Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery

Terri G. Monk, M.D., M.S., Michael R. Bronsert, Ph.D., M.S., William G. Henderson, M.P.H., Ph.D., Michael P. Mangione, M.D., S. T. John Sum-Ping, M.D., Deyne R. Bentt, M.D., C.P.H.I.M.S., Jennifer D. Nguyen, M.D., Joshua S. Richman, M.D., Ph.D., Robert A. Meguid, M.D., M.P.H., Karl E. Hammermeister, M.D.

ABSTRACT

Background: Although deviations in intraoperative blood pressure are assumed to be associated with postoperative mortality, critical blood pressure thresholds remain undefined. Therefore, the authors estimated the intraoperative thresholds of systolic blood pressure (SBP), mean blood pressure (MAP), and diastolic blood pressure (DBP) associated with increased risk-adjusted 30-day mortality.

Methods: This retrospective cohort study combined intraoperative blood pressure data from six Veterans Affairs medical centers with 30-day outcomes to determine the risk-adjusted associations between intraoperative blood pressure and 30-day mortality. Deviations in blood pressure were assessed using three methods: (1) population thresholds (individual patient sum of area under threshold [AUT] or area over threshold 2 SDs from the mean of the population intraoperative blood pressure values), (2). absolute thresholds, and (3) percent change from baseline blood pressure.

Results: Thirty-day mortality was associated with (1) population threshold: systolic AUT (odds ratio, 3.3; 95% CI, 2.2 to 4.8), mean AUT (2.8; 1.9 to 4.3), and diastolic AUT (2.4; 1.6 to 3.8). Approximate conversions of AUT into its separate components of pressure and time were SBP < 67 mmHg for more than 8.2 min, MAP < 49 mmHg for more than 3.9 min, DBP < 33 mmHg for more than 4.4 min. (2) Absolute threshold: SBP < 70 mmHg for more than or equal to 5 min (odds ratio, 2.9; 95% CI, 1.7 to 4.9), MAP < 49 mmHg for more than or equal to 5 min (2.4; 1.3 to 4.6), and DBP < 30 mmHg for more than or equal to 5 min (3.2; 1.8 to 5.5). (3) Percent change: MAP decreases to more than 50% from baseline for more than or equal to 5 min (2.7; 1.5 to 5.0). Intraoperative hypertension was not associated with 30-day mortality with any of these techniques.

Conclusion: Intraoperative hypotension, but not hypertension, is associated with increased 30-day operative mortality. **(Anesthesiology 2015; 123:307-19)**

INTRAOPERATIVE blood pressure variations outside of accepted physiologic ranges are common during noncardiac surgery. A recent publication analyzing blood pressure data from anesthesia information monitoring systems (AIMS) found hypotension (systolic blood pressure [SBP] < 80 for >5 min) in 26% and hypertension (SBP > 160 for >5 min) in 20% of 16,913 anesthetic cases.[1] Both hypotension and hypertension have been reported to be associated with postoperative complications or mortality.[2–7] Despite the widely assumed importance of blood pressure management on postoperative outcomes, there are no accepted definitions for intraoperative blood pressure levels requiring intervention.[8] A systematic literature

What We Already Know about This Topic

- Although the American Society of Anesthesiologists recommends monitoring blood pressure during surgery, the association between blood pressure deviations during surgery and mortality are confounded by lack of agreed upon definitions

What This Article Tells Us That Is New

- In a review of more than 18,000 patients undergoing noncardiac surgery within the Veterans Administration Hospital system, application of three definitions of blood pressure deviation based on population and individual patient level data showed that hypotension but not hypertension was associated with increased 30-day mortality

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

Submitted for publication June 4, 2014. Accepted for publication April 2, 2015. Corrected on February 20, 2017. From the Emeritus Faculty, Durham VA Medical Center, Durham, North Carolina (T.G.M.); Department of Anesthesiology and Perioperative Medicine, University of Missouri, Columbia, Missouri (T.G.M.); Adult and Child Center for Outcomes Research and Delivery Science (ACCORDS), Aurora, Colorado (M.R.B., W.G.H.); Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora, Colorado (W.G.H.); Department of Anesthesiology, University of Pittsburgh School of Medicine, VA Pittsburgh Healthcare System, Pittsburgh, Pennsylvania (M.P.M.); Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, VA North Texas Health Care System, Dallas, Texas (S.T.J.S.-P.); Department of Anesthesiology and Critical Care Medicine, George Washington University School of Medicine, Washington DC VA Medical Center, Washington, D.C. (D.R.B.); Department of Anesthesiology, Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (J.D.N.); Department of Surgery, University of Alabama Birmingham, Birmingham VA Medical Center, Birmingham, Alabama (J.S.R.); Department of Surgery, University of Colorado School of Medicine, Aurora, Colorado (R.A.M.); and Department of Medicine (Cardiology), University of Colorado School of Medicine, Aurora, Colorado (K.E.H.).

<zdoi;10.1097/ALN.0000000000000756>

review found 130 articles with 140 definitions of intraoperative hypotension.[9] When these various definitions were applied to a large cohort of adult patients undergoing noncardiac surgery, the occurrence of intraoperative hypotension varied from 5 to 99%.[9] The lack of accepted definitions for intraoperative hypotensive and hypertensive events requiring intervention likely exists because there are few studies linking observed intraoperative blood pressure levels with patient outcomes (*i.e.*, perioperative death or complications). Therefore, further research is needed to define the levels of hypotension and hypertension associated with adverse postoperative outcomes.

We have been unable to identify evidence-based guidelines for the maintenance of intraoperative blood pressures. The American Society of Anesthesiologists Standards for Basic Anesthetic Monitoring only state, "Every patient receiving anesthesia shall have arterial blood pressure and heart rate determined and evaluated at least every five minutes."[10]

In the current era of computers automatically recording and storing data on intraoperative vital signs (AIMS), physiologic data can be combined with outcomes data from perioperative registries to identify associations among hypotension, hypertension, and postoperative mortality.[11] The Veterans Affairs Surgical Quality Improvement Program (VASQIP) prospectively collects data on patient-related risks, operative procedures, and 30-day outcomes.[12] The objective of this retrospective cohort study was to combine blood pressure data collected by AIMS at six Veterans Affairs (VA) medical centers with patient-related risk, procedural, and 30-day mortality data from the VASQIP database to test two hypotheses: (1) There are levels of intraoperative hypotension below which 30-day operative mortality is increased and (2) there are levels of intraoperative hypertension above which 30-day operative mortality is increased. With input from anesthesia providers, these levels could then be incorporated into data-driven guidelines for maintaining intraoperative blood pressure.

Materials and Methods

Approvals

The study was approved by the University of Colorado Multiple Institutional Review Board (IRB), Denver, Colorado; the IRB at the Durham, NC VA Medical Center; the IRBs at each of the six participating VA medical centers (Cleveland, Dallas, Houston, Pittsburgh, Seattle, and Washington, D.C.); and the VA Surgical Quality Data Use Group, Brockton, Massachusetts.

Data Sources

The data used for this study came from two sources: AIMS data for the years 2001 to 2008 and data from the same surgical cases in the VASQIP database. The six participating VA sites were the Cleveland, Dallas, Houston, Pittsburgh, Seattle, and Washington, DC Medical Centers.

The participating VA medical centers used AIMS systems from three different vendors—Draeger Medical Inc. (USA), Eko Systems Inc. (USA), and Phillips Healthcare (USA). For the current investigation, we combined AIMS data for intraarterial and noninvasive SBP and diastolic blood pressure (DBP) measurements and calculated mean blood pressure (MAP). Noninvasive blood pressures were measured every 3 to 5 min, and invasive blood pressures were measured at 15- to 30-s intervals.

The VASQIP is a surgical quality improvement program, in existence in the VA since 1991, which collects data on preoperative risk factors, aspects of the operation, and 30-day postoperative mortality and morbidity outcomes for the majority of major surgical operations performed in the VA healthcare system.[12–16] These data are fed back to the Chiefs of Surgical Services at each VA medical center and the Director of the National Surgery Office for the VA in the form of both center-specific unadjusted and risk-adjusted mortality and complication rates to facilitate assessment and promote improvement in the quality of surgical care delivered. The VASQIP data are collected by a specially trained nurse at each VA medical center. A previous study has documented that the VASQIP data are complete and reliable.[17]

The primary outcome for this study is death from any cause within 30 days after surgery, as recorded in the VASQIP database. This outcome is almost 100% complete, because the VASQIP data are merged periodically with the VA Vital Status File to ensure that all 30-day deaths are captured.[18,19] The VASQIP database was also the source of preoperative demographic variables and risk factors used to perform risk-adjusted analyses for this report. Ten preoperative patient-related risk variables have been found to be the most important preoperative predictors of 30-day postoperative mortality in previous VASQIP studies: serum albumin, American Society of Anesthesiologist physical status classification, presence of disseminated cancer, emergency operation, patient age, a do not resuscitate order, the work relative value unit associated with the primary Current Procedural Terminology code (a measure of the complexity of the procedure), weight loss >10% of body weight in the 6 months before surgery, surgeon subspecialty, and serum creatinine.[15,16] The laboratory values used for risk adjustment were measured within 30 days before surgery. These preoperative risk factors along with intraoperative blood pressure. measurements from the AIMS systems were used as the independent variables in multivariable logistic regression analyses in which death within 30 days of surgery was the dependent (outcome) variable.

The AIMS and VASQIP databases were matched using patient Social Security number and date of surgery. Only those operations that had both the AIMS and the VASQIP data available were retained for analysis. Patients who received only monitored anesthesia care or local anesthesia were excluded. For patients with more than one operation recorded in the database, only the first operation for each patient was retained for analysis.

Cleaning and Summarizing the AIMS Data

A written detailed analysis plan was developed for cleaning and summarizing the AIMS data. This plan was reviewed and revised by the investigative team before analyzing any postoperative outcomes.

Of the many tables in the AIMS, the fields containing intraarterial and noninvasive blood pressure measurements were identified by the physician investigators based on the table identifiers, the amount of data present, and, when necessary, inspecting frequency distribution to confirm that values were compatible with the blood pressure variable under consideration. Nonphysiologic blood pressure values (defined as SBP <20 mmHg and >300 mmHg and DBP <20 mmHg and >200 mmHg) were excluded. MAP was calculated using the following formula: MAP = DBP + 1/3 × (SBP − DBP).

Our hypotheses testing analyses were limited to intraoperative blood pressures, which we identified by the appearance of expired carbon dioxide. All pressure values between the first and last expired carbon dioxide measurements were retained for analysis. For the few patients without end-tidal carbon dioxide measurements, all blood pressures were used. When duplicate pressures (occurring in the same patient, the same operation, and with the same date/time stamp) occurred, one was selected at random. Most of the duplicate pressures had the same value. In instances where either SBP or DBP were missing, or DBP was greater than SBP, or DBP was less than 20 mmHg below SBP, all pressures at that time point were deleted. Finally, we smoothed the intraarterial blood pressure data by calculating the median of all pressure values in consecutive 2-min epochs and then combined the smoothed intraarterial values with the noninvasive values. If a patient had both intraarterial and noninvasive pressures at the same time point, the intraarterial pressures were used preferentially.

Statistical Analyses

Three distinct sets of statistical analyses were performed using different methods for assessing intraoperative blood pressure deviations: (1) area over (AOT) and area under (AUT) the population-defined blood pressure thresholds, (2) absolute blood pressure thresholds, and (3) blood pressure thresholds relative to each patient's baseline blood pressure.

Areas over and under the Population-defined Blood Pressure Thresholds. Means and SDs for SBP, MAP, and DBP were calculated using all pressure values for all patients. Hypertensive and hypotensive thresholds were defined as the population mean ± 2 SDs from the mean. We made the *a priori* decision to define the acceptable blood pressure as the mean of the blood pressure data ± 2 SDs (about 95% of all observations), because this definition is commonly used to define a reference range for laboratory measurements.[20] Intuitively, abnormal intraoperative blood pressure has both magnitude and time or duration components. Therefore, the sum of all areas defined by the blood pressure curve above the upper threshold (AOT) is a measure of the severity of intraoperative hypertension; similarly, the sum of all areas defined by the blood pressure curve below the lower threshold (AUT) is a measure of the severity of intraoperative hypotension. The time component is calculated as the sum of the durations of all intraoperative hypertensive (time over the threshold [TOT]) or hypotensive episodes (time under the threshold [TUT]). Figure 1 illustrates the triangulation/trapezoidal method for calculation of AOT and AUT in mmHg × minutes for two episodes of hypotension and one of hypertension. Area was calculated using the trapezoid method, area = $(d_1 – d_2) \times h \times 0.5$, where d_1 and d_2 are the first and second blood pressure deviations (mmHg), respectively, from the given threshold, and h is the time (minutes) between the two deviations. However, anesthesia providers commonly manage blood pressure in mmHg and are not

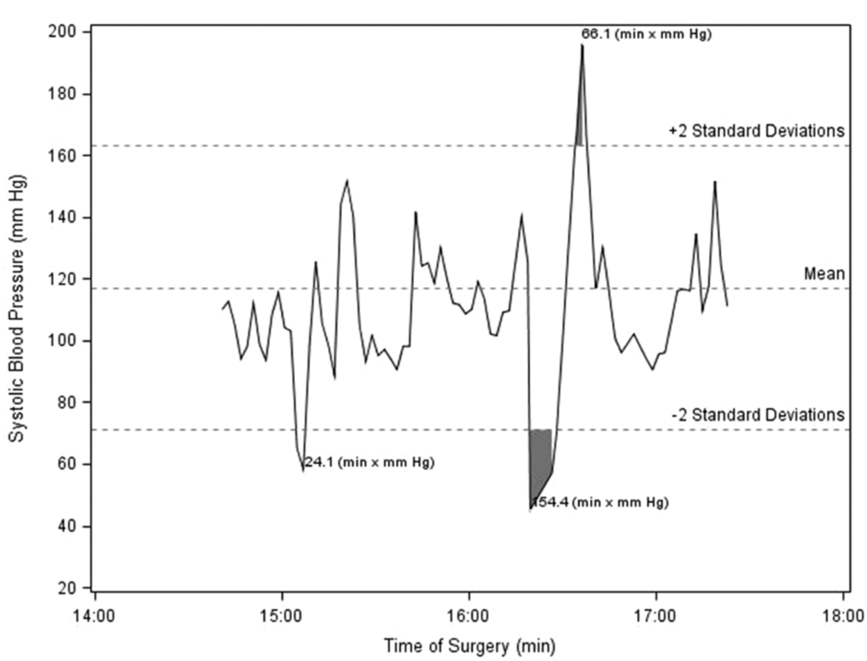

Fig. 1. Example of the triangulation/trapezoid method with slope estimates for the calculation of area over (163 mmHg) and under (71 mmHg) systolic blood pressure threshold for a single patient.

familiar with measures of AUT or AOT, so we also calculated the average pressure under the threshold (PUT) or pressure over the threshold (POT) as AUT/TUT and AOT/TOT, respectively. To estimate the relationship between severity of blood pressure aberration and mortality, patients were grouped into quartiles according to AUT, AOT, TUT, TOT, PUT, and POT separately for area, time, and pressure.

Absolute Blood Pressure Thresholds. Absolute thresholds were defined by a consensus of the clinicians in the research group after review of publications that used this method;[21,22] this resulted in a reference SBP of 90 to 159 mmHg, reference MAP of 60 to 109 mmHg, and the reference DBP of 50 to 99 mmHg. Gradients of aberration were defined in 10 mmHg intervals for durations of 2 to 4.9 and more than or equal to 5 min.

Blood Pressure Thresholds Relative to Each Patient's Baseline Blood Pressure. We also examined the effect of decreases and increases of SBP, MAP, and DBP of 30 to 39, 40 to 49, and more than or equal to 50% from each patient's preanesthesia blood pressures for durations of 2 to 4.9 and more than or equal to 5 min. The patient's preanesthesia baseline blood pressure was calculated by taking the average of all noninvasive blood pressure measurements before the appearance of end-tidal carbon dioxide.

Note that in all three types of analyses (population-defined blood pressure thresholds, absolute blood pressure thresholds, and blood pressure thresholds relative to each patient's baseline blood pressure), by definition, the hypotensive and hypertensive episodes cannot overlap. However, some patients have both hypotensive and hypertensive episodes.

The association of blood pressure deviations with operative mortality was assessed using separate logistic regression analyses for each of the three measures of blood pressure deviation for SBP, MAP, and DBP. The independent variables were the measures of blood pressure aberrancy and patient preoperative risk variables, and the 30-day postoperative mortality was the dependent variable. The statistical significance of the association between blood pressure and 30-day postoperative mortality was assessed with an overall *P* value, which assesses the simultaneous statistical significance of the difference in the odds ratios (ORs) from 1.0 across all blood pressure deviation groups. We only report the statistical significance of the ORs for individual blood pressure deviation groups of hypotension or hypertension when the overall *P* value was statistically significant ($P \leq 0.05$). The *P* values were adjusted for multiple comparisons using the Bonferroni correction for each of the three sets of statistical analyses.

The VASQIP data were 100% complete, with the exception of preoperative serum albumin and creatinine in cases where these laboratory tests were not ordered for the patients. In the adjusted analyses, we imputed serum albumin using standard methods used in previous VASQIP publications,[23,24] and serum creatinine was assumed to be normal when it was missing. All statistical analyses were performed using SAS®, version 9.3 (SAS Inc., USA).

Results

Patient Population

The initial AIMS data included 46,496 operations on 30,650 patients. As shown in the Strengthening the Reporting of Observational Studies in Epidemiology diagram[25] (fig. 2), the VASQIP data included 24,548 operations on 20,523 patients. After matching AIMS data with VASQIP data, there were 23,163 operations on 19,383 patients. Exclusions included the second or more operations for 3,780 patients with 2 or more operations, 91 patients with fewer than 5 intraoperative blood pressures, and 536 patients who received only monitored anesthesia care or local anesthetics. The final cohort for analysis included 18,756 patients. The contribution of data from each VA site to the final database was Cleveland, 6,223 patients; Houston, 3,898 patients; Dallas, 3,728 patients; Seattle, 2,715 patients; Pittsburgh, 1,626 patients; and Washington, 566 patients. The average number of blood pressure readings per case was 52 ± 33 for noninvasive blood pressure monitoring and 617 ± 432 for invasive blood pressure monitoring.

The preoperative, intraoperative, and postoperative characteristics of the 18,756 patients are shown in table 1. Consistent with a VA population, this was an older (mean age, 59.5 yr), largely male (92.8%) cohort. Race/ethnicity was unknown for 16% of the sample, but for those with known race/ethnicity, 61% were Caucasian, 20% were African American, and 3% were Hispanic. The 30-day postoperative mortality rate was 1.8% in patients who had surgery with general anesthesia, 1.8% with spinal anesthesia, and 2.3% with epidural anesthesia.

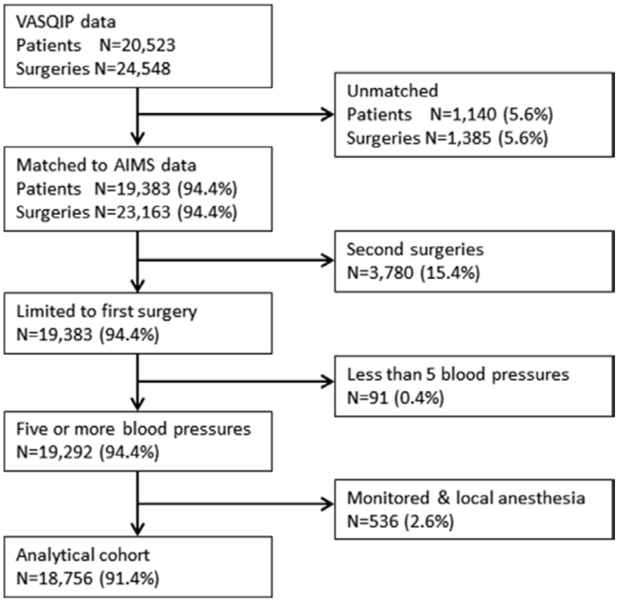

Fig. 2. STROBE diagram of included patients with matched VASQIP and AIMS blood pressure data. AIMS = anesthesia information monitoring systems; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; VASQIP = Veterans Affairs Surgical Quality Improvement Program.

Table 1. Preoperative, Intraoperative, and Postoperative Patient Characteristics

Characteristics	n = 18,756
Age (yr), mean (SD)	59.5 (12.8)
Male, n (%)	17,412 (92.8)
Race/ethnicity, n (%)	
White	11,515 (61.4)
Black	3,707 (19.8)
Hispanic	478 (2.6)
Other	3,056 (16.3)
Preoperative albumin* (g/dl), mean (SD)	3.9 (0.7)
Disseminated cancer, n (%)	367 (2.0)
Do not resuscitate status, n (%)	133 (0.7)
>10% loss body weight in past 6 mo, n (%)	910 (4.9)
Preoperative creatinine >1.2 mg/dl, n (%)	3,479 (18.6)
Emergency case, n (%)	1,414 (7.5)
ASA classification, n (%)	
1	497 (2.7)
2	4,890 (26.1)
3	10,889 (58.1)
4	2,443 (13.0)
5	37 (0.2)
Work RVU, mean (SD)	15.2 (8.7)
Operative time (h), median (IQR)	2.0 (1.2–3.1)
Postoperative length of stay† (d), median (IQR)	5.0 (2.0–10.0)
30-d mortality, n (%)	334 (1.8)
Surgeon specialty, n (%)	
General surgery	5,905 (31.5)
Orthopedic surgery	4,252 (24.1)
Peripheral vascular surgery	2,187 (11.7)
Urology	2,030 (10.8)
Neurosurgery	1,050 (5.6)
Thoracic surgery	1,010 (5.4)
Other surgery	2,049 (10.9)

* A total of 5,109 (27.2%) patients were missing preoperative albumin. † A total of 5,351 (28.5%) patients were missing postoperative length of stay.

ASA = American Society of Anesthesiologists; IQR = interquartile range; RVU = relative value unit.

Areas over and under Population-defined Blood Pressure Thresholds

Unadjusted Mortality. Table 2 presents the sample sizes and unadjusted 30-day mortality rates for the patient groups in the population-defined blood pressure threshold analyses. In this analysis, the reference range for SBP was 71 to 163 mmHg, MAP was 55 to 119 mmHg, and DBP was 35 to 95 mmHg (table 2). The reference group (no hypotension or hypertension during surgery) for SBP included 40% (7,573) of the patients compared with 9% (1,714) with only hypotension, 41% (7,648) with only hypertension, and 10% (1821) with both hypotensive and hypertensive episodes during surgery (table 2). There is a severalfold increase in unadjusted operative mortality for the fourth quartile of hypotensive AUT, TUT, and PUT with generally graded intermediate mortality rates for the first three quartiles. Similar mortality gradients by AUT, TUT, and PUT were seen for MAP and DBP. However, the unadjusted death rates increased modestly or not at all for hypertensive AOT, TOT, and POT for SBP, MAP, and DBP. The mortality rate was 3% for the patients who experienced both hypotension and hypertension during the surgical procedure, which is similar to the rate in the hypotension-only group (table 2).

Risk-adjusted Mortality. The c-index for predicting 30-day mortality using only VASQIP preoperative patient characteristics was high at 0.908. When intraoperative blood pressure variables from each of the three analysis techniques were added to the model, the c-index values were essentially unchanged. Likewise, the addition of intraoperative erythrocyte transfusion and sepsis or year of surgery did not appreciably change the c-index or improve the model.

The risk-adjusted results for the population-defined threshold are presented in table 3. After adjustment for the patient preoperative risk variables, the ORs for mortality for AUT, TUT, and PUT measures of SBP, MAP, and DBP hypotension groups were statistically significant compared with the reference groups (overall $P < 0.007$), whereas there were no statistically significant results for the hypertension groups. Conversions of AUT into its separate components of pressure and time allow us to define approximate thresholds for increased mortality (table 3): (1) SBP < 67 mmHg (OR, 1.7; 95% CI, 1.1 to 2.7) with duration of more than 8.2 min (3.3; 2.2 to 4.8), (2) MAP < 49 mmHg (3.0; 2.0 to 4.5) for more than 3.9 min (1.8; 1.1 to 2.9), and (3) DBP < 33 mmHg (1.8; 1.2 to 2.9) for more than 4.4 min (2.0; 1.2 to 3.1). These data are also graphically represented in figures 3 and 4.

Absolute Blood Pressure Thresholds

Table 4 presents unadjusted and risk-adjusted results for the analyses based on the absolute blood pressure thresholds. In this analysis, the reference range for SBP was 90 to 159 mmHg, MAP 60 to 109 mmHg, and DBP 50 to 99 mmHg. Again, the unadjusted results show a generally increasing gradient of mortality with greater severity of intraoperative hypotension; this gradient is substantially less for hypertension. In risk-adjusted analyses, the association between operative mortality and hypotension is statistically significant (overall $P < 0.001$) with ORs of 2.9 (95% CI, 1.7 to 4.9) for SBP < 70 mmHg for more than or equal to 5 min, 2.4 (1.3 to 4.6) for MAP < 49 mmHg for more than or equal to 5 min, and 3.2 (1.8 to 5.5) for DBP < 30 mmHg for more than or equal to 5 min. There is no statistically significant relationship between hypertension and mortality in the risk-adjusted analyses.

Blood Pressure Thresholds Relative to Each Patient's Baseline Blood Pressure

Table 5 presents unadjusted and risk-adjusted analyses based on the blood pressure thresholds relative to each patient's baseline blood pressure before expired carbon dioxide measurements. Only 12,675 (67.6%) of the 18,756 subjects had baseline blood pressure measurements in AIMS; these patients tended to be at a lower risk than those without baseline blood pressure measurements (*e.g.*, less emergent surgery, fewer other preoperative risk factors, and lower 30-day postoperative mortality and morbidity rates). In the risk-adjusted analyses, the only clinically meaningful association with 30-day mortality

Table 2. Patient Counts and 30-day Mortality Rates by Area under Curve,* Total Time, and Absolute Pressure Deviations from Population-defined Thresholds (n = 18,756)

	Systolic		Mean		Diastolic	
Thresholds†	N	Deaths (%)	N	Deaths (%)	N	Deaths (%)
Hypotension	Threshold 71 mmHg		Threshold 55 mmHg		Threshold 35 mmHg	
Area under threshold (min × mmHg)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	884	25 (2.8)	851	22 (2.6)	817	22 (2.7)
Second quartile	883	23 (2.6)	852	26 (3.1)	817	17 (2.1)
Third quartile	884	16 (1.8)	852	23 (2.7)	818	32 (3.9)
Fourth quartile	884	60 (6.8)	852	46 (5.4)	817	39 (4.8)
Time under threshold (min)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	883	29 (3.3)	851	21 (2.5)	817	26 (3.2)
Second quartile	884	20 (2.3)	852	24 (2.8)	817	14 (1.7)
Third quartile	884	16 (1.8)	852	28 (3.3)	818	29 (3.5)
Fourth quartile	884	59 (6.7)	852	44 (5.2)	817	41 (5.0)
Pressure under threshold (mmHg)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	890	21 (2.4)	849	20 (2.4)	817	19 (2.3)
Second quartile	877	20 (2.3)	854	29 (3.4)	817	29 (3.5)
Third quartile	884	32 (3.6)	852	23 (2.7)	818	24 (2.9)
Fourth quartile	884	51 (5.8)	852	45 (5.3)	817	38 (4.7)
Hypertension	Threshold 163 mmHg		Threshold 119 mmHg		Threshold 95 mmHg	
Area over threshold (min × mmHg)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	2,367	30 (1.3)	2,648	49 (1.9)	2,553	41 (1.6)
Second quartile	2,367	41 (1.7)	2,648	37 (1.4)	2,553	37 (1.4)
Third quartile	2,368	46 (1.9)	2,649	41 (1.5)	2,553	40 (1.6)
Fourth quartile	2,367	54 (2.3)	2,648	55 (2.1)	2,553	42 (1.6)
Time over threshold (min)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	2,368	34 (1.4)	2,648	52 (2.0)	2,554	43 (1.7)
Second quartile	2,366	41 (1.7)	2,648	40 (1.5)	2,552	38 (1.5)
Third quartile	2,368	41 (1.7)	2,649	41 (1.5)	2,553	41 (1.6)
Fourth quartile	2,367	55 (2.3)	2,648	49 (1.9)	2,553	38 (1.5)
Pressure over threshold (mmHg)						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
First quartile	2,367	38 (1.6)	2,648	42 (1.6)	2,594	40 (1.5)
Second quartile	2,367	35 (1.5)	2,648	46 (1.7)	2,512	37 (1.5)
Third quartile	2,368	39 (1.6)	2,649	45 (1.7)	2,553	33 (1.3)
Fourth quartile	2,367	59 (2.5)	2,648	49 (1.9)	2,553	50 (2.0)
Hypotension and hypertension						
Reference	7,573	99 (1.3)	6,480	101 (1.6)	6,706	111 (1.7)
Both	1,821	60 (3.3)	1,724	66 (3.8)	1,431	47 (3.3)
Only hypotension	1,714	64 (3.7)	1,683	51 (3.0)	1,838	63 (3.4)
Only hypertension	7,648	111 (1.5)	8,869	116 (1.3)	8,781	113 (1.3)

* See text for definition. † Thresholds were established in relationship to the population mean pressure ± 2 SDs.

was a MAP decrease of more than 50% from baseline for more than or equal to 5 min (OR, 2.7; 95% CI, 1.5 to 5.0). The reduced sample size with this technique may have contributed to broad CIs and decreased power to detect associations.

Discussion

Overview of Results

Intraoperative hypotension and hypertension were assessed from AIMS data in 18,756 major surgical procedures using three different methods: (1) AUT (hypotension) or AOT (hypertension), which incorporates simultaneously the magnitude and duration of the pressure aberration; (2) absolute thresholds based on our clinical judgment and the literature; and (3) relative thresholds, defined as percent change from a patient's preoperative baseline blood pressure. The first two methods showed statistically significant associations between increased 30-day mortality and hypotension in multiple cells (tables 3 and 4); however, in the third analysis using the patient's

Table 3. Area, Total Time, and Absolute Pressure Deviations from Population-defined Thresholds and Adjusted Odds Ratios for 30-day Mortality (n = 18,756)

Thresholds*	Systolic Median (IQR)	Systolic OR (95% CI)	Systolic *P* Value†	Mean Median (IQR)	Mean OR (95% CI)	Mean *P* Value†	Diastolic Median (IQR)	Diastolic OR (95% CI)	Diastolic *P* Value†
Hypotension	Threshold 71 mmHg			Threshold 55 mmHg			Threshold 35 mmHg		
Area under threshold (min × mmHg)									
First quartile	0.5 (0.2–1.0)	1.42 (0.86–2.34)	**<0.0001**	0.5 (0.2–1.0)	1.24 (0.75–2.07)	**<0.001**	0.6 (0.2–1.0)	1.37 (0.83–2.26)	**<0.001**
Second quartile	3.9 (2.6–5.5)	1.13 (0.68–1.89)		3.3 (2.3–4.9)	**1.64 (1.02–2.64)**		3.4 (2.3–4.8)	1.13 (0.65–1.96)	
Third quartile	13.4 (10.0–17.8)	0.92 (0.52–1.64)		12.2 (9.1–17.0)	1.35 (0.81–2.25)		12.6 (9.2–17.8)	**2.43 (1.56–3.79)**	
Fourth quartile	51.5 (35.2–92.9)	**3.27 (2.23–4.79)**		46.8 (30.6–81.6)	**2.84 (1.88–4.27)**		63.9 (36.5–131.2)	**2.59 (1.71–3.94)**	
Time under threshold (min)									
First quartile	0.5 (0.3–0.7)	1.54 (0.96–2.47)	**<0.0001**	0.6 (0.3–0.8)	1.18 (0.71–1.98)	**0.007**	0.5 (0.3–0.8)	1.53 (0.95–2.46)	**<0.001**
Second quartile	1.5 (1.2–1.9)	1.03 (0.60–1.77)		1.8 (1.4–2.2)	1.55 (0.95–2.53)		1.7 (1.3–2.1)	1.16 (0.64–2.09)	
Third quartile	3.2 (2.7–3.9)	0.89 (0.50–1.60)		3.9 (3.3–4.8)	**1.81 (1.12–2.91)**		4.4 (3.4–5.9)	**1.97 (1.24–3.11)**	
Fourth quartile	8.2 (6.1–12.8)	**3.25 (2.22–4.77)**		11.1 (8.2–17.9)	**2.46 (1.63–3.73)**		19.1 (11.5–37.7)	**2.71 (1.79–4.10)**	
Pressure under threshold + threshold pressure (mmHg)*									
First quartile	70 (69.8–70.5)	1.17 (0.69–1.99)	**0.001**	54.3 (54.0–54.5)	1.16 (0.68–1.96)		34.3 (34.0–34.5)	1.15 (0.67–1.97)	**<0.001**
Second quartile	68.6 (68.3–69)	1.13 (0.66–1.95)		53.2 (53.0–53.5)	1.56 (0.97–2.49)	**<0.001**	33.1 (33.0–33.5)	**1.81 (1.15–2.86)**	
Third quartile	66.7 (66–67.4)	**1.71 (1.09–2.70)**		51.9 (51.5–52.3)	1.41 (0.85–2.34)		32.0 (31.5–32.4)	**1.67 (1.02–2.73)**	
Fourth quartile	63.0 (60.5–64.3)	**2.62 (1.76–3.91)**		49.3 (47.8–50.3)	**3.02 (2.01–4.54)**		29.7 (28.6–30.5)	**2.91 (1.92–4.42)**	
Hypertension	Threshold 163 mmHg			Threshold 119 mmHg			Threshold 95 mmHg		
Area over threshold (min × mmHg)									
First quartile	3.7 (1.1–7.8)	0.81 (0.52–1.25)	1.0	2.6 (0.8–5.6)	1.09 (0.75–1.59)	1.0	2.1 (0.7–4.3)	1.01 (0.69–1.49)	1.0
Second quartile	33.2 (22.6–46.8)	0.87 (0.58–1.30)		23.8 (15.8–33.8)	0.85 (0.56–1.27)		18.3 (12.5–25.7)	1.04 (0.70–1.56)	
Third quartile	118.1 (88.6–154.9)	0.92 (0.63–1.35)		78.9 (60.5–103.6)	0.96 (0.65–1.43)		66.0 (49.1–85.9)	1.21 (0.82–1.79)	
Fourth quartile	410.7 (280.2–699.9)	0.83 (0.57–1.20)		256.4 (182.7–413.6)	1.22 (0.85–1.75)		227.0 (158.8–376.4)	1.27 (0.86–1.87)	
Time over threshold (min)									
First quartile	1.2 (0.6–1.9)	0.91 (0.60–1.39)	1.0	1.2 (0.6–1.8)	1.19 (0.82–1.71)	1.0	1.0 (0.5–1.5)	0.99 (0.68–1.44)	1.0
Second quartile	4.3 (3.4–5.3)	0.93 (0.62–1.38)		4.2 (3.3–5.2)	0.91 (0.61–1.35)		3.5 (2.8–4.4)	1.11 (0.74–1.64)	
Third quartile	9.9 (8–12.2)	0.82 (0.55–1.22)		9.7 (7.8–11.8)	0.95 (0.64–1.41)		8.4 (6.7–10.5)	1.23 (0.84–1.82)	
Fourth quartile	27.0 (19.8–41.1)	0.80 (0.56–1.16)		24.7 (18.4–37.0)	1.07 (0.74–1.56)		24.2 (17.5–37.7)	1.23 (0.83–1.83)	
Pressure over threshold + threshold pressure (mmHg)*									
First quartile	165.5 (164.5–166.6)	0.95 (0.63–1.42)	1.0	120.7 (120.0–121.5)	0.90 (0.61–1.33)	1.0	96.5 (96.0–97.3)	1.04 (0.71–1.53)	1.0
Second quartile	170 (168.8–171.0)	0.68 (0.45–1.04)		123.8 (123.0–124.6)	1.06 (0.72–1.55)		99.5 (98.7–100.2)	1.12 (0.75–1.67)	
Third quartile	174.8 (173.5–176.4)	0.77 (0.52–1.16)		127.2 (126.3–128.3)	1.10 (0.75–1.61)		102.6 (101.7–103.6)	0.96 (0.63–1.45)	
Fourth quartile	183.2 (180.3–187.9)	1.02 (0.71–1.46)		133.4 (131.1–137.0)	1.09 (0.75–1.58)		108.5 (106.3–112.7)	1.39 (0.96–1.99)	

* Thresholds were established in relationship to the population mean ± 2 SDs of the mean. To make the pressure values more clinically meaningful, we have summed the pressure under the threshold value with the threshold value. † The Bonferroni method was used to adjust for the 18 multiple comparisons, and bolded adjusted *P* values are less than or equal to 0.05.

IQR = interquartile range; OR = odds ratio.

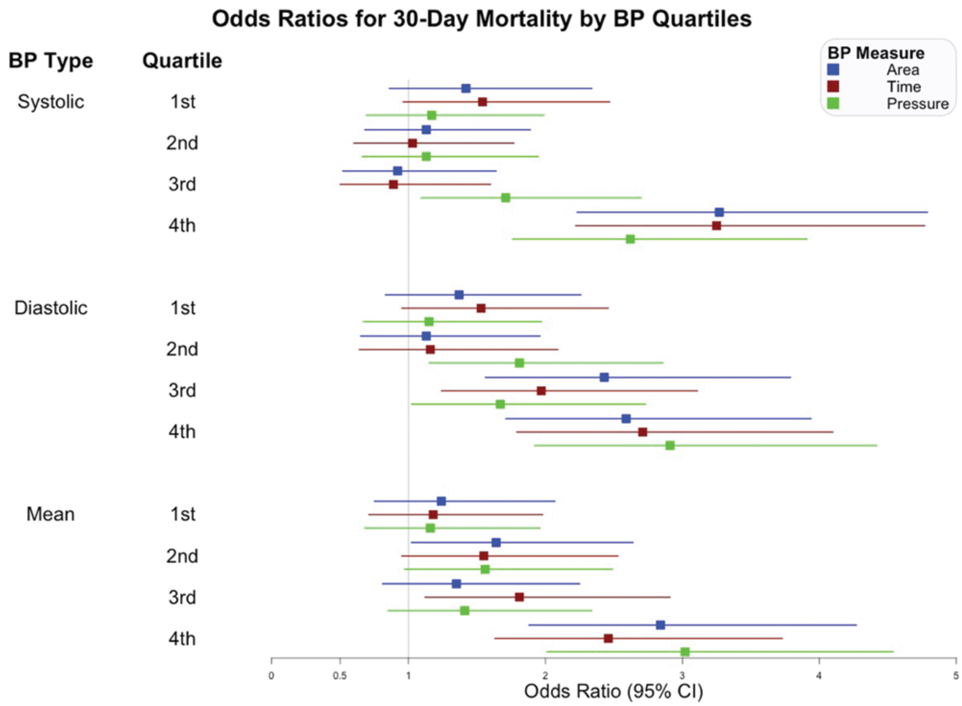

Fig. 3. Forest plots depicting odds ratios and 95% CI for the association between population-based blood pressure (BP) thresholds for hypotension and 30-day operative mortality.

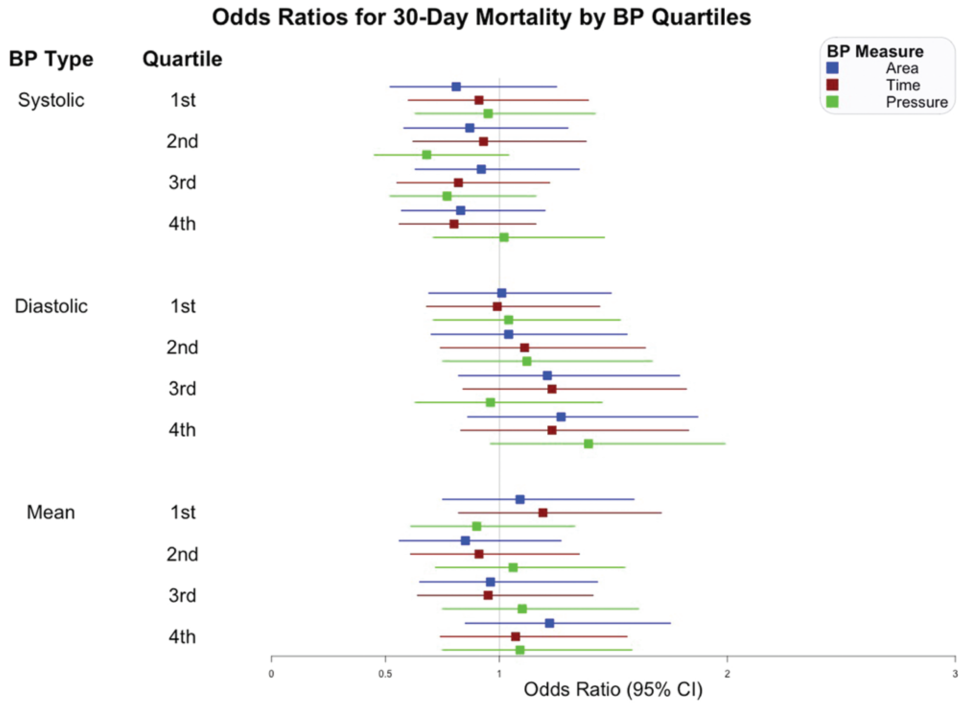

Fig. 4. Forest plots depicting odds ratios and 95% CI for the association between population-based blood pressure (BP) thresholds for hypertension and 30-day operative mortality.

baseline blood pressure, a significant association between mortality and relative reduction from baseline was only seen for MAP decreases of more than 50% for more than or equal to 5 min (table 5). Each of the first two methods arrived at similar magnitudes and duration of hypotension associated with increased mortality (SBP < 67 to 70 mmHg for >5 to 8 min, MAP < 49 mmHg for 4 to 5 min, and DBP < 30 to 33 mmHg for >4 to 5 min). None of the three methods showed a significant association between hypertension and operative mortality. We believe the third method (percent change from

Table 4. Patient Counts, 30-day Mortality Rates, and Adjusted Odds Ratios for Absolute Thresholds (n = 18,756)

	Unadjusted		Risk Adjusted*	
Threshold	Total Patients	Death (%)	OR (95% CI)	*P* Value
Systolic absolute threshold				
Reference (90–159 mmHg)	2,728	25 (0.92)		**<0.0001**
SBP 80–89 mmHg for 2–4.9 min	1,936	37 (1.91)	1.092 (0.632–1.888)	
SBP 80–89 mmHg for >5 min	3,718	57 (1.53)	1.063 (0.640–1.764)	
SBP 70–79 mmHg for 2–4.9 min	2,361	41 (1.74)	0.889 (0.518–1.524)	
SBP 70–79 mmHg for >5 min	1,954	31 (1.59)	0.953 (0.539–1.682)	
SBP < 70 mmHg for 2–4.9 min	1,553	39 (2.51)	1.377 (0.795–2.385)	
SBP < 70 mmHg for >5 min	961	57 (5.93)	**2.898 (1.719–4.886)**	
Reference (90–159 mmHg)	2,728	25 (0.92)		1.0
SBP 160–169 mmHg for 2–4.9 min	1,607	32 (1.99)	1.277 (0.726–2.247)	
SBP 160–169 mmHg for >5 min	1,048	18 (1.72)	0.984 (0.513–1.887)	
SBP 170–179 mmHg for 2–4.9 min	1,490	16 (1.07)	0.560 (0.287–1.094)	
SBP 170–179 mmHg for >5 min	745	14 (1.88)	0.816 (0.405–1.643)	
SBP > 180 mmHg for 2–4.9 min	2,245	43 (1.92)	0.988 (0.578–1.690)	
SBP > 180 mmHg for >5 min	2,919	63 (2.16)	0.904 (0.545–1.500)	
Mean absolute threshold				
Reference (60–109 mmHg)	2,906	48 (1.65)		**<0.0001**
MAP 50–59 mmHg for 2–4.9 min	2,136	51 (2.39)	1.093 (0.704–1.697)	
MAP 50–59 mmHg for >5 min	2,239	54 (2.41)	1.083 (0.698–1.681)	
MAP 40–49 mmHg for 2–4.9 min	730	19 (2.60)	1.232 (0.677–2.242)	
MAP 40–49 mmHg for >5 min	352	17 (4.83)	**2.433 (1.285–4.608)**	
MAP < 40 mmHg for 2–4.9 min	102	7 (6.86)	2.415 (0.965–6.047)	
MAP < 40 mmHg for >5 min	39	14 (35.9)	**20.826 (8.884–48.822)**	
Reference (60–109 mmHg)	2,906	48 (1.65)		1.0
MAP 110–119 mmHg for 2–4.9 min	1,738	30 (1.73)	0.807 (0.490–1.328)	
MAP 110–119 mmHg for >5 min	2,347	27 (1.15)	0.685 (0.414–1.135)	
MAP 120–129 mmHg for 2–4.9 min	2,095	36 (1.72)	0.913 (0.569–1.465)	
MAP 120–129 mmHg for >5 min	1,770	20 (1.13)	0.577 (0.331–1.003)	
MAP > 130 mmHg for 2–4.9 min	2,782	47 (1.69)	0.900 (0.580–1.397)	
MAP > 130 mmHg for >5 min	3,333	60 (1.80)	0.947 (0.624–1.435)	
Diastolic absolute threshold				
Reference (50–99 mmHg)	3,171	39 (1.23)		**<0.001**
DBP 40–49 mmHg for 2–4.9 min	1,883	29 (1.54)	1.120 (0.670–1.871)	
DBP 40–49 mmHg for >5 min	4,677	74 (1.58)	0.960 (0.631–1.461)	
DBP 30–39 mmHg for 2–4.9 min	1,831	51 (2.79)	1.571 (0.991–2.491)	
DBP 30–39 mmHg for >5 min	2,188	59 (2.70)	1.391 (0.890–2.172)	
DBP < 30 mmHg for 2–4.9 min	755	21 (2.78)	1.645 (0.918–2.948)	
DBP < 30 mmHg for >5 min	508	28 (5.51)	**3.181 (1.826–5.540**)	
Reference (50–99 mmHg)	3,171	39 (1.23)		1.0
DBP 100–109 mmHg for 2–4.9 min	1,952	32 (1.64)	1.269 (0.761–2.118)	
DBP 100–109 mmHg for > 5 min	1,401	16 (1.14)	0.681 (0.359–1.292)	
DBP 110–119 mmHg for 2–4.9 min	1,459	22 (1.51)	1.166 (0.659–2.063)	
DBP 110–119 mmHg for >5 min	630	6 (0.95)	0.788 (0.319–1.949)	
DBP > 120 mmHg for 2–4.9 min	1,431	23 (1.61)	1.075 (0.611–1.889)	
DBP > 120 mmHg for >5 min	729	16 (2.19)	1.357 (0.714–2.580)	

* The Bonferroni method was used to adjust for the six multiple comparisons, and bolded adjusted *P* values are less than or equal to 0.05.
DBP = diastolic blood pressure; MAP = mean blood pressure; OR = odds ratio; SBP = systolic blood pressure.

baseline) is flawed because almost a third of procedures had no baseline or only a single blood pressure recorded in the AIMS data, and patients with baseline blood pressure measurements tended to have fewer preoperative risk factors and were more likely to be having elective surgery compared with those without baseline blood pressure measurements.

Table 5. Patient Counts, 30-day Mortality Rates, and Adjusted Odds Ratios for Percent Change from Baseline Thresholds (n = 12,675)

	Unadjusted		Risk Adjusted*	
Threshold	Total Patients	Death (%)	OR (95% CI)	*P* Value
Percent change from baseline SBP				
Reference (≤ 29%)	2,288	23 (1.01)		
SBP decrease 30%–39% for 2–4.9 min	1,017	13 (1.28)	0.783 (0.379–1.618)	
SBP decrease 30%–39% for >5 min	2,665	25 (0.94)	0.568 (0.310–1.039)	
SBP decrease 40%–49% for 2–4.9 min	1,276	16 (1.25)	0.619 (0.311–1.231)	0.16
SBP decrease 40%–49% for >5 min	2,124	33 (1.55)	0.786 (0.439–1.405)	
SBP decrease ≥50% for 2–4.9 min	896	24 (2.68)	1.306 (0.701–2.436)	
SBP decrease ≥50% for >5 min	1,075	28 (2.60)	1.338 (0.738–2.423)	
Reference (≤ 29%)	2,288	23 (1.01)		
SBP increase 30%–39% for 2–4.9 min	981	25 (2.55)	1.428 (0.757–2.693)	
SBP increase 30%–39% for > 5 min	489	5 (1.02)	0.581 (0.208–1.619)	
SBP increase 40%–49% for 2–4.9 min	623	7 (1.12)	0.560 (0.224–1.400)	1.0
SBP increase 40%–49% for >5 min	274	4 (1.46)	0.769 (0.242–2.438)	
SBP increase ≥50% for 2–4.9 min	646	19 (2.94)	1.530 (0.764–3.063)	
SBP increase ≥50% for >5 min	542	18 (3.32)	1.307 (0.651–2.622)	
Percent change from baseline MBP				
Reference (<29%)	2,697	27 (1.00)		
MBP decrease 30–39% for 2–4.9 min	1,088	17 (1.56)	1.059 (0.551–2.035)	
MBP decrease 30–39% for >5 min	2,928	30 (1.02)	0.688 (0.394–1.204)	
MBP decrease 40–49% for 2–4.9 min	1,266	21 (1.66)	1.240 (0.671–2.293)	**0.005**
MBP decrease 40–49% for >5 min	1,924	28 (1.46)	0.999 (0.564–1.770)	
MBP decrease >50% for 2–4.9 min	627	15 (2.39)	1.421 (0.707–2.856)	
MBP decrease >50% for >5 min	656	25 (3.81)	**2.721 (1.489–4.974)**	
Reference (<29%)	2,697	27 (1.00)		
MBP increase 30–39% for 2–4.9 min	1,013	17 (1.68)	1.423 (0.724–2.796)	
MBP increase 30–39% for >5 min	511	8 (1.57)	1.179 (0.496–2.803)	
MBP increase 40–49% for 2–4.9 min	596	11 (1.85)	1.492 (0.683–3.260)	0.97
MBP increase 40–49% for >5 min	248	3 (1.21)	0.888 (0.246–3.199)	
MBP increase >50% for 2–4.9 min	587	13 (2.21)	1.653 (0.783–3.492)	
MBP increase >50% for >5 min	385	15 (3.90)	2.800 (1.376–5.694)	
Percent change from baseline DBP				
Reference (<29%)	1,520	13 (0.86)		
DBP decrease 30–39% for 2–4.9 min	953	7 (0.73)	0.648 (0.248–1.688)	
DBP decrease 30–39% for >5 min	2,335	22 (0.94)	0.987 (0.477–2.039)	
DBP decrease 40–49% for 2–4.9 min	1,239	23 (1.86)	1.560 (0.754–3.226)	0.06
DBP decrease 40–49% for >5 min	1,931	31 (1.61)	1.578 (0.790–3.150)	
DBP decrease >50% for 2–4.9 min	1,266	22 (1.74)	1.630 (0.782–3.397)	
DBP decrease >50% for >5 min	1,728	43 (2.49)	2.359 (1.204–4.625)	
Reference (<29%)	1,520	13 (0.86)		
DBP increase 30–39% for 2–4.9 min	1,159	17 (1.47)	1.464 (0.674–3.182)	
DBP increase 30–39% for >5 min	547	6 (1.10)	0.965 (0.345–2.700)	
DBP increase 40–49% for 2–4.9 min	795	9 (1.13)	1.216 (0.494–2.988)	1.0
DBP increase 40–49% for >5 min	307	5 (1.63)	1.287 (0.418–3.960)	
DBP increase >50% for 2–4.9 min	1,111	24 (2.16)	2.227 (1.069–4.639)	
DBP increase >50% for >5 min	879	21 (2.39)	1.975 (0.934–4.174)	

* The Bonferroni method was used to adjust for the six multiple comparisons, and bolded adjusted *P* values are less than or equal to 0.05.
DBP = diastolic blood pressure; MBP = mean blood pressure; OR = odds ratio; SBP = systolic blood pressure.

Comparison with Previous Studies

Anesthesia providers have long assumed that a smooth intraoperative course with minimal blood pressure aberrations is associated with better postoperative outcomes.[26] However, there is limited and conflicting evidence to support this assumption. In 1978, Goldman *et al.*[2] reported in a multivariable analysis that a more than 33% decrease from baseline for more than 10 min in intraoperative SBP was associated with postoperative cardiac death. In 1990, Charlson *et al.*[3] reported that prolonged increases or decreases in intraoperative MAP > 20 mmHg resulted in an increase in serious postoperative complications. Bijker *et al.*[22] found no association between intraoperative hypotension and risk-adjusted 1-yr mortality after general or vascular surgery in 1,705 adults. Monk *et al.*[5] reported a statistically significant association between duration of SBP < 80 mmHg and 1-yr risk-adjusted mortality in 1,064 patients undergoing major noncardiac surgery. In the largest (33,330 noncardiac surgeries) and most recently published study, Walsh *et al.*[7] reported that patients with a MAP < 55 mmHg for 1 to 5, 6 to 10, 11 to 20, and more than 20 min had graded increases in their risk for acute kidney injury or myocardial injury.

Strengths

Population-based Thresholds. In a systematic literature review, Bijker *et al.*[9] identified 140 different definitions of intraoperative hypotension. This plethora of definitions led us to the concept that intraoperative blood pressure thresholds should be population based and that definitions of intraoperative hypotension and hypertension should be based on the association of deviations from these thresholds. We defined the thresholds for hypotension and hypertension as 2 SDs below and above the population mean, respectively. We hypothesized that the adverse effects from both hypotension and hypertension were likely due to both the magnitude of the deviations from these thresholds and the duration of these deviations. One way to capture both magnitude and duration is the area between the threshold and the pressure curve, which has units of mmHg × minutes. We also assumed that any adverse effect of these deviations is additive if the patient has more than one deviation (as is common) during the operation; thus, we summed these areas. Finally, we assumed that hypotension and hypertension were likely to have different effects on operative mortality as their pathophysiologic effects are very different; therefore, we tested separate hypotheses for hypotension and hypertension.

Similar Results with Two Analytic Techniques. The estimation of the magnitude and duration of hypotension significantly associated with increased 30-day mortality was virtually identical between population-based thresholds and the absolute thresholds. However, the results based on the blood pressure thresholds relative to each patient's baseline blood pressure seem to be much less sensitive in detecting an association with mortality. There are several factors that might explain this difference between the techniques: (1) approximately 31% of the patients did not have a baseline blood pressure measurement in the AIMS data and were not included in this analysis; (2) patients with baseline blood pressure measurements differed from those without in ways that suggest lower risk (*e.g.*, fewer preoperative risk factors and greater likelihood of having elective surgery compared with those without baseline blood pressures); and (3) preoperative anxiety may have resulted in higher baseline blood pressures. This phenomenon of "white coat" hypertension has been well studied in ambulatory care and is usually felt to be benign.[27] Regardless, we did not find a statistically significant risk-adjusted increase in mortality with intraoperative hypertension with any of our three analytic methods. Despite these limitations, we included the percent change from baseline technique because a decrease in SBP of more than 20 to 30% below baseline is one of the most frequently used definitions of intraoperative hypotension in the literature.[9] Bijker *et al.*[9] reviewed 111 definitions of intraoperative hypotension and found that only 50% of the manuscripts actually defined the baseline blood pressure, and in those that did, baseline blood pressure was most frequently based on the blood pressure measurements taken immediately before the induction of anesthesia. A previous publication also stated that a prolonged intraoperative change of 20% from preoperative blood pressure levels was significantly related to complications.[3] In our analysis, we also defined the baseline blood pressure as the mean blood pressures in the operating room immediately before the appearance of end-tidal carbon dioxide. The lack of agreement of this technique with the population-based and absolute threshold technique suggests that the percent change from baseline technique is flawed, most likely because it is extremely difficult to define valid, reproducible baseline blood pressure, especially if it is based on blood pressures obtained in the operating room.

Large Sample Size. Our sample size of 18,756 is one of the largest we have identified in the literature, exceeded only by the study by Walsh *et al.*,[7] which studied 33,330 noncardiac surgeries at the Cleveland Clinic. They reported a significantly increased risk of 30-day mortality with a MAP < 55 mmHg for more than 20 min, which differs only modestly with our finding of an increased risk for MAP ≤ 49 mmHg for more than 5 min.[7]

Risk-adjusted Outcomes. By using the risk factors in the VASQIP database, the c-index for predicting 30-day postoperative mortality in our model was 0.91. We found that the addition of blood pressure variables or intraoperative sepsis and erythrocyte transfusion to this robust risk model did not appreciably change the c-index, suggesting that preoperative comorbidity, not intraoperative anesthesia management, is the major predictor of mortality after noncardiac surgery.

Limitations

First and most importantly, this is an observational study and therefore can only address association and not causality. Despite our risk adjustment model based on more than 20 yr experience with risk-adjusting surgical outcomes in the VASQIP program, the probability of bias (*i.e.*, that the larger proportion of patients dying within 30 days in the more severely hypotensive groups were at a greater risk to begin with because of unmeasured variables) remains, as in all observational studies. Hypotension may be a marker of other direct causes of death (*i.e.*, hemorrhage, sepsis, frailty), and it is unknown whether interventions to improve or maintain blood pressure would improve outcome. Although the usual response to this uncertainty is to conduct a randomized trial, we agree with the statement by Freundlich and Kheterpal,[28] "it is ethically – and morally – not feasible to randomly assign patients to a potentially detrimental intervention that deviates from accepted standards of care." We acknowledge that randomized trials of deliberate hypotensive anesthesia have been conducted in the past, but these patient populations were generally healthy.[29,30] Currently, it would likely be impossible to obtain IRB approval for such trials.

A second limitation is the nonrepresentative nature of the patients in this analysis who received their surgery in VA hospitals. Patients who use the VA health services tend to be predominately male, older, less well educated, sicker, and of lower socioeconomic status than the overall U.S. population as a whole.[31] Therefore, it is possible that these differences between VA and U.S. populations limit the generalizability of our findings to non-VA populations.

Another limitation is that the data for this study were collected between 2001 and 2008, and anesthesia practice has changed since 2001. To adjust the analysis for secular trends in practices, the year of surgery was included in the model, but the results were not changed. The c-index for predicting 30-day mortality using only VASQIP preoperative patient characteristics was already high at 0.908, and the addition of additional variables such as year of surgery or intraoperative blood pressure variables did not appreciably change the predictive power of the model. This finding is in agreement with previous studies demonstrating that the patient's preoperative comorbidities are the most important determinants of intermediate- and long-term mortality.[5,32]

Clinical Implications

When our results are combined with the findings of Walsh *et al.*[7] we believe that there is strong evidence that intraoperative hypotension, namely SBP < 70 mmHg, MAP < 50 mmHg, and DBP < 30 mmHg, is associated with excess operative morbidity and mortality. The only evidence-based guideline, from the American Society of Anesthesiologists, for the management of intraoperative blood pressure states that blood pressure should be measured intraoperatively at least at 5-min intervals. Clearly, additional guidelines should be developed, but first, confirmatory data from a third observational study with a population of 50,000 to 100,000 operations are needed. Fortunately, a study of this size may soon be feasible with electronic information management of AIMS datasets and risk and outcome datasets, such as VASQIP.

Acknowledgments

This study is supported by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development Grant Number IIR 05-229, Washington, D.C.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Monk: Department of Anesthesiology and Perioperative Medicine, One Hospital Drive, 3w-27F, DC005.00, Columbia, Missouri 65212. monkt@health.missouri.edu. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. 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
2. Goldman L, Caldera DL, Southwick FS, Nussbaum SR, Murray B, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Burke DS, Krogstad D, Carabello B, Slater EE: Cardiac risk factors and complications in non-cardiac surgery. Medicine (Baltimore) 1978; 57:357–70
3. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT: Intraoperative blood pressure. What patterns identify patients at risk for postoperative complications? Ann Surg 1990; 212:567–80
4. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M: Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. Anesth Analg 2002; 95:273–7
5. Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100:4–10
6. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. Anesthesiology 2012; 116:658–64
7. 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
8. Warner MA, Monk TG: The impact of lack of standardized definitions on the specialty. Anesthesiology 2007; 107:198–9
9. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007; 107:213–20
10. Standards and Practice Parameters Committee. Standards for basic anesthetic monitoring. Available at: http://www.asahq.org. Accessed February 20, 2014
11. Muravchick S, Caldwell JE, Epstein RH, Galati M, Levy WJ, O'Reilly M, Plagenhoef JS, Rehman M, Reich DL, Vigoda MM: Anesthesia information management system implementation: A practical guide. Anesth Analg 2008; 107:1598–608
12. Khuri SF, Daley J, Henderson W, Barbour G, Lowry P, Irvin G, Gibbs J, Grover F, Hammermeister K, Stremple JF: The National Veterans Administration Surgical Risk Study: Risk adjustment for the comparative assessment of the quality of surgical care. J Am Coll Surg 1995; 180:519–31
13. Daley J, Khuri SF, Henderson W, Hur K, Gibbs JO, Barbour G, Demakis J, Irvin G III, Stremple JF, Grover F, McDonald G, Passaro E Jr, Fabri PJ, Spencer J, Hammermeister K, Aust JB, Oprian C: Risk adjustment of the postoperative morbidity rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997; 185:328–40

14. Daley J, Forbes MG, Young GJ, Charns MP, Gibbs JO, Hur K, Henderson W, Khuri SF: Validating risk-adjusted surgical outcomes: Site visit assessment of process and structure. National VA Surgical Risk Study. J Am Coll Surg 1997; 185:341–51
15. Khuri SF, Daley J, Henderson W, Hur K, Gibbs JO, Barbour G, Demakis J, Irvin G III, Stremple JF, Grover F, McDonald G, Passaro E Jr, Fabri PJ, Spencer J, Hammermeister K, Aust JB: Risk adjustment of the postoperative mortality rate for the comparative assessment of the quality of surgical care: Results of the National Veterans Affairs Surgical Risk Study. J Am Coll Surg 1997; 185:315–27
16. Khuri SF, Daley J, Henderson W, Hur K, Demakis J, Aust JB, Chong V, Fabri PJ, Gibbs JO, Grover F, Hammermeister K, Irvin G III, McDonald G, Passaro E Jr, Phillips L, Scamman F, Spencer J, Stremple JF: The Department of Veterans Affairs' NSQIP: The first national, validated, outcome-based, risk-adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. National VA Surgical Quality Improvement Program. Ann Surg 1998; 228:491–507
17. Davis CL, Pierce JR, Henderson W, Spencer CD, Tyler C, Langberg R, Swafford J, Felan GS, Kearns MA, Booker B: Assessment of the reliability of data collected for the Department of Veterans Affairs national surgical quality improvement program. J Am Coll Surg 2007; 204:550–60
18. Arnold N: Improving Mortality Ascertainment Using the VA Vital Status File. 2009–2010 VIReC Database and Methods Cyber Seminar Series. Hines, Illinois, VA Information Resource Center (VIReC), U.S. Department of Veterans Affairs
19. Sohn MW, Arnold N, Maynard C, Hynes DM: Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006; 4:2
20. International Federation of Clinical Chemistry, Scientific Committee, Clinical Section. Expert Panel on Theory of Reference Values (EPTRV). The theory of reference values. Part 5. Statistical treatment of collected reference values. Determination of reference limits. Clin Chem Acta 1984; 137:97F–114F
21. Reich DL, Bodian CA, Krol M, Kuroda M, Osinski T, Thys DM: Intraoperative hemodynamic predictors of mortality, stroke, and myocardial infarction after coronary artery bypass surgery. Anesth Analg 1999; 89:814–22
22. 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
23. Buck SF: A method of estimation of missing values in multivariate data suitable for use with an electronic computer. J Roy Stat Soc 1960; 22:302–7
24. Roberts JS, Capalbo GM: A SAS macro for estimating missing values in multivariate data. Proceedings of the 12th Annual SAS User's Group International Conference. Cary, SAS Institute Inc, 1987, 939–1
25. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M; STROBE Initiative: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. Ann Intern Med 2007; 147:W163–94
26. Reich DL, Fischer GW: Perioperative interventions to modify risk of morbidity and mortality. Semin Cardiothorac Vasc Anesth 2007; 11:224–30
27. Howell SJ, Sear JW, Foëx P: Hypertension, hypertensive heart disease and perioperative cardiac risk. Br J Anaesth 2004; 92:570–83
28. Freundlich RE, Kheterpal S: Perioperative effectiveness research using large databases. Best Pract Res Clin Anaesthesiol 2011; 25:489–98
29. Townes BD, Dikmen SS, Bledsoe SW, Hornbein TF, Martin DC, Janesheski JA: Neuropsychological changes in a young, healthy population after controlled hypotensive anesthesia. Anesth Analg 1986; 65:955–9
30. Williams-Russo P, Sharrock NE, Mattis S, Liguori GA, Mancuso C, Peterson MG, Hollenberg J, Ranawat C, Salvati E, Sculco T: Randomized trial of hypotensive epidural anesthesia in older adults. Anesthesiology 1999; 91:926–35
31. Agha Z, Lofgren RP, VanRuiswyk JV, Layde PM: Are patients at Veterans Affairs Medical Centers sicker? A comparative analysis of health status and medical resource use. Arch Intern Med 2000; 160:3252–7
32. Vacanti CJ, VanHouten RJ, Hill RC: A statistical analysis of the relationship of physical status to postoperative mortality in 68,388 cases. Anesth Analg 1970; 49:564–6