

Effectiveness of an Electronic Alert for Hypotension and Low Bispectral Index on 90-day Postoperative Mortality

A Prospective, Randomized Trial

Patrick J. McCormick, M.D., Matthew A. Levin, M.D., Hung-Mo Lin, Sc.D., Daniel I. Sessler, M.D., David L. Reich, M.D.

ABSTRACT

Background: We tested the hypothesis that an electronic alert for a “double low” of mean arterial pressure less than 75 mmHg and a bispectral index less than 45 reduces the primary outcome of 90-day mortality.

Methods: Adults having noncardiac surgery were randomized to receive either intraoperative alerts for double-low events or no alerts. Anesthesiologists were not blinded and not required to alter care based upon the alerts. The primary outcome was all-cause 90-day mortality.

Results: Patients (20,239) were randomized over 33 months, and 19,092 were analyzed. After adjusting for age, comorbidities, and perioperative factors, patients with more than 60 min of cumulative double-low time were twice as likely to die (hazard ratio, 1.99; 95% CI, 1.2 to 3.2; $P = 0.005$). The median number of double-low minutes (quartiles) was only slightly lower in the alert arm: 10 (2 to 30) versus 12 (2 to 34) min. Ninety-day mortality was 135 (1.4%) in the alert arm and 123 (1.3%) in the control arm. The difference in percent mortality was 0.18% (99% CI, -0.25 to 0.61).

Conclusions: Ninety-day mortality was not significantly lower in patients cared for by anesthesiologists who received automated alerts to double-low states. Prolonged cumulative double-low conditions were strongly associated with mortality. (ANESTHESIOLOGY 2016; 125:1113-20)

THE combination of low end-organ perfusion pressure, deep hypnosis, and low volatile anesthetic concentration is associated with postoperative mortality. Two studies have shown an association between the cumulative duration of a “triple low” of low mean arterial pressure (MAP), low bispectral index (BIS), low end-tidal minimum alveolar concentration (MAC), and mortality.^{1,2}

The known associations between triple-low duration and mortality do not prove causality. It is conceivable that triple-low events simply identify high-risk patients. Similarly, intraoperative hypotension is also associated with myocardial infarction and postoperative mortality³⁻⁶ and, to a lesser extent, with acute kidney injury.^{7,8} Intraoperative blood pressure is a modifiable factor, and hypotension is largely preventable. To the extent that triple-low events are causal, anesthesiologists may be able to intervene and reduce mortality.

Among the triple-low elements, hypotension and low BIS seem likely to be the most important. Moreover, in modern anesthesia practice, total intravenous anesthesia is common, which precludes those patients from meeting triple-low criteria. We therefore tested the hypothesis that an automated intraoperative decision support alert for double-low conditions, defined by MAP less than 75 mmHg and BIS less than 45, reduces 90-day all-cause mortality. A secondary outcome

What We Already Know about This Topic

- The combination of low blood pressure and low bispectral index (double low) during surgery has been associated with increased postoperative mortality, but whether specific alerts to anesthesiologists of this condition during surgery would reduce mortality is unknown

What This Article Tells Us That Is New

- In a randomized trial of over 19,000 patients, the duration of double low was slightly reduced when alarms occurred during this condition, but 90-day mortality was not affected

was the fraction of cases with excess hospital length of stay compared with benchmark values.

Materials and Methods

Study Design

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (New York, New York) and registered at ClinicalTrials.gov (NCT01545596, Principal Investigator: David Reich, registered on March 1, 2012). The IRB waived individual consent for patients and anesthesiologists for several reasons. First, it would be impractical to individually consent each patient, given the number of subjects required to generate a meaningful result.

This article is featured in “This Month in Anesthesiology,” page 1A. This article has an audio podcast.

Submitted for publication February 23, 2016. Accepted for publication June 29, 2016. Departments of Anesthesiology (P.J.M., M.A.L., D.L.R.), Genetics and Genomic Sciences (M.A.L.), and Population Health Science and Policy (H.-M.L.), Icahn School of Medicine at Mount Sinai, New York, New York; and Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, Cleveland, Ohio (D.I.S.).

Copyright © 2016, the American Society of Anesthesiologists, Inc. Wolters Kluwer Health, Inc. All Rights Reserved. Anesthesiology 2016; 125:1113-20

Second, the intervention was purely advisory in nature, so all patients would continue to receive whatever treatment the anesthesiologist felt to be appropriate. Third, the intervention is of low risk and likely to be beneficial. Finally, as a secondary outcome was to assess the response to the intervention, we could not restrict the study to a subset of anesthesiologists. Patients were given a letter describing the trial preoperatively and given the opportunity to opt out of the trial *via* several means.

All adults (18 yr or older) presenting for noncardiac nonemergent surgery in the general operating rooms of the Mount Sinai Hospital were automatically screened for eligibility using data entered into the Anesthesia Information Management System (AIMS; CompuRecord, Philips, USA) and captured by our custom near real-time perioperative data warehouse. Patients having procedures in the endoscopy, obstetric, and interventional radiology areas were excluded. Patients were also excluded from the trial if no BIS monitor was used, they previously participated in the trial, they opted out, deliberate hypotension was used (as determined by AIMS flag), cardiopulmonary bypass was used, or the local workstation pop-up software failed to communicate with the decision support server.

Patients meeting the eligibility criteria were randomized in real time by the decision support software to the control or alert arms of the trial. The trial used a simple randomization protocol with a 1:1 ratio. If AIMS data changed after randomization to make the patient ineligible (*e.g.*, age below 18 yr, procedure marked as cardiac, anesthesia technique changed to MAC, or opt-out flag set), then the patient was immediately removed from the trial and any data collected were not used. When patients contacted the study coordinators after their procedure asking to opt out, their data were removed from the study.

After enrollment and during surgery, the MAP and BIS were evaluated at 1-min intervals. The AIMS records vital sign data in 15-s increments, so the median value was used for each minute. If sequential 1-min measurements were below the study thresholds of 75 mmHg for MAP and 45 for BIS, an initial double-low event was recorded. Subsequent minutes with both MAP and BIS values below the thresholds were also flagged as double-low events. For patients in the alert arm, double-low events prompted a pop-up message to appear on the anesthesia workstation and a pager message to be sent to the attending anesthesiologist. If a double-low event occurred more than 5 min after the last pop-up, a repeat pop-up was sent to the workstation. If a double-low event occurred more than 10 min after the last page, another page was sent to the current attending. No alerts were generated for patients in the control arm. If a noninvasive blood pressure cuff was being used, the last blood pressure was brought forward to be evaluated alongside the current BIS value. Any communication interruption lasting longer than 10 min between the anesthesia machine

or BIS monitor and the AIMS, or interruption between the AIMS and the real-time data warehouse, resulted in the case data being discarded.

Anesthesiologists were not notified of study assignment but were not blinded. The appearance of a double-low alert revealed that the patient had been randomized to the alert arm. Similarly, the lack of an alert after a double-low event revealed that the patient was assigned to the control arm, assuming the practitioner was aware that a double-low event occurred. Although infrequent, anesthesiologists whose patients did not experience any double-low events remained unaware if the patient was in the control or alert arm.

Patient Follow-up

To complement the intraoperative vital sign data, we collected administrative data for each patient from the hospital data warehouse. Data included Social Security Numbers (SSNs), *International Classification of Diseases*, Ninth Revision–Clinical Modification diagnostic and procedure codes, discharge disposition, length of stay, and expected length of stay. The expected length of stay was generated by the University Health System methodology.⁹

For patients who were alive at discharge, we searched the Social Security Administration's Death Master File (DMF)¹⁰ using the patient's name, date of birth, and SSN. The final search against the DMF was performed on May 1, 2015. Computerized matching to the DMF was performed using SSN with date of birth or SSN with the first four characters of first and last names. To capture patients with missing or inaccurate SSNs, the remaining unmatched patients were then matched using date of birth and the first three letters of first and last names or matched with date of birth and the Soundex¹¹ codes for first and last names. First and last name mismatches were detected with a manual review and discarded. The DMF is incomplete, particularly due to the removal of state death reports starting in November 2011.¹² We augmented our mortality data with in-hospital death dates recorded in the hospital electronic medical record. Patients with laboratory results after 90 days were assumed to be alive.

We collected comorbidity data for each patient from the data entered by the anesthesiologist into the AIMS, the patient's medication list, and *International Classification of Diseases*, Ninth Revision–Clinical Modification codes using the Elixhauser coding algorithm described by Quan *et al.*¹³

Statistical Analysis

To determine the number of subjects required, we estimated 90-day all-cause mortality to be no more than 1.85%, based on previous work.¹⁴ A 30% reduction in mortality would be a rate of 1.30%. For a study to have a power of 80% and a type I error of 0.05 to detect that degree of mortality decrease, a total of 16,090 patients are required. The

objective of the study analysis was to demonstrate superiority of the intervention over usual practice.

Descriptive data are presented as mean (SD), median (quartile 1 to quartile 3), and count (percent). Differences between the control and alert arms were assessed using the Pearson chi-square test for categorical values. Differences in age were assessed with Student's *t* test. Differences in other continuous values, including body mass index, were assessed with the Wilcoxon rank sum test. The differences in mortality rate were determined by Pearson chi-square tests. End-tidal MAC fractions were estimated from minute-by-minute medians of end-tidal concentrations of desflurane, sevoflurane, isoflurane, and nitrous oxide, with age adjustment.¹⁵

The primary outcome of 90-day mortality was assessed using a multivariable Cox proportional hazards regression, stratified by surgical specialty. The analysis was stratified by surgical specialty because the baseline hazards for mortality depended on the types of surgery in our previous work. Surgical specialties were grouped into four categories: general (reference), subspecialty, vascular, and other (ophthalmology and oral maxillofacial). Starting with all factors listed in table 1, we performed backward elimination with inclusion criteria of $\alpha = 0.05$ to identify covariates.

Table 1. Characteristics of Patient Cohort

Variable	Alert Group, n = 9,343	Control Group, n = 9,749
Age, yr	54.1 (16.2)	53.9 (16.4)
Women	5,230 (56.0)	5,482 (56.2)
ASA PS > 2	4,137 (44.3)	4,266 (43.8)
BMI, kg/m ²	27 (23–31)	27 (23–31)
Hypertension	4,059 (43.4)	4,216 (43.2)
Diabetes	1,323 (14.2)	1,282 (13.2)
Congestive heart failure	323 (3.5)	343 (3.5)
Pulmonary disease	1,239 (13.3)	1,295 (13.3)
Arrhythmia	926 (9.9)	949 (9.7)
Valvular disease	320 (3.4)	338 (3.5)
Pulmonary circulation disorder	143 (1.5)	142 (1.5)
Peripheral vascular disease	352 (3.8)	373 (3.8)
Neurologic disorder	267 (2.9)	259 (2.7)
Hypothyroidism	692 (7.4)	761 (7.8)
Liver disease	436 (4.7)	440 (4.5)
Malignancy	2,004 (21.4)	2,054 (21.1)
Rheumatoid arthritis	153 (1.6)	176 (1.8)
Coagulopathy	190 (2.0)	226 (2.3)
Psychiatric disease	777 (8.3)	795 (8.2)
Renal failure	490 (5.2)	519 (5.3)
Charlson Comorbidity Index		
0	4,985 (53.4)	5,232 (53.7)
1–2	2,324 (24.9)	2,490 (25.5)
3–5	1,177 (12.6)	1,116 (11.4)
> 5	857 (9.2)	911 (9.3)

Count variables are shown with group percentage as n (%), age is shown as mean (SD), and BMI is shown as median (Q1–Q3).

ASA PS = American Society of Anesthesiologists physical status; BMI = body mass index.

Treatment arm, study month, and the number of double-low minutes were forced into the model. The final model was adjusted for age, American Society of Anesthesiologists (ASA) physical status, the presence of five comorbidities (arrhythmia, neurologic disease, liver disease, malignancy, and pulmonary circulation disorder), blood transfusion, and case duration.

The response to double-low notifications was statistically characterized by determining the percent change in MAP, BIS, and MAC at 5 min after the double-low pop-up notification in the alert arm. Within the control arm, the events that would have triggered a pop-up notification were used. For each event that triggered a notification, we determined which events were followed by a vasopressor bolus, increase in vasopressor infusion, or decrease in the propofol infusion rate within 5 min after notification. For each case, we calculated the median percentage change in BIS, MAP, and MAC for all notifications.

We assessed the period between 5 and 20 min after a notification to determine the persistence of the notification effect—the “double-low free period.” We investigated the proportion of postnotification intervals that were free of subsequent double-low events. To test the association with group assignment, we performed a multivariable Poisson regression, with offset being the logarithm of the total number of notification events. We also used the backward selection strategy starting with the same set of covariates described above. Overdispersion was investigated and not detected.

All calculations were performed using R version 3.2.3 (R Foundation for Statistical Computing, Austria). The R package *medicalrisk* version 1.2 was used to determine Charlson Comorbidity Index values and Elixhauser comorbidity categories.¹⁶

Results

Patients were enrolled over 33 months between May 2011 and February 2014. A total of 82,248 patients were assessed for eligibility. Of these, 20,239 patients met inclusion and exclusion criteria and were randomized. Among these, 19,092 completed the study (fig. 1). Among patients who completed the trial, 9,343 (48.9%) were allocated to the alert arm. Demographic characteristics, preoperative comorbidities, and intraoperative parameters were similar in the randomized groups (tables 1 and 2). Invasive arterial monitoring was used in 26% of cases. Propofol infusions were used in 21% of the cases studied. Intraoperative nitrous oxide (defined as more than 25% of anesthesia minutes with detectable end-tidal nitrous oxide) was present in 15% of cases.

There were significantly fewer double-low minutes per case in patients randomized to alerts (median, 10 [IQR, 2 to 30] min *vs.* 12 [IQR, 2 to 34] min; $P < 0.001$) and normalized to anesthesia duration (3.5 [0.5 to 9.0] min per anesthesia hour *vs.* 3.9 [0.5 to 10.4]; $P < 0.001$; table 3).

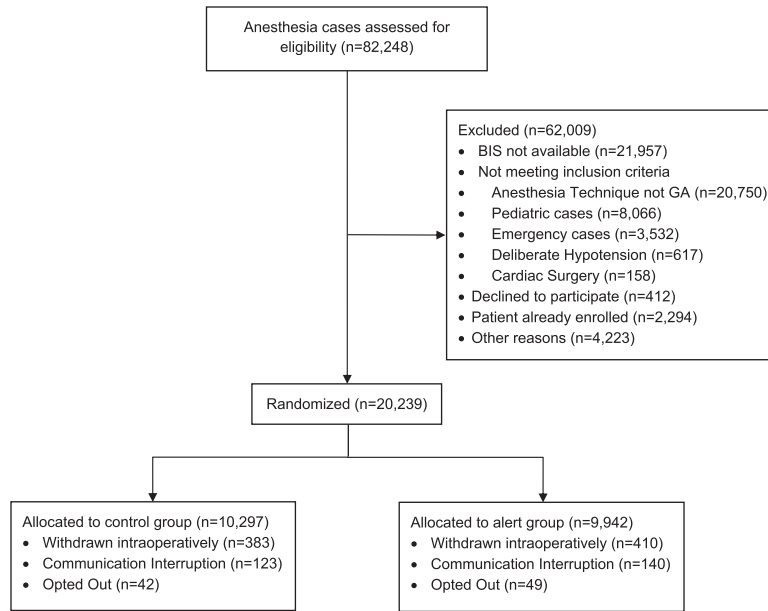


Fig. 1. Patient enrollment and allocation to control and alert arms. Patients could be withdrawn intraoperatively if case data were changed after the case started to exclude a patient, for example, if an anesthesia technique other than general was used. BIS = bispectral index; GA = general anesthesia.

We investigated the pattern of double-low exposure per anesthesia hour over the 33-month study interval. As illustrated in figure 2, there was less double-low exposure in the alert group throughout the study. However, the amount of double-low exposure in the non-alert group decreased approximately 12 months after study initiation. In a multivariate model, there were 5.0% (95% CI, 4.5 to 5.5;

$P < 0.001$) more double-low minutes per anesthesia hour in the first year than in subsequent years, suggesting a training effect.

The fraction of alerts that were followed by no double-low events for 15 min was greater in patients randomized to alerts (40% [22% to 67%]) than in the control group (33% [19% to 67%]; $P < 0.001$). The relative likelihood of an alert being followed by no double-low events for 15 min in the alert arm was 1.15 (95% CI, 1.121 to 1.183; $P < 0.001$), compared with the control group.

Based on hospital discharge disposition and DMF data, 258 patients died within 90 days of surgery: 135 (1.4%) were in the alert group and 123 (1.3%) were in the control group ($P = 0.301$; $P = 0.524$ for the arm and duration interaction term). The difference in percent mortality was 0.18% (99% CI, -0.25 to 0.61). Sensitivity analyses were performed for cases within the first year of the study, for inpatients, and for patients with ASA physical status 4 or 5. No treatment effect was seen in any subset. A model for in-hospital mortality also did not show a treatment effect. There was no significant difference between the randomized groups in the proportion of patients whose observed length of stay exceeded the estimate for the diagnosis group (24.2 vs. 24.0%; $P = 0.788$). Thirty-day mortality in each group was also similar.

Ninety-day mortality as a function of double-low exposure duration is shown for each study arm in figure 3. With the exception of 31 to 60 min in the control group, mortality increased with greater double-low exposure across both groups, even after adjusting for age, comorbidities, and perioperative factors (table 4). Patients with more than 60 min of cumulative double-low time were twice as likely to die (hazard ratio, 1.99; 95% CI, 1.2 to 3.2; $P = 0.005$).

Table 2. Perioperative Factors within Patient Cohort

Variable	Alert Group, n = 9,343	Control Group, n = 9,749
Surgical specialty		
Colorectal surgery	167 (1.8)	198 (2.0)
General surgery	3,415 (36.6)	3,400 (34.9)
Gynecologic surgery	1,081 (11.6)	1,168 (12.0)
Neurosurgery	238 (2.5)	269 (2.8)
Orthopedics	721 (7.7)	839 (8.6)
Otolaryngology	444 (4.8)	460 (4.7)
Plastic surgery	255 (2.7)	263 (2.7)
Spinal surgery	1,375 (14.7)	1,463 (15.0)
Thoracic surgery	413 (4.4)	431 (4.4)
Transplant	140 (1.5)	136 (1.4)
Urology	637 (6.8)	648 (6.6)
Vascular surgery	336 (3.6)	339 (3.5)
Other	121 (1.3)	135 (1.4)
Erythrocyte transfusion	511 (5.5)	554 (5.7)
Platelet transfusion	84 (0.9)	87 (0.9)
Propofol infusion used	1,937 (20.7)	2,049 (21.0)
Total crystalloid, l	1.0 (0.6–2.0)	1.0 (0.6–2.0)
Length of anesthesia, min	184 (132–264)	185 (132–270)
Length of surgery, min	115 (70–180)	114 (71–183)

Count variables are shown with group percentage as n (%), and other variables are shown as median (Q1–Q3).

Table 3. Results of Outcomes

Outcomes	Alert Group, n = 9,343	Control Group, n = 9,749	P
Mortality within 90 d	135 (1.4)	123 (1.3)	0.301
Mortality within 30 d	62 (0.66)	66 (0.68)	0.980
At least one DL minute	7,128 (76)	7,451 (76)	0.838
DL minutes	10 (2–30)	12 (2–34)	< 0.001
DL minutes per anesthesia hour	3.5 (0.5–9.0)	3.9 (0.5–10.4)	< 0.001
Proportion of alerts free of subsequent DL, %	40 (22–67)	33 (19–67)	< 0.001
Excess length of stay	2,261 (24)	2,342 (24)	0.788

“Proportion of alerts free of subsequent DL” is the percentage of double-low alerts followed by 15 min without a double-low condition. Categorical variables are shown with group percentage as n (%), and nonparametric variables shown are as median (Q1–Q3).

DL = double low.

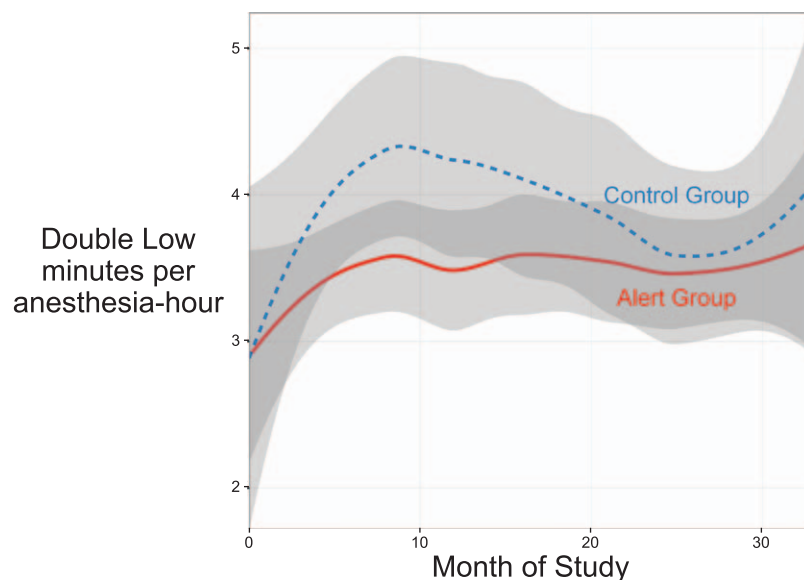


Fig. 2. Graph of median double-low minutes per anesthesia hour as a function of study month. The *solid line* shows smoothed trend for alert group, while *dashed line* shows smoothed line for control group. Smoothing was performed using local polynomial regression fitting; *gray penumbra* shows 95% CI.

Compared with double-low events in the control arm, notifications in the alert arm were associated with mild increases in blood pressure and BIS and mild decreases in MAC (table 5). Among all notifications in the study, 11.8% were followed by a vasopressor bolus within 5 min compared to 10.8% in the control arm ($P < 0.001$). Patients in the alert group were also more likely to have the dose of an existing vasopressor infusion increased (1.3 *vs.* 1.1%; $P = 0.001$) and have the dose of an existing propofol infusion reduced (3.0 *vs.* 2.6%; $P < 0.001$).

Discussion

This randomized, prospective, single-center trial demonstrates that clinical decision alerts for the double-low states prompted clinical intervention, which decreased the double-low duration to a small extent but did not decrease 90-day mortality. The median cumulative double-low time was 2 min lower in the alert arm. Controlling for patient and procedural risk factors, this investigation confirmed that

exposure to double low was associated with increased 90-day mortality, independent of group assignment.

The double-low conditions of MAP less than 75 mmHg and BIS less than 45 were quite common in our patients: 76% of all cases had at least one event, and 26% of cases had longer than 30 min of cumulative double-low exposure. Alerts led the clinicians to eliminate the double-low state within 15 min after 40% of alerts *versus* 33% in the control arm. The hemodynamic management and anesthetic administration changes elicited by the alerts were generally of a small magnitude. The median MAP, BIS, and MAC changes were +5, +3, and -1.5%, respectively. Few alerts resulted in vasopressor boluses or vasopressor infusion increases. Due to the large enrollment in the study, relatively small changes in clinical parameters were statistically significant in comparison with the control arm.

The triple-low state (which includes low MAC in addition to low MAP and low BIS) has been investigated in a retrospective fashion in several studies. Kertai *et al.*¹⁷ found that the

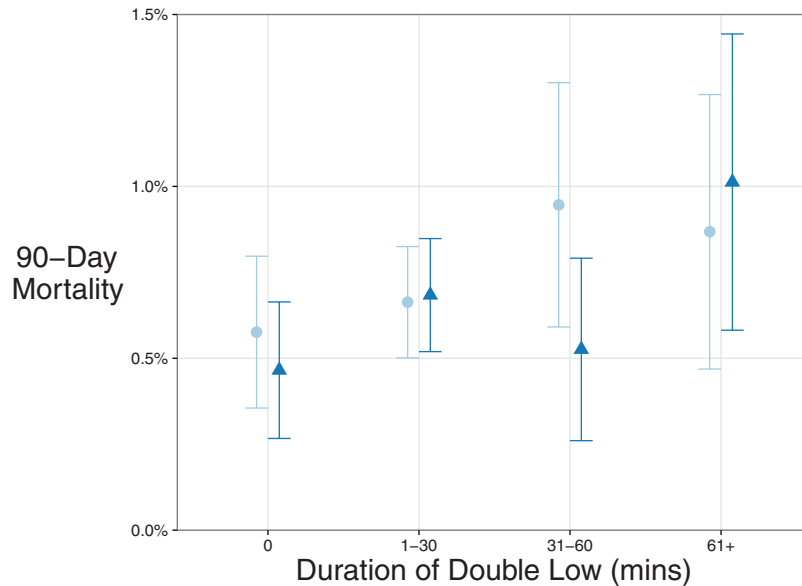


Fig. 3. Ninety-day all-cause mortality grouped by cumulative double-low minutes. Alert group uses *circle symbols*, and control group uses *triangle symbols*. Error bars indicate 95% CIs. See table 4 for statistical significance of trend.

Table 4. Multivariate Predictors of 90-day Mortality

Factors	90-d Hazard Ratio (95% CI)	P
Alert arm (vs. control)	1.14 (0.887–1.45)	0.312
Months into study	0.987 (0.974–1)	0.059
Age, 51–65 yr (vs. < 51)	1.26 (0.814–1.94)	0.302
Age, 66–75 yr (vs. < 51)	1.47 (0.939–2.3)	0.092
Age, >75 yr (vs. < 51)	2.69 (1.73–4.17)	< 0.001
ASA physical status score, 3 (vs. 1–2)	9.26 (4.78–17.9)	< 0.001
ASA physical status score, 4–5 (vs. 1–2)	28.6 (14.4–56.7)	< 0.001
Clinical comorbidities*		
Arrhythmia	2.03 (1.55–2.65)	< 0.001
Neurologic disease	3.01 (2.16–4.19)	< 0.001
Liver disease	2.24 (1.59–3.14)	< 0.001
Malignancy	3.21 (2.47–4.16)	< 0.001
Pulmonary circulation disorder	2.34 (1.64–3.33)	< 0.001
Blood transfusion	2.06 (1.46–2.91)	< 0.001
Length of surgery, 1–2 h (vs. 0–1)	0.445 (0.31–0.637)	< 0.001
Length of surgery, 2–4 h (vs. 0–1)	0.36 (0.251–0.518)	< 0.001
Length of surgery, 4–6 h (vs. 0–1)	0.266 (0.16–0.442)	< 0.001
Length of surgery, > 6 h (vs. 0–1)	0.48 (0.278–0.827)	0.008
Total DL minutes, 1–30 (vs. 0)	1.28 (0.914–1.8)	0.151
Total DL minutes, 31–60 (vs. 0)	1.74 (1.13–2.7)	0.012
Total DL minutes, > 60 (vs. 0)	1.98 (1.23–3.21)	0.005

Data are presented as hazard ratios followed by 95% CIs. Factors entered in the regression that were eliminated included gender, hypertension, diabetes mellitus, congestive heart failure, pulmonary disease, valvular heart disease, peripheral vascular disease, renal failure, hypothyroidism, liver disease, paraplegia, fresh frozen plasma transfusion, platelets given, and total crystalloid given.

*Elixhauser clinical comorbidity categories determined using *International Classification of Diseases*, Ninth Revision–Clinical Modification diagnostic codes as described by Quan *et al.*¹³

ASA = American Society of Anesthesiologists; DL = double low.

association between triple-low and mortality became insignificant when the Cleveland Clinic Risk Stratification Index¹⁸ was included in the statistical model. A recent multicenter retrospective study² found that the likelihood of 30-day mortality was increased by 8% for every 15 cumulative minutes in the triple-low state, after adjustment for individual comorbidities.

That study also demonstrated that low MAP and BIS were not associated with mortality after propensity score matching.

This study's multivariate model of 90-day mortality confirms that advanced age, ASA physical status of 3 or higher, and clinical comorbidities are all strong predictors of mortality. This result has also been seen in retrospective studies

Table 5. Absolute and Percentage Change in Median MAP, BIS, and Age-adjusted MAC

Clinical Parameter	Alert Group, n = 7,128	Control Group, n = 7,451	P
MAP at 5 min, mmHg	75 (71 to 80)	74 (70 to 79)	< 0.001
BIS at 5 min	40 (35 to 44)	40 (34 to 43)	< 0.001
MAC at 5 min	0.63 (0.40 to 0.81)	0.64 (0.39 to 0.83)	0.031
MAP % change at 5 min	5.0 (1.0 to 12)	4.0 (1.0 to 11)	< 0.001
BIS % change at 5 min	3.0 (0.0 to 8.0)	2.5 (0.0 to 7.0)	< 0.001
MAC % change at 5 min	0.0 (−6.6 to 0.0)	0.0 (−5.7 to 0.0)	< 0.001

Change in median MAP, BIS, and age-adjusted MAC 5 min after double low alerts in the treatment group and after double low events (alerts suppressed) in the control group. Values are presented as the median (Q1–Q3).

BIS = bispectral index; MAC = minimum alveolar concentration; MAP = mean arterial pressure.

of intraoperative hemodynamic lability, low intraoperative tidal volume ventilation, and the triple-low studies mentioned above.^{2,17,19,20}

Clinical decision support for hemodynamic events is not well studied in anesthetized patients. Clinical decision support for AIMS has been developed to achieve many goals, including intraoperative alerts based on near real-time physiologic data.^{21–25} A recent prospective randomized trial that investigated an alert for systolic blood pressure less than 80 mmHg did not show a change in duration of hypotension or hospital stay.²⁶ Similar to the current study, the alert did not direct the anesthesiologist to perform any specific interventions.

The current study was limited in several respects. While prospective in nature, the study was heavily automated in order to facilitate the enrollment of a large number of patients. There were no standardized protocols for anesthesiologists to respond to the double-low alerts. Comorbidity capture was based on a combination of anesthesiologist input and administrative data, both of which can be inaccurate. Mortality data may have been incomplete, especially if the patient expired after hospital discharge and the death was not recorded in the Social Security Death Index, which has known limitations of data coverage.¹² The study was conducted at a single teaching hospital, and thus, the findings may not be generalizable to other practices.

An unexpected limitation of this study design is that there was a training effect observed in the control group that affected blood pressure and depth of anesthesia, as illustrated in figure 2. As expected, the alert group demonstrated fewer double-low events per anesthesia hour that appeared to achieve a steady state approximately 6 months after study initiation. Approximately 12 months after study initiation, however, double-low minutes per anesthesia hour also declined in the control group.

We believe that the most likely explanation for declining double-low events in the control group is that the study fits the pattern of a discriminated avoidance experiment.²⁷ When the clinicians were caring for patients assigned to the alert group, operant conditioning occurred because the neutral stimulus of the double-low condition was followed by an aversive stimulus—the double-low alert. As learning progressed, the clinicians began to respond during the

neutral stimulus so as to prevent the aversive stimulus from occurring. In other words, the clinicians caring for alert group patients learned that more intensive monitoring and interventions to prevent or terminate the double-low condition avoided the appearance of pop-up warnings on workstations and text pages to the attending anesthesiologists. Since they were blinded to group assignment and did not know that the alerts would not be occurring, the learning also affected the incidence of double-low events in the control group over time. Most studies of decision support to influence anesthesia provider behavior have presented similarly aversive stimuli in response to various undesirable states.²¹

Despite its limitations, the current study should not lead to the conclusion that decision support alerts that decrease the severity and duration of hypotension and/or deep anesthesia do not improve clinical outcomes. The thresholds for hypotension and deep anesthesia investigated were derived from a cohort investigation of the triple-low state and were relatively mild. The study sample in the current trial included many healthy patients (56% were with ASA physical status 1 or 2) with a low predicted mortality rate. The study sample also included many surgical procedures with a low predicted mortality rate. Future clinical decision support trials targeting hypotension and/or depth of anesthesia could be targeted to more severe thresholds, ASA physical status 3 to 4 patients, and/or patients undergoing higher risk procedures.

Conclusions

Ninety-day mortality was not significantly lower in patients cared for by anesthesiologists who received automated alerts to double-low states. Overall mortality was significantly greater in patients who experienced double-low events independent of group assignment, controlling for known risk factors. Automated alerts affected blood pressure and BIS less than expected, likely due to training effects in the control group.

Research Support

Supported by departmental funds and Covidien Investigator Sponsored Research grant ISR-2012-10142, Boulder, Colorado.

Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Levin: matthew.levin@mountsinai.org. Raw data available from Dr. Levin: matthew.levin@mountsinai.org.

Correspondence

Address correspondence to Dr. Reich: Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place Box 1010, New York, New York 10029. david.reich@mountsinai.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

- 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
- Willingham MD, Karren E, Shanks AM, O'Connor MF, Jacobsohn E, Kheterpal S, Avidan MS: Concurrence of intraoperative hypotension, low minimum alveolar concentration, and low bispectral index is associated with postoperative death. *ANESTHESIOLOGY* 2015; 123:775–85
- Bijker JB, van Klei WA, Vergouwe Y, Eleveld DJ, van Wolfswinkel L, Moons KG, Kalkman CJ: Intraoperative hypotension and 1-year mortality after noncardiac surgery. *ANESTHESIOLOGY* 2009; 111:1217–26
- Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. *Anesth Analg* 2005; 100:4–10
- Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE: Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *ANESTHESIOLOGY* 2015; 123:307–19
- Lienhart A, Auroy Y, Péquignot F, Benhamou D, Warszawski J, Bovet M, Jouglà E: Survey of anesthesia-related mortality in France. *ANESTHESIOLOGY* 2006; 105:1087–97
- Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. *ANESTHESIOLOGY* 2013; 119:507–15
- Aronson S, Phillips-Bute B, Stafford-Smith M, Fontes M, Gaca J, Mathew JP, Newman MF: The association of postcardiac surgery acute kidney injury with intraoperative systolic blood pressure hypotension. *Anesthesiol Res Pract* 2013; 2013:174091
- Meurer S: Mortality Risk Adjustment Methodology for University Health System's Clinical Data Base. AHRQ/IHI Mortal Measurement Meeting, 2008, pp 1–13 Available at: <http://archive.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/mortality/Meurer.pdf>. Accessed May 7, 2016
- National Technical Information Service: Social Security Agency Death Master File. Available at: <http://www.ntis.gov/products/ssa-dmf/>. Accessed May 7, 2016
- National Archives: Soundex System. Available at: <http://www.archives.gov/research/census/soundex.html>. Accessed May 7, 2016
- Sack K: Researchers Wring Hands As U.S. Clamps Down On Death Record Access. *New York Times*, 2012, p A17. Available at: <http://www.nytimes.com/2012/10/09/us/social-security-death-record-limits-hinder-researchers.html>. Accessed May 2, 2016
- Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, Saunders LD, Beck CA, Feasby TE, Ghali WA: Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005; 43:1130–9
- Noordzij PG, Poldermans D, Schouten O, Bax JJ, Schreiner FA, Boersma E: Postoperative mortality in The Netherlands: A population-based analysis of surgery-specific risk in adults. *ANESTHESIOLOGY* 2010; 112:1105–15
- Nickalls RW, Mapleson WW: Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *Br J Anaesth* 2003; 91:170–4
- McCormick PJ, Joseph TT: medicalrisk: Medical Risk and Comorbidity Tools for ICD-9-CM Data. Available at: <http://cran.r-project.org/web/packages/medicalrisk/>. Accessed May 7, 2016
- Kertai MD, White WD, Gan TJ: 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. *ANESTHESIOLOGY* 2014; 121:18–28
- Sessler DI, Sigl JC, Manberg PJ, Kelley SD, Schubert A, Chamoun NG: Broadly applicable risk stratification system for predicting duration of hospitalization and mortality. *ANESTHESIOLOGY* 2010; 113:1026–37
- Levin MA, Fischer GW, Lin HM, McCormick PJ, Krol M, Reich DL: Intraoperative arterial blood pressure lability is associated with improved 30 day survival. *Br J Anaesth* 2015; 115:716–26
- Levin MA, McCormick PJ, Lin HM, Hosseinian L, Fischer GW: Low intraoperative tidal volume ventilation with minimal PEEP is associated with increased mortality. *Br J Anaesth* 2014; 113:97–108
- Epstein RH, Dexter F, Patel N: Influencing anesthesia provider behavior using anesthesia information management system data for near real-time alerts and *post hoc* reports. *Anesth Analg* 2015; 121:1
- Ehrenfeld JM, Epstein RH, Bader S, Kheterpal S, Sandberg WS: Automatic notifications mediated by anesthesia information management systems reduce the frequency of prolonged gaps in blood pressure documentation. *Anesth Analg* 2011; 113:356–63
- Blum JM, Stentz MJ, Maile MD, Jewell E, Raghavendran K, Engoren M, Ehrenfeld JM: Automated alerting and recommendations for the management of patients with preexisting hypoxia and potential acute lung injury: A pilot study. *ANESTHESIOLOGY* 2013; 119:295–302
- Nair BG, Peterson GN, Neradilek MB, Newman SF, Huang EY, Schwid HA: Reducing wastage of inhalation anesthetics using real-time decision support to notify of excessive fresh gas flow. *ANESTHESIOLOGY* 2013; 118:874–84
- Nair BG, Horibe M, Newman SF, Wu WY, Peterson GN, Schwid HA: Anesthesia information management system-based near real-time decision support to manage intraoperative hypotension and hypertension. *Anesth Analg* 2014; 118:206–14
- Panjasawatwong K, Sessler DI, Stapelfeldt WH, Mayers DB, Mascha EJ, Yang D, Kurz A: A randomized trial of a supplemental alarm for critically low systolic blood pressure. *Anesth Analg* 2015; 121:1500–7
- Skinner BF: Behaviorism at fifty. *Science* 1963; 140:951–8