and 8 were missing information on the race designation; thus, these patients were excluded from multivariable analysis. When patients with missing information were compared with those included in the multivariable model, the intermediate-term mortality rate (9.57 *vs.* 9.51%; $P = 0.966$), Cleveland Clinic Risk Index score (mean of −0.524 *vs.* −0.591; $P = 0.564$), and cumulative duration of triple low (mean = 12.7 *vs.* 12.2 min; $P = 0.741$) were not statistically different.

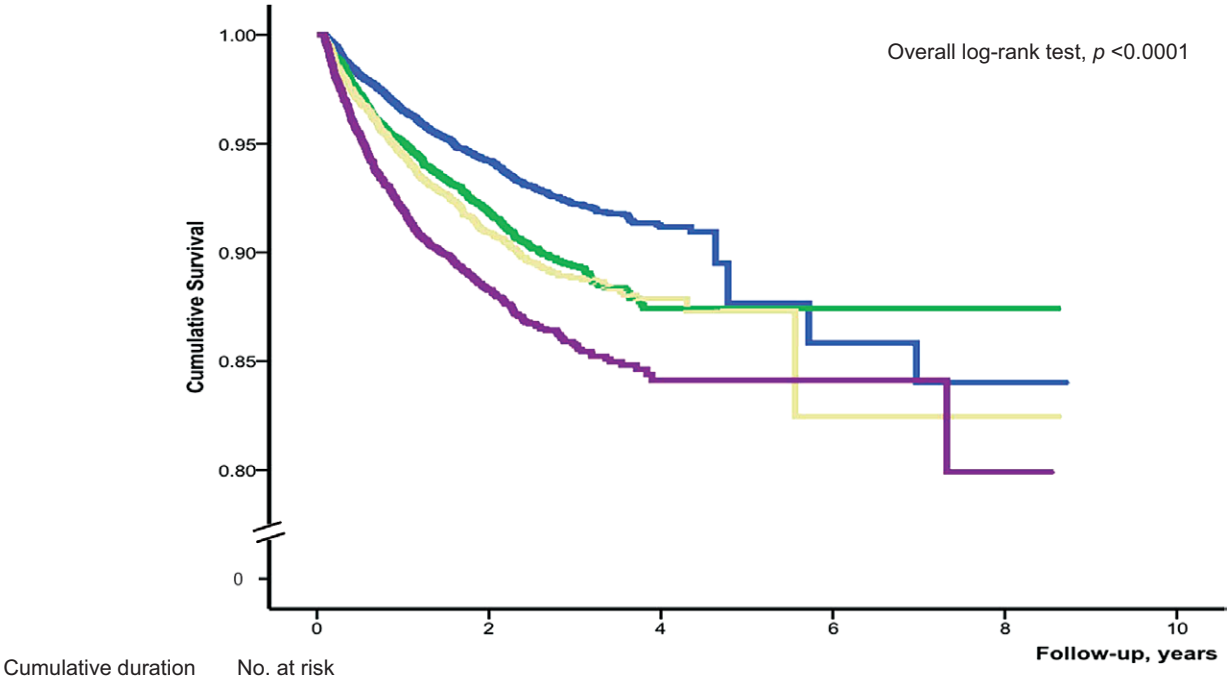
In multivariable analysis, age at surgery, ASA Physical Status Classification System category, and a higher Cleveland Clinic Risk Index score were significant predictors of intermediate-term mortality (table 3). Female sex, emergency surgery, year of surgery, and duration of operating room time were associated with decreased intermediate-term mortality. After adjusting for differences in baseline and clinical characteristics, there was no significant association between the cumulative duration of triple low state and the risk for intermediate-term mortality ($P = 0.37$). Similar to the analysis of 30-day mortality, we repeated our multivariable analysis by adding, in a stepwise manner, the cumulative duration of low MAP followed by the cumulative duration of low BIS. With the Cleveland Clinic Risk Index score and age in the model, we found no significant association with intermediate-term mortality of either cumulative duration of low MAP (multivariable hazard ratio, 0.991 per 15 min; 95% CI, 0.980 to 1.003; $P = 0.1394$) or of low BIS (multivariable hazard ratio, 0.997 per 15 min; 95% CI, 0.988 to 1.007; $P = 0.5803$).

The final multivariable Cox regression model for intermediate-term mortality showed good discriminative ability (c-index = 0.860). The degree of overoptimism was minimal (0.00032), and the adjusted c-index remained 0.860. The calibration of the final model (observed *vs.* predicted) showed agreement between the predicted and observed intermediate-term mortality rates across deciles of predicted risk (fig. 2). The model-estimated effect of cumulative duration of triple low state on intermediate-term mortality is shown in figure 3. With covariates held constant, the four lines representing the quartile values of duration virtually overlap.

Discussion

This study of patients undergoing noncardiac surgery demonstrates that the combination of intraoperative hypotension, low MAC fraction of volatile anesthetics, and low BIS is not associated with worse 30-day and intermediate-term mortality after adjusting for specific patient- and procedure-related characteristics. In contrast, our results reinforce previous findings that specific patient- and procedure-related characteristics are strongly associated with 30-day and intermediate-term mortality after noncardiac surgery.

Several studies have shown that cumulative duration of BIS less than 45 alone is a predictor of mortality after noncardiac[7–9] and cardiac surgery.[10] Other studies in noncardiac surgery patients have either failed to adjust for preexisting malignant disease status[7] or, when preexisting malignancy status was taken into consideration, have found that the association between cumulative duration of BIS less than 45 and mortality no longer persists.[8] A more recent study suggests that BIS monitoring and the absence of BIS values less than 40 for more than 5 min are associated with improved survival, but again, this study failed to adjust for diagnosis and procedure categories as well as other clinical risk factors.[9] In a subset of cardiac patients, the association between cumulative duration of BIS less than 45 and an increased risk for mortality was explained by an observed association among clinical variables, intraoperative factors, and BIS values less than 45.[10] The results of that study indicated that BIS values less than 45 are likely markers of systemic illness, poor



Cumulative duration of triple low	No. at risk				
None	6,211	4,408	1,013	47	16
1 to 5 min	3,491	2,269	395	25	13
6 to 17 min	3,211	2,053	328	17	12
≥ 18 min	3,220	2,008	239	20	13

Fig. 1. Kaplan–Meier estimates of intermediate-term mortality according to the quartiles of duration of cumulative triple low state. *P* value (log-rank test) indicates the differences in survival.

cardiac function, or complicated intraoperative course.[10] These observations were also supported by a substudy of the B-Unaware Trial,[12] which found no evidence that cumulative BIS values below a threshold of 40 or 45 were associated with an increased risk for intermediate-term mortality. However, there was strong association between perioperative risk factors, diagnosis and procedure categories, and mortality.

Recently, Sessler *et al.*[11] reported that mortality after noncardiac surgery is increased in patients who have low blood pressure and low BIS during a low MAC fraction, indicating that triple low state may represent anesthetic sensitivity. This study was a retrospective, single-center study in 24,120 patients who underwent noncardiac surgery. The investigators defined low blood pressure, low BIS, and low MAC fraction values as 1SD from the single-center population means, rather than clinical thresholds. Therefore, center-specific patterns of care likely influenced the authors' observations and limit the generalizability of the study findings.[2]

In the current study, therefore, we sought to validate these findings and study the potential role of triple low monitoring in relation to 30-day and intermediate-term mortality in patients who underwent noncardiac surgery. In contrast to the Sessler *et al.'s* study,[11] we found no relation between cumulative duration of triple low state and 30-day or intermediate-term mortality. This discrepancy suggests that the association between cumulative duration of triple low state and mortality is likely epiphenomenal and, when present, is reflective of specific patient- or procedure-related characteristics rather than anesthetic management.[2,12] For instance, advanced age, higher ASA Physical Status Classification System category, emergency surgery, and higher Cleveland Clinic Risk Index score were significantly associated with longer cumulative duration of triple low state. Indeed, in an exploratory stepwise analysis, we found that the strongest risk factor associated with 30-day mortality and intermediate-term mortality was the Cleveland Clinic Risk Index score. When only the Cleveland Clinic Risk Index score was added to either statistical model with the cumulative duration of triple low state, the association between the cumulative duration of triple low state and mortality was no longer significant.

The role of optimal perioperative management strategies in preventing perioperative and intermediate-term mortality in high-risk patients undergoing noncardiac surgery has been controversial. In our study, we confirmed the value of many previously described risk factors for predicting perioperative

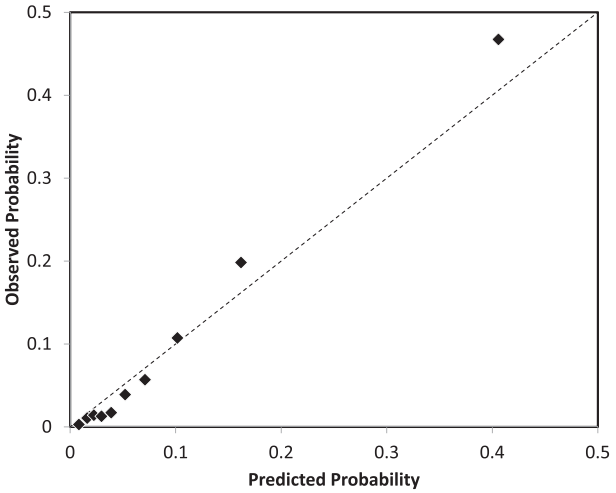


Fig. 2. Observed *versus* predicted probability of intermediate-term mortality at 2.5 yr. The figure represents the calibration of the final multivariable Cox proportional hazard model presented in table 3. Perfect fit is represented by the *dotted line*. The *diamonds* indicate the mean model–predicted event risks per decile plotted against Kaplan–Meier-observed event risks.

and intermediate-term mortality after noncardiac surgery. In particular, higher age,[20] higher categories within the ASA Physical Status Classification System,[21] and higher Cleveland Clinic Risk Index scores,[11] an aggregate of diagnosis and surgical procedure categories, were consistently significant predictors of perioperative and intermediate-term mortality. We also found, however, that these strong risk factors were associated with cumulative duration of triple low state.

In a secondary analysis, we determined whether there was an association between cumulative duration of low BIS as an individual component of triple low state, and 30-day and intermediate-term mortality, adjusting for cumulative duration of low MAP and clinical risk factors. The cumulative duration of low BIS was not significantly associated with 30-day or intermediate-term mortality indicating, as described in the editorial by Kheterpal and Avidan,[2] "that the interaction between cumulative duration of low MAP, clinical risk factors, and postoperative outcomes is more complex than the concept that exposure to an increased duration of 'deeper hypnotic time' can be potentially dangerous."

Our study also showed that emergency surgery was significantly associated with increased risk for perioperative mortality but carried a significantly lower risk for intermediate-term mortality. This may seem contradictory; however, it is likely that this discrepancy arises from the fact that patients who survive their emergency surgical procedure beyond 30 days gain survival benefit and are at significantly lower risk for intermediate-term mortality.

Many of these patient- and surgery-related factors have previously been identified as modifiable predictors of perioperative[20,22] and intermediate-term[12] and long-term[12,23–25] outcomes after noncardiac surgery. Identifying patients at risk for perioperative complications has improved considerably in recent years. We observed that a more recent year of surgery was associated with a significantly decreased risk for perioperative and intermediate-term mortality, which indeed could reflect recent improvements in perioperative management of patients undergoing noncardiac surgery.[1,20,22] Our

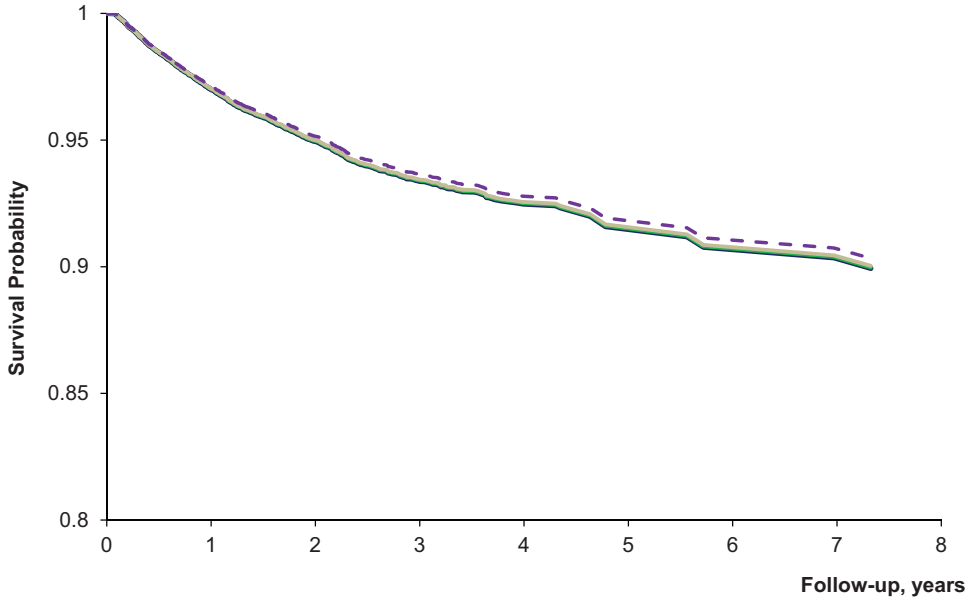


Fig. 3. Covariate-adjusted estimates of intermediate-term mortality for cumulative duration of triple low states of 0 (*blue solid line*), 5 (*green solid line*), 15 (*grey solid line*), and 60 (*purple dotted line*) min (to match quartiles observed; fig. 1). Covariates for the estimates are held constant at their median or most frequent category: age = 55 yr, female sex, white race, American Society of Anesthesiologists Physical Status Classification System = P2, Cleveland Clinic Risk Index score = 0, date of surgery = April 17, 2008, and duration of surgery = 180 min.

findings reinforce the need to identify and address modifiable risk factors so that both perioperative and intermediate-term postoperative outcomes can be improved.

Study Limitations

Our study has some limitations. First, data were derived from the Duke Perioperative Electronic Database, which was designed for documentation and administrative purposes, and not for scientific research. Thus, data on specific patient, diagnosis, and procedure-related characteristics may not have been entered properly or may have been overlooked. Consequently, the relative contribution of these factors to perioperative and intermediate-term mortality may have been over- or underestimated.[26]

Second, data on other important clinical risk factors including previous or current medical history and pharmacotherapy are not recorded into the Duke Perioperative Electronic Database, and thus, were not available for our analyses. Furthermore, we could adjust the association between cumulative duration of triple low state and mortality only for clinical diagnoses that were coded according to the International Classification of Diseases and Procedures, version 9, system. As a result of these limitations, residual confounding may still exist.

Third, we did not characterize hospital length of stay but chose perioperative and intermediate-term mortality as our principal outcomes. The length of stay is influenced by many patient- and procedure-related characteristics, but most importantly, by the number of complications after surgery.[27] Because the information on postoperative complications was not available for electronic retrieval, we did not consider hospital length of stay as an outcome measure in the current study.

Finally, as part of modern multimodal anesthesia, patients receive a combination of intravenous and inhalational anesthetic agents and potent opioids in varying concentrations. Therefore, assessing the potential impact of anesthetic dose on mortality can be challenging. Given the retrospective nature of our study and its sample size, we were not able to retrieve information on total intravenous hypnotic and potent opioid doses, and thus, could not study their potential effect on perioperative and intermediate-term mortality.

Conclusions

In this study, we observed a univariable association between cumulative duration of triple low state—a combination of low MAP, low MAC, and low BIS—and 30-day and intermediate-term mortality. However, after adjusting for differences in baseline and clinical characteristics, this association no longer persisted. In contrast, mortality was strongly associated with perioperative risk factors, disease, and procedure categories. This study does not support the hypothesis that a triple low state may identify patients who are unusually sensitive to anesthesia and at risk for perioperative and intermediate-term mortality after noncardiac surgery. However, only an appropriately designed, randomized, prospective trial# clarifies further the presence and strength, or absence, of an association between triple low state and perioperative and intermediate-term mortality.

Available at: http://clinicaltrials.gov/ct2/show/NCT00998894. Accessed August 12, 2013.

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Competing Interests

The authors declare no competing interests.

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"Triple Low"

Murderer, Mediator, or Mirror

EVERY anesthesiologist has encountered the difficult case of a patient that simply does not "tolerate" a typical general anesthetic; even low concentrations of a potent volatile agent may result in significant hypotension that requires aggressive treatment. In this issue of ANESTHESIOLOGY, Sessler *et al.*, from the Cleveland Clinic (Cleveland, Ohio) and Covidien (Mansfield, Massachusetts), demonstrate that this intraoperative observation may hold clinical significance for the patient's postoperative outcome.[1]

"Although patients with triple low had increased mortality, … whether preventing a triple low would change outcomes or even be feasible [is uncertain]."

By integrating physiologic monitoring, electronic health record, administrative, and national death data, they evaluated the mortality and hospital length of stay for patients having inpatient surgery. Some patients concurrently demonstrated intraoperative retrospectively defined "low" volatile minimum alveolar concentration (MAC) equivalents, "low" blood pressure, and "low" bispectral index values, a phenomenon the investigators have dubbed "triple low." They observed that, although the study adjusted for patient age, sex, comorbidities, and surgical complexity, patients demonstrating "triple low" still had four times the hazard of death within 30 days compared to patients who did not have a triple low. Reinforcing the plausibility of their findings, Sessler *et al.* showed that a combination of any "double low" was associated with increased postoperative mortality. In addition, patients who had triple low episodes were more likely to have a prolonged hospital stay. The analysis is sophisticated and has many strengths. Notably, short-term 30-day mortality was the primary outcome, which increases the possibility of a causal contribution of intraoperative events. The inclusion of age, comorbidities, and surgical complexity in the multivariate analyses improves the likelihood of quantifying the independent association of intraoperative parameters and postoperative outcomes.

These data add to the existing body of literature evaluating associations among intraoperative parameters and postoperative outcomes. Although early single-center literature intimated that relatively excessive anesthetic depth, suggested by low bispectral index values, might be associated with mortality,[2] other investigators were unable to reproduce this finding after adjusting for cancer-related deaths.[3,4] The data of Sessler *et al.* appear to confirm that patients with low bispectral index values without concomitant low blood pressure or low volatile anesthetic concentration do not have increased 30-day mortality. Thus, the accumulating evidence suggests that the interaction between intraoperative parameters and postoperative outcomes is more complicated than the notion that "deep hypnotic time" is dangerous. More recently, two different centers have observed intraoperative hypotension to be a predictor of mortality.[5,6] In fact, the period of time with a mean arterial blood pressure less than 75 mmHg was just as predictive as was the duration of triple low.[6]

Overall, the data presented by Sessler *et al.* are thought-provoking. As the authors state, it is unclear whether triple low causes increased mortality or is simply detecting patients with underlying risk of increased mortality. Triple low may simply be an intraoperative stress test. It is also conceivable that a hybrid of the two concepts is at play: for a given patient, triple low may serve as a marker of disease, but allowing the patient to remain hypotensive may cause end organ hypoperfusion. Future studies involving controlled, protocol-driven management to prevent triple low will be needed to elucidate the causal *versus* epiphenomenon conundrum. It will also be important to determine whether intraoperative alerts based on triple low confer any advantage over alerts based on hypotension alone.

Sessler *et al.* appropriately caution that it would be premature to alter intraoperative care based solely on their ob-

◆ This Editorial View accompanies the following article: Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, Kurz A, Greenwald S: Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. ANESTHESIOLOGY 2012; 116:1195–203.

Photo: J. P. Rathmell.

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servational, hypothesis-generating study. Several important limitations to the data, many highlighted by the authors, limit their ability to warrant intraoperative anesthetic management changes. As a single-center data set, the applicability of the findings to other patient care settings is debatable. Because low blood pressure, low MAC equivalents, and low bispectral index values were defined as one standard deviation from the single-center population means rather than clinical thresholds, center-specific patterns of care are intertwined inextricably with the authors' observations. Although patients with triple low had increased mortality, the observational nature of the analysis leaves uncertain whether preventing a triple low would change outcomes or even be feasible. A triple low may simply reflect the patient's underlying disease. The authors attempted to control for patient comorbidities and procedural risk using their recently published Risk Stratification Index.[7] However, the index is based upon billing data using International Classification of Diseases discharge diagnoses and procedural codes. Triple low may be detecting the important clinical differences between two patients both defined as having "congestive heart failure" according to billing data. It may be an objective proxy for the "eyeball test" performed by clinicians to assess a patient's frailty. Recent surgical literature has established quantitative measures of patient frailty by examining the cross-sectional area of the psoas muscle. Researchers have observed a risk-adjusted relationship between decreasing psoas muscle size and postoperative mortality for patients undergoing a variety of procedures.[8–10] Triple low may be a similar phenomenon: an objective measure of the historically subjective concept of patient frailty.

If the association between triple low and death is causal, the pathophysiologic mechanisms by which triple low could increase all-cause mortality are unclear. Certainly, untreated hypotension could contribute to damage of major organs, such as the brain, heart, and kidneys. Low bispectral index values (less than 40 to 30) typically occur when there is electroencephalographic burst suppression.[11,12] Unlike many other electroencephalographic features seen during general anesthesia, such as spindles and slow delta waves, burst suppression is not a physiologically normal rhythm. Burst suppression appears more frequently during general anesthesia in patients who have coronary artery disease[11] and has been implicated as a harbinger of 6-month mortality in medical intensive care unit patients.[13] It is hypothesized that prolonged burst suppression might precipitate neurologic injury.[11,13] Thus, it is conceivable that the triple low combination could be causally implicated in some deaths. However, it is hard to imagine how hypotension, burst suppression, or low volatile anesthetic concentration could promote cancer-related deaths. The current study by Sessler *et al.* does not identify the causes of death, but based on previous studies, a substantial proportion of deaths are likely to have been related to advanced cancer.[2–4,14]

The analysis presented in this issue of ANESTHESIOLOGY lacks several important data elements needed to establish a convincing relationship between intraoperative parameters and postoperative outcomes. For example, the calculated MAC equivalents did not include nitrous oxide, which may explain why the average MAC across 24,120 patients was a surprisingly low 0.56. Next, maintenance doses of MAC-sparing agents, such as propofol, dexmedetomidine, and opiates, apparently were not incorporated into the analysis. Because the primary outcome of mortality has a low baseline rate of 0.5% in the studied population, the authors were forced to amalgamate a diverse group of patient and procedural risks into a single population by the need to achieve statistical power. Intuitively, specific groups of patients may be more likely to exhibit or be affected by triple low and warrant focused analyses.

Despite its limitations, this impressive study demonstrates that the era of anesthesiology insularism is coming to a close. What we observe, and possibly what we do, during our brief intraoperative relationship with the patient probably is relevant to long-term patient outcomes. Future research efforts must be dedicated to reproducing or refuting the current findings and exploring how perioperative management could contribute to improved patient trajectories. In doing so, the field of anesthesiology will demonstrate its value to patients long after they have left the operating room.

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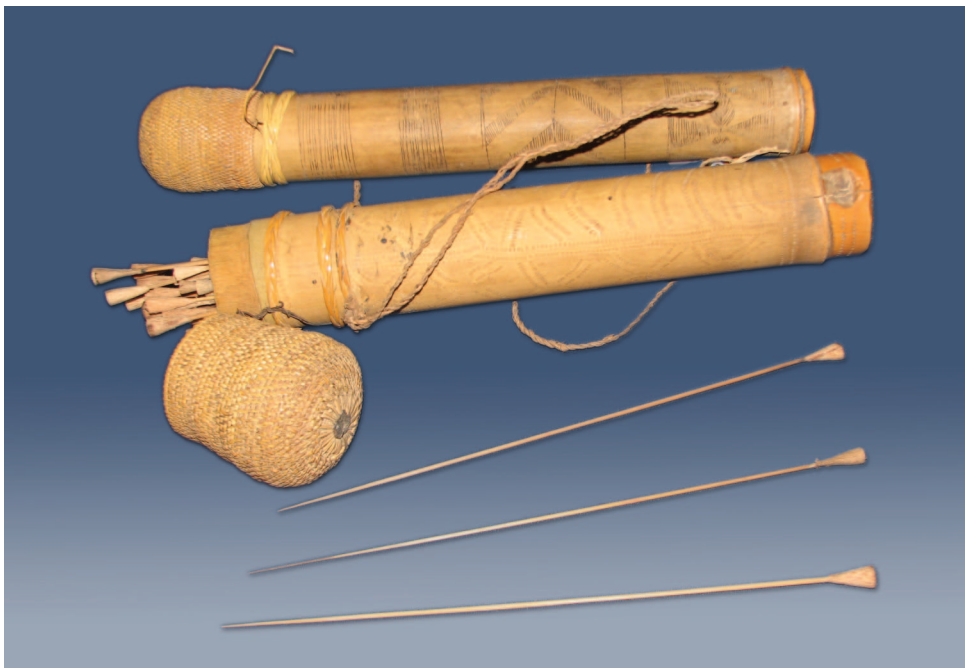
ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Quivers of Curare-tipped Blow Gun Darts



Today's anesthesiologists use curare-like agents as adjuvants for decreasing patients' total anesthetic drug load, particularly of the ether-like organic solvents employed for general inhalational anesthesia. Few physicians realize the debt that we owe to Ecuador and surrounding countries, whose indigenous hunters wore blow gun quivers (above) full of curare-tipped missiles to dart overhead prey, such as monkeys and birds. Sadly, hunters who failed to dart away quickly enough were occasionally themselves darted by their own missile's return to earth. When a hunter would spot the telltale signs of his companion's eyelids growing heavy from the curare poison, the pair would rest against a tree and reminisce about their adventures together as the companion's respirations faltered and finally failed. (Copyright © the American Society of Anesthesiologists, Inc.)

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