Intraoperative Mean Arterial Pressure Variability and 30-day Mortality in Patients Having Noncardiac Surgery

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ABSTRACT

Background: Little is known about the relationship between intraoperative blood pressure variability and mortality after noncardiac surgery. Therefore, the authors tested the hypothesis that blood pressure variability, independent from absolute blood pressure, is associated with increased 30-day mortality.

Methods: Baseline and intraoperative variables plus 30-day mortality were obtained for 104,401 adults having noncardiac surgery lasting 60 min or longer. In confounder-adjusted models, the authors evaluated the associations between 30-day mortality and both time-weighted average intraoperative mean arterial pressure (TWA-MAP) and measures of intraoperative MAP variability—including generalized average real variability of MAP (ARV-MAP) and SD of MAP (SD-MAP).

Results: Mean ± SD TWA-MAP was 84 ± 10 mmHg, and ARV-MAP was 2.5 ± 1.3 mmHg/min. TWA-MAP was strongly related to 30-day mortality, which more than tripled as TWA-MAP decreased from 80 to 50 mmHg. ARV-MAP was only marginally related to 30-day mortality (P = 0.033) after adjusting for TWA-MAP. Compared with median ARV-MAP, odds ratio (95% CI) for 30-day mortality was 1.14 (1.03 to 1.25) for low ARV-MAP (first quartile) and 0.94 (0.88 to 0.99) for high ARV-MAP (third quartile). Odds of 30-day mortality decreased as five-level categorized ARV-MAP increased (0.92; 0.87 to 0.99 for one category increase; P = 0.015). Secondarily, cumulative duration of MAP less than 50, 55, 60, 70, and 80 mmHg was associated with increased odds of 30-day mortality (all P < 0.001).

Conclusion: Although lower mean arterial pressure is strongly associated with mortality, *lower* intraoperative blood pressure variability *per se* is only mildly associated with postoperative mortality after noncardiac surgery. **(ANESTHESIOLOGY 2015; 123:79-91)**

ALTHOUGH the relationship between mean blood pressure and organ damage or death[1–4] is well established, there is also some evidence for a relationship between blood pressure variability and death or organ damage.[1,2,5–7] For example, in a study of approximately 9,000 ambulatory patients, Hansen *et al.*[8] found that higher 24-h variability in systolic blood pressure (SBP) was significantly associated with long-term mortality and cardiovascular events after adjusting for mean blood pressure although including it did not substantially change predicted values for mortality. Control of variability in blood pressure is also thought to reduce morbidity or mortality, leading some investigators to suggest that longer-acting perioperative antihypertensive drugs may be preferable to shorter-acting drugs.[7,9]

A correlation between mean blood pressure and subsequent cardiovascular events has been observed in medical[7] and surgical[10,11] patients. In addition, recent studies have found that intraoperative excursions in SBP outside of a targeted range (measured by magnitude × duration, *i.e.*, area under the curve) were associated with 30-day mortality in cardiac surgery patients.[12,13] However, such hypotensive and hypertensive indices measure the average level of the blood pressure rather than reading-to-reading

What We Already Know about This Topic

- Recent studies have found that intraoperative excursions in systolic blood pressure outside of a targeted range were associated with 30-day mortality in cardiac surgery patients.
- However, such hypotensive and hypertensive indices measure the average level of the blood pressure rather than reading-to-reading variability. The relationship between blood pressure variability *per se* (distinct from mean blood pressure) and mortality remains unclear in noncardiac surgical patients.
- This study determined whether patient variability in mean arterial pressure, independent of time-weighted average mean arterial pressure and other confounding variables, is associated with 30-day postoperative mortality in patients having noncardiac surgery.

What This Article Tells Us That Is New

- Average mean arterial pressure and mean pressure variability were nonlinearly related to 30-day mortality in noncardiac surgical patients. After adjusting for time-weighted average mean arterial pressure and other important covariables, low blood pressure variability as measured by an improved formula was still associated with higher 30-day mortality, but the differences were not clinically important. Anesthesiologists might thus pay more attention to overall trends in the mean blood pressure for a case than in the minute-to-minute variation.

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variability. The relationship between blood pressure variability *per se* (distinct from mean blood pressure) and mortality remains unclear in noncardiac surgical patients. In fact, some intraoperative variability may indicate healthy autonomic control. A constant blood pressure, either very high or very low, might indicate issues with perfusion of the patient, important fluid imbalances, or other problems.

We therefore tested the hypothesis that patient variability in mean arterial pressure (MAP), independent of time-weighted average MAP (TWA-MAP) and other confounding variables, is associated with 30-day postoperative mortality in patients having noncardiac surgery.

Materials and Methods

With institutional review board approval (Cleveland Clinic Institutional Review Board, Cleveland, Ohio), we extracted data on 140,312 adult patients with noncardiac surgery and American Society of Anesthesiologists physical status (ASA-PS) less than 5 between January 2005 and December 2012 from the Cleveland Clinic Perioperative Health Documentation System, which is an electronic medical record–based registry that pulls and merges data from various Cleveland Clinic electronic databases including EPIC (Epic Systems Corporation, USA), the anesthesia automated record keeping system (Talis Clinical, Inc., USA), billing data, laboratory data, pharmacy data, and others. Data are regularly scrutinized using range checks, cross-variable and table checks, and other data quality programs to assure good quality data for research.

Vital status was updated as of December 31, 2012. Only the longest lasting surgery was considered for patients who had more than one operation. Patients were excluded if their surgery duration (induction to emergence) was less than 60 min or missing baseline variables. We also excluded patients with inadequate information on blood pressure readings (periods of artifacts/unavailable data of >10 min or <6 measurements per hour). Thus, a total of 104,401 patients were included in the study.

Artifact Algorithm for Blood Pressure Measurements

Mean arterial pressure data from our monitors are stored in our automated record keeping system, in which MAP was recorded at 1-min intervals for patients with an arterial catheter and every 1 to 5 min for those with noninvasive blood pressure monitoring. Because electronic anesthesia records are known to contain considerable artifact, we removed artifacts using the following rules, in order: (1) blood pressure readings documented as artifacts; (2) out of range: values—if (a) SBP 300 mmHg or greater or SBP 20 mmHg or less, (b) SBP ≤ diastolic blood pressure (DBP) + 5 mmHg, or (c) DBP 5 mmHg or less or DBP 225 mmHg or more; and (3) abrupt change, defined as SBP change 80 mmHg or greater from last reading within 1 min in either direction, or abrupt SBP change 40 mmHg or greater within 1 min in both directions.

Blood Pressure Variability

There is no definitive standard for evaluating blood pressure variability although within-patient SD is most commonly used.[5,14] Hansen *et al.*[8] proposed an index of short-term reading-to-reading blood pressure variation called average real variability (ARV), calculated by the following formula (sum of the product of time between measurements and absolute change divided by total time):

$$\text{ARV} = \frac{1}{\sum t}\sum_{k=1}^{N-1} t\left|\text{BP}_{k+1} - \text{BP}_k\right| \quad (1)$$

where N is the number of blood pressure (BP) readings and t is the time interval between each set of readings, BP_k and BP_{k+1}.

Hansen *et al.* showed that the ARV more reliably estimates variability for time-series data than the SD. But a limitation is that Hansen's approach is only valid for equally distant blood pressure readings. For pressures at unequal intervals, this index overestimates the variability of steep changes. For example, consider five consecutive MAP readings of 50, 60, 70, 60, and 50 at 1-min intervals so that:

$$\text{ARV} = \frac{1|60-50|+1|70-60|+1|60-70|+1|50-60|}{1+1+1+1} = \frac{40}{4} = 10 \text{ mmHg/min}$$

Now consider the same patient, but with data recorded at 1, 3, 4, and 5 min, so

$$\text{ARV} = \frac{2|70-50|+1|70-60|+1|60-50|}{2+1+1} = \frac{60}{4} = 15 \text{ mmHg/min}$$

or 50% more variability compared with the same patient with blood pressure recorded each minute.

To avoid incorrect estimates resulting from unequal measurement periods, we propose (and use) a better ARV index, generalized ARV, which does not require equally distant data. We calculate it simply as the sum of the absolute value of all changes across measurements divided by total time:

$$\text{Generalized ARV} = \frac{1}{T}\sum_{k=1}^{N-1}\left|\text{BP}_{k+1} - \text{BP}_k\right| \text{ mmHg/min} \quad (2)$$

where T is the total time from first to last BP reading (equivalent to $\sum t$ in equation 1). In our example, generalized ARV is the same for both sets of the above data, demonstrating that the new measure is robust to varying distances between readings:

$$\text{Generalized ARV} = \frac{|60-50|+|70-60|+|60-70|+|50-60|}{1+1+1+1} = \frac{40}{4} = 10,$$

and

$$\text{Generalized ARV} = \frac{|70-50|+|60-70|+|50-60|}{2+1+1} = \frac{40}{4} = 10.$$

The units for ARV-MAP are mmHg/min, so an ARV-MAP of 1 would mean that the MAP changes (either up or down) on average approximately 1 mmHg between consecutive minutes during the case for a given patient. Hereafter, we refer to our measure of variability (equation 2) as generalized ARV, and when referring to its use with MAP data, generalized ARV–MAP.

Mena *et al.*[15] proposed an earlier version of the ARV that was calculated as the sum of absolute differences divided by the number of readings minus 1 or $\text{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1}|\text{BP}_{k+1} - \text{BP}_k|$. Although they found that it predicted cardiovascular events better than the SD index, the difficulty with this version of the ARV, as with the SD index (see next paragraph), is that it ignores the distance between the consecutive readings, and thus does not have a "change per minute" interpretation as does our generalized ARV.

For comparative purposes, we also report on the SD of MAP, or SD-MAP, as a measure of blood pressure variability. The difficulty with SD-MAP as a measure of variability is that it ignores the timing of the measurements. For example, SD-MAP for consecutive values of 60, 60, 80, 80, and 80 mmHg and 80, 60, 80, 60, and 80 mmHg has the same SD although the latter is obviously more variable. Generalized ARV analysis gives a value of 5 for the first set and 20 for the second set and thus clearly better estimating variability for the time series than the SD. Although we report SD-MAP as a measure of variability to facilitate comparisons with previous work, we do not consider it an optimal estimate of variability in sequential data.

Finally, to give more weight to steep changes (slope), we also consider a squared version of the generalized ARV called ARV_S, as follows:

$$\text{Squared ARV} = \frac{1}{T}\sum_{k=1}^{N-1}\frac{|\text{BP}_{k+1} - \text{BP}_k|^2}{t_{k+1} - t_k}. \quad (3)$$

In our example, we have for the 1-min data

$$\text{Squared ARV} = \frac{|60-50|^2+|70-60|^2+|60-70|^2+|50-60|^2}{1+1+1+1} = \frac{400}{4} = 100,$$

and for the mixed distance data

$$\frac{|70-50|^2+|60-70|^2+|50-60|^2}{2+1+1} = \frac{600}{4} = 150.$$

Because of the squared term, this ARV measure does not give the same result with equal and unequal data intervals. However, it does penalize large jumps and is thus a generally intuitive variability measure.

We *a priori* selected generalized ARV-MAP as our primary estimate of MAP variability, with SD-MAP and squared ARV-MAP as secondary indices.

As a measure of mean MAP across a case, we also calculated TWA-MAP for each patient's surgery. We assess its interplay with the relationship between blood pressure variability measures and 30-day mortality. TWA-MAP was calculated as the area under the curve of the MAP measurements divided by total measurement time (note that the area under the curve alone is insufficient because it ignores total time). TWA-MAP is equal to the mean of all measurements when all data are equidistant and is more accurate than a simple mean when the readings are not all equidistant,[16] as in most intraoperative data. TWA-MAP is thus not an estimate of variability but rather a measure of patient severity or average level (see Discussion).

Statistical Analysis

We first assessed the relationship between categories (for display purposes) of generalized ARV-MAP and all baseline characteristics, medical history, and important surgical factors by using chi-square tests and ANOVA.

In our multivariable models, we adjusted for all confounding variables in table 1. We defined preexisting medical conditions used International Classification of Diseases, Ninth Revision (ICD-9) billing codes and included only those fulfilling at least one of the following (1) appeared in the patient "problem list" with a date preceding the date of surgery, (2) appeared in an ICD-9 list before the index surgery, or (3) were flagged as a chronic ICD-9 condition based on the Healthcare Cost and Utilization Project definitions.[17] Because there were many types of surgical procedures, we characterized each procedure code into 1 of 244 clinically meaningful categories using the Agency for Healthcare Research and Quality's Clinical Classifications Software for Services and Procedures. We then aggregated low-frequency-event categories (N <5 death) into one group and used that as the reference group (a low-risk group). Pearson correlation coefficient was used to assess the correlations among the three variability measures (generalized ARV, SD, and squared ARV) and TWA of MAP. Discrimination (ability to discriminate events from nonevents) of models was assessed with the *c*-statistic; several model diagnostics were assessed as well.

We used univariable and multivariable logistic regression models to assess the relationship between 30-day mortality and each of generalized ARV-MAP, SD-MAP, squared ARV, and TWA-MAP. We assessed the linearity of the relationship between each exposure and 30-day mortality using a restricted cubic spline function with three knots (located at 10th, 50th, and 90th percentiles).[18] Because all relationships were nonlinear, we used continuous versions of each exposure with a restricted cubic spline function (three knots) as our primary analyses. A restricted cubic spline function was used to obtain

Table 1. Baseline Characteristics and Intraoperative Factors by Generalized Average Real Variability of MAP

Potential Confounding Variables	Average Real Variability of MAP (mmHg/min)* ≤1 (n = 7,651)	1–2 (n = 34,531)	2–3 (n = 30,749)	3–4 (n = 18,354)	>4 (n = 13,202)	*P* Value
Female (%)	53.3	55.6	51.6	51.4	54.8	<0.001
Age (yr)	47 ± 16	52 ± 19	57 ± 19	61 ± 14	66 ± 22	<0.001
Weight (kg)	82 ± 23	85 ± 25	86 ± 24	85 ± 24	82 ± 22	<0.001
White (%)	83.5	83.3	83.3	83.5	81.9	<0.001
Emergency (%)	1.9	3.0	4.7	5.9	7.7	<0.001
ASA physical status (%)						<0.001
1	18.0	8.6	3.3	1.5	0.6	
2	52.7	50.9	39.9	30.1	20.1	
3	26.4	36.7	48.8	57.1	64.0	
4	2.9	3.8	7.9	11.3	15.3	
Use of arterial catheter (%)	0.6	8.5	37.5	61.2	74.5	<0.001
Medical history (%)						
Congestive heart failure	2.8	3.1	5.3	6.9	8.1	<0.001
Valvular disease	2.9	3.4	4.5	5.7	7.3	<0.001
Pulmonary circulation disease	0.7	0.9	1.6	1.8	2.2	<0.001
Peripheral vascular disease	2.7	3.6	7.2	11.3	17.4	<0.001
Hypertension	27.2	38.0	50.1	59.0	68.9	<0.001
Paralysis	1.1	1.5	2.2	2.7	4.2	<0.001
Other neurological disorders	3.5	4.7	6.4	6.9	8.5	<0.001
Chronic pulmonary disease	10.1	11.5	13.2	15.5	18.5	<0.001
Diabetes	9.9	12.9	17.3	20.6	23.1	<0.001
Hypothyroidism	8.1	9.9	11.2	12.3	13.9	<0.001
Renal failure	5.0	4.9	6.7	7.3	8.4	<0.001
Liver disease	2.4	3.9	4.5	4.4	3.6	<0.001
Lymphoma	1.3	1.3	1.5	1.6	1.7	<0.001
Metastatic cancer	3.5	4.0	6.3	8.9	9.0	<0.001
Solid tumor without metastasis	10.8	15.2	21.1	22.6	19.9	<0.001
Rheumatoid arthritis/collagen	3.0	3.1	3.5	3.6	4.5	<0.001
Coagulopathy	2.5	2.9	5.5	7.3	8.3	<0.001
Weight loss	1.7	2.6	4.6	6.5	6.9	<0.001
Fluid and electrolyte disorders	0.1	0.2	0.3	0.4	0.4	<0.001
Chronic blood loss anemia	0.7	1.2	1.9	2.4	2.7	<0.001
Deficiency anemia	2.5	2.6	3.2	3.3	3.6	<0.001
Alcohol abuse	1.1	1.3	1.9	2.3	2.2	<0.001
Drug abuse	1.0	0.9	1.0	1.0	1.1	0.34
Psychoses	2.2	2.8	2.8	3.0	3.0	<0.001
Depression	10.5	11.6	12.5	12.7	12.7	<0.001
Hyperlipidemia	21.8	26.6	32.6	37.3	43.6	<0.001
Coronary heart disease	5.9	7.9	13.8	19.6	27.2	<0.001
Cardiac rhythms	5.7	7.6	11.6	14.2	17.2	<0.001
Myocardial infarction	0.4	0.5	1.0	1.4	2.3	<0.001
Transient ischemic attack	0.2	0.3	0.5	0.7	1.2	<0.001
Seizure	0.1	0.1	0.2	0.2	0.2	0.027
Stroke	0.1	0.2	0.6	1.0	2.8	<0.001
Top 10 surgical procedures (%)						<0.001
Other*	50.4	38.8	28.4	21.9	19.1	
Colorectal resection	1.0	3.9	5.2	5.6	5.4	
Arthroplasty knee	9.3	5.7	2.6	1.3	0.9	
Nephrectomy	0.8	2.1	4.6	6.2	3.3	
Spinal fusion	0.5	2.0	4.4	5.6	5.0	
Other OR upper GI therapeutic procedures	1.5	4.3	3.7	3.0	2.2	
Hysterectomy	1.9	4.4	3.6	2.3	2.0	
Laminectomy	2.7	3.2	3.0	2.8	2.4	
Hip replacement	2.8	3.3	2.7	2.4	2.7	
Incision and excision of CNS	0.3	1.5	3.1	3.7	4.3	
Surgical time (h)	2.4 [1.7, 4.4]	2.7 [1.9, 3.8]	3.0 [2, 4.4]	3.2 [2, 4.7]	2.8 [1.8, 4]	<0.001

(*Continued*)

Table 1. Continued

Potential Confounding Variables	Average Real Variability of MAP (mmHg/min)* ≤1 (n = 7,651)	1–2 (n = 34,531)	2–3 (n = 30,749)	3–4 (n = 18,354)	>4 (n = 13,202)	*P* Value
Exposure variables						
TWA-MAP, mmHg	79 ± 9	82 ± 10	84 ± 10	85 ± 10	87 ± 10	<0.001
ARV-MAP, mmHg/min	0.8 ± 0.1	1.5 ± 0.3	2.5 ± 0.3	3.4 ± 0.3	5.0 ± 1.0	<0.001
SD-MAP, mmHg/min	6.9 ± 2.5	10.4 ± 3.1	12.6 ± 3.6	14.0 ± 4.0	16.4 ± 4.5	<0.001
Squared ARV-MAP, $mmHg^2$/min	1.4 [1, 1.8]	5.1 [3.5,7.2]	14 [11, 19]	29 [23, 35]	55 [44, 72]	<0.001

Data are presented as mean ± SD, median [25th, 75th percentiles], or %. *P* values from chi-square test or *F* test (ANOVA).

* The units for ARV-MAP are mmHg/min, so an ARV-MAP of 1 indicates that the MAP changes (either up or down) on average approximately 1 mmHg between consecutive minutes during the case for a given patient.

ARV-MAP = generalized average real variability of mean arterial pressure; ASA = American Society of Anesthesiologists; CNS = central nervous system; GI = gastrointestinal; MAP = mean arterial pressure; OR = operating room; TWA = time-weighted average.

a smoothed relationship between selected predictor variables and response; this is a useful technique when a relationship appears quite nonlinear (*i.e.*, not a straight line). Results in our logistic regression model setting were then interpreted by (1) simply observing the resulting curve and also by (2) reporting odds ratios for the outcome comparing certain values of the predictor (*e.g.*, generalized ARV-MAP) to a reference value.

We estimated odds ratios (95% CIs) from the spline models using the median of each exposure as the reference. In addition, we categorized the primary exposure of generalized ARV into five equal-distant groups (≤1, 1–2, 2–3, 3–4, and >4 mmHg/min) and used the lowest (≤1 mmHg/min) as the reference. A sensitivity analysis for the association between generalized ARV-MAP and 30-day mortality was conducted including only patients having minute-by-minute invasive blood pressure measurements. We further assessed the interaction between history of hypertension and the relationship between generalized ARV-MAP and 30-day mortality.

We conducted secondary analyses to assess the relationship between 30-day mortality and amount of time MAP is sustained below certain thresholds, independent of minute-to-minute variations in MAP (*i.e.*, adjusting for generalized ARV-MAP). These analyses help to understand implications of the relationship between the overall mean (TWA-MAP) and 30-day mortality. Specifically, we assessed the relationship between 30-day mortality and minimum 10-min sustained MAP (*i.e.*, the minimum MAP sustained continuously for ≥10 min) and cumulative time of MAP less than 50, 55, 60, 70, and 80 mmHg during surgery using multivariable logistic regression models. We adjusted for generalized ARV-MAP and baseline confounding variables (as in primary analyses).

We used a significance level of 0.05 for main effects and 0.10 for interaction effects. SAS software version 9.4 for Windows (SAS Institute, USA) was used for all statistical analyses and graphics.

Results

Among 104,401 patients included in the study (fig. 1), the overall incidence of 30-day mortality was 1.3% (1,348). The overall mean (± SD) of TWA-MAP was 84 ± 10 mmHg, generalized ARV-MAP was 2.5 ± 1.3 mmHg/min, and SD-MAP was 12.2 ± 4.3 mmHg. Arterial line was used in 33% of patients and noninvasive measurement in 66%, whereas 1% used both.

Table 1 shows the characteristics of patients as a function of generalized ARV-MAP category. Patients with higher generalized ARV-MAP were more likely to be older, to have higher ASA-PS, to be designated as emergency cases, to have had arterial catheters inserted, to have a history of serious chronic disease, and to have higher SD-MAP and TWA-MAP.

Time-weighted average of MAP was only weakly correlated with variability measured by generalized ARV-MAP

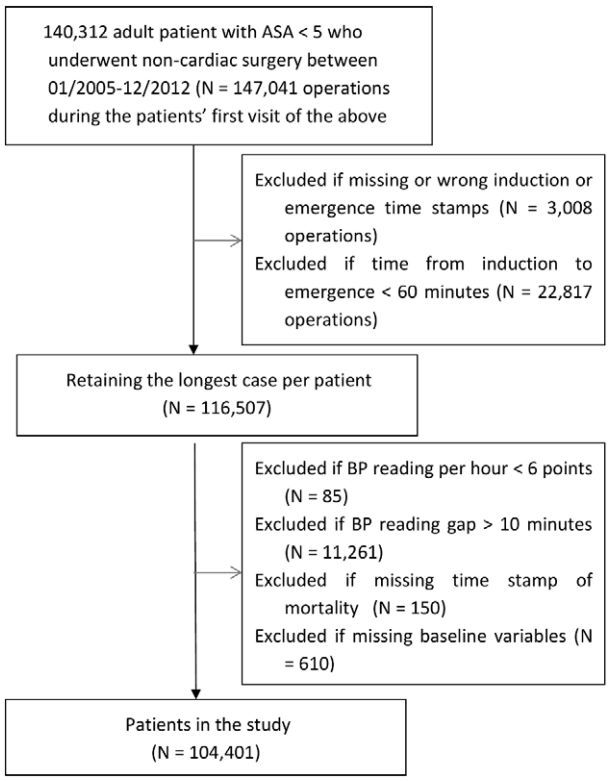

Fig. 1. Study population. Consort diagram showing study population. ASA = American Society of Anesthesiologists; BP = blood pressure.

(Pearson correlation coefficient, 0.20; 95% CI, 0.19 to 0.21; $P < 0.001$) but moderately correlated with SD-MAP (0.41; 0.40 to 0.42; $P < 0.001$). A weak correlation between generalized ARV-MAP and TWA-MAP implies that variability as measured with ARV is fairly independent of a patient's mean MAP during surgery. ARV-MAP was moderately-to-strongly correlated with SD-MAP (0.57; 0.567 to 0.574; $P < 0.001$) and highly correlated with squared ARV-MAP (0.92; 0.921 to 0.923; $P = 0.001$).

Univariably, 30-day mortality increased steeply as the generalized ARV-MAP increased to 3 mmHg/min but thereafter increased only slowly ($P < 0.001$; fig. 2A); conversely, there was a slight U-shaped univariable relationship between the SD-MAP and 30-day mortality ($P < 0.001$; fig. 2B); finally, 30-day mortality decreased steeply as the TWA of MAP increased up to approximately 80 mmHg and then slowly increased ($P < 0.001$; fig. 2C).

Multivariable Analyses

ARV–MAP. In a multivariable model using cubic splines, we found no interaction between generalized ARV-MAP and TWA-MAP on 30-day mortality ($P = 0.36$). Both continuous ARV-MAP ($P = 0.033$) and continuous TWA-MAP ($P < 0.001$) were independently associated with 30-day mortality (fig. 3). Compared with the univariable analysis, TWA-MAP had a similarly shaped but attenuated relationship with mortality (fig. 3C). However, generalized ARV-MAP (fig. 3A) was only weakly associated with mortality (nearly flat curve) after adjusting for covariates as well as TWA-MAP. A plot of odds ratios using the multivariable spline fit (from fig. 3) showed that an ARV-MAP of approximately 3.8 had the lowest risk of 30-day mortality (fig. 4A). A generalized ARV-MAP of 1 mmHg/min indicates that the MAP changes (either up or down) an average of 1 mmHg between consecutive minutes during the case for a given patient. The odds ratio (95% CI) at the 25th percentile for a 1-mmHg/min increase in generalized ARV-MAP *versus* the median ARV-MAP (2.3) was 1.14 (1.03 to 1.25, $P = 0.01$) and at the 75th percentile was 0.94 (0.88 to 0.99, $P = 0.02$) (table 2). The *c*-statistic for this model was 0.93, indicating very good discrimination. In contrast, odds ratios of mortality for SD of MAP had a more U-shaped relationship (fig. 4B).

Because the relationship between generalized ARV-MAP and mortality was nonlinear, we also assessed the multivariable association using evenly spaced categories of ARV-MAP and mortality. We observed a decreasing trend of mortality ($P = 0.015$, test for linear trend) from low to high generalized ARV-MAP category (0.30 to 0.21%). However, none of the categories of generalized ARV-MAP differed significantly from the reference (lowest) category in their relationship with 30-day mortality (table 2).

Sensitivity analyses using only patients who had minute-by-minute invasive blood pressure measurements (N = 34,547) gave the same conclusions for the association between 30-day mortality and generalized ARV-MAP (both continuous and categorized ARV-MAP) as when using all data. Squared ARV

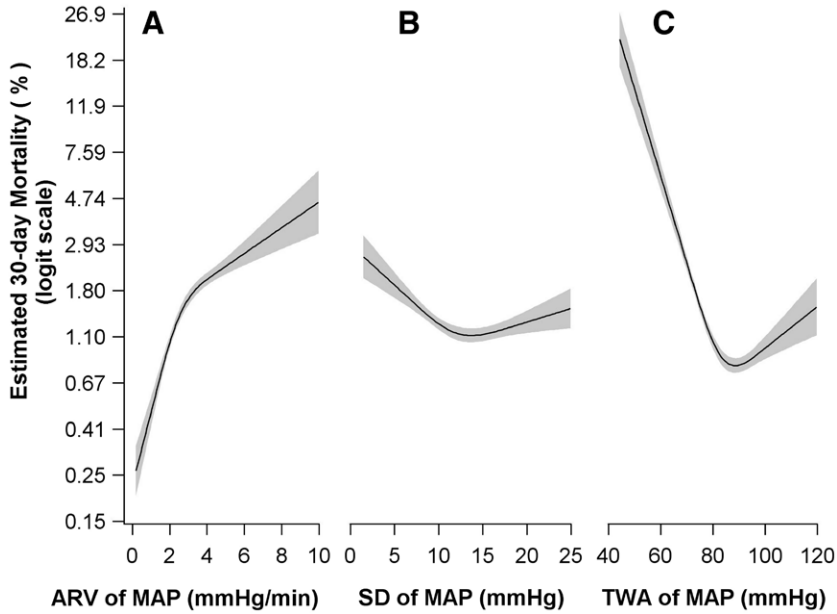

Fig. 2. Univariable association between 30-day mortality and measures of mean arterial pressure (MAP) variability and location. Univariable association between 30-day mortality and (*A*) generalized average real variability (ARV) of MAP, (*B*) SD of MAP, and (*C*) time-weighted average (TWA) of MAP. Curves derived from univariable logistic regression smoothed by restricted cubic spline with 3 degrees of freedom and knots at 10th, 50th, and 90th percentiles of predictor. *Shaded areas* represent estimated 95% point-wise CIs. Results: (*A*) 30-day mortality increases steeply with increasing ARV of MAP to approximately 3 mmHg/min and then more slowly; (*B*) SD of MAP has slight U-shaped relationship with 30-day mortality; and (*C*) 30-day mortality decreases steeply up to TWA of MAP of approximately 90 mmHg and then increases. See figure 3 for multivariable results—that is, the independent association of each factor with 30-day mortality.

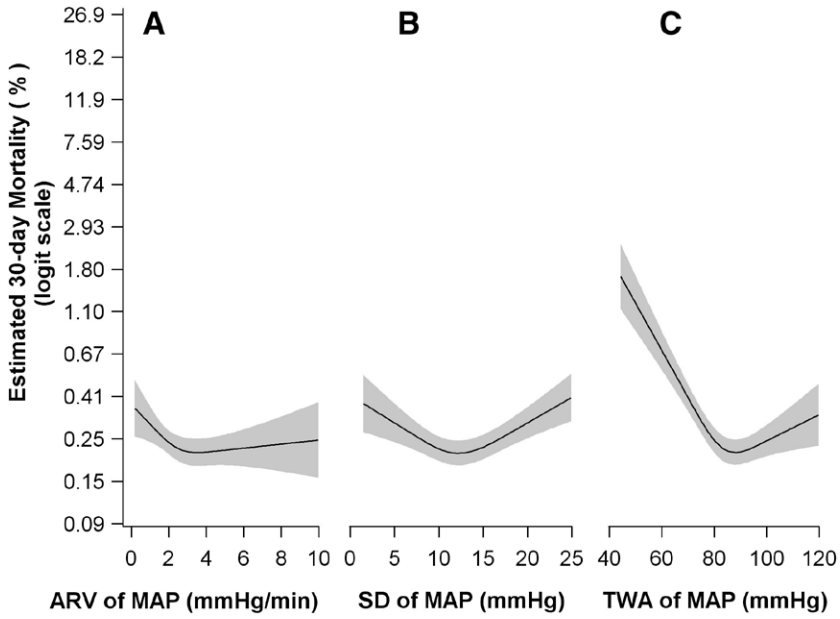

Fig. 3. Multivariable association between 30-day mortality and measures of mean arterial pressure (MAP) variability and location. Multivariable association between 30-day mortality and (*A*) generalized average real variability (ARV) of MAP, (*B*) SD of MAP, and (*C*) time-weighted average (TWA) of MAP. (*A* and *B*) Mild multivariable relationship between 30-day mortality and both generalized ARV of MAP and SD of MAP. (*C*) Estimated 30-day mortality decreases steeply up to TWA of MAP approximately 85 mmHg and then flattens. Estimated 30-day mortality curves derived from multivariable logistic regression smoothed by restricted cubic spline with 3 degrees of freedom and knots at 10th, 50th, and 90th percentiles of given variable. *A* and *C* are from the same model; *B* is from a separate multivariable model (with TWA-MAP relationship similar to *C*). Both models adjusted for all variables in table 1. *Shaded areas* represent estimated 95% point-wise CIs.

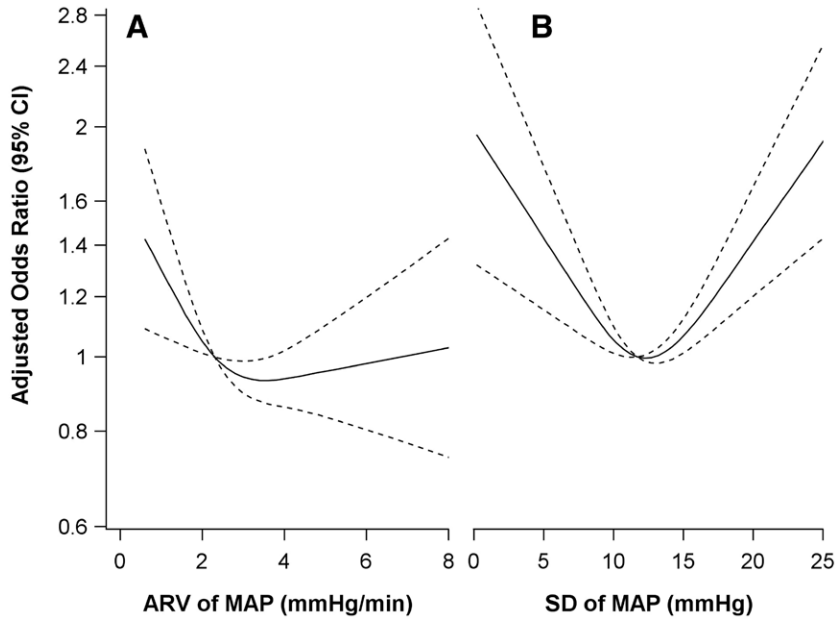

Fig. 4. Multivariable odds ratios for relationship between 30-day mortality and mean arterial pressure (MAP) variability measures. Spline plot of odds ratios from separate multivariable logistic regression models for generalized average real variability (ARV) of MAP (*A*) and SD of MAP (*B*). The reference category for each odds ratio is the median value of the respective variability measure. *Dashed lines* represent estimated 95% point-wise CIs. There is no variability (and hence no CI) at the median, where odds ratio = 1.0. Whereas odds ratios for the relationship between SD-MAP and mortality are symmetric around the median, odds ratios for ARV-MAP remain flat above the median because predicted mortality did not increase for higher ARV-MAP.

Table 2. Multivariable Association between 30-day Mortality and Primary and Secondary Outcomes (N = 104,401)

Factors	Units	Adjusted Odds Ratio (95% CI)*	*P* Value*
ARV-MAP (mmHg/min)†			0.033
25th (ARV = 1.6)	−0.7	1.14 (1.03–1.25)	0.01
Median (ARV = 2.3)		1.0 (reference)	
75th (ARV = 3.2)	0.9	0.94 (0.88–0.99)	0.018
Categorized ARV-MAP (mmHg/min)	Death N (raw %/model %)		0.015‡
≤1 (N = 7,565)	35 (0.46/0.30)	1.0 (reference)	
1–2 (n = 34,531)	246 (0.71/0.26)	0.85 (0.57–1.26)	0.42
2–3 (n = 30,315)	434 (1.4/0.24)	0.79 (0.53–1.17)	0.23
3–4 (n = 18,026)	328 (1.8/0.21)	0.70 (0.47–1.06)	0.09
>4 (n = 12,896)	306 (2.3/0.21)	0.69 (0.45–1.04)	0.08
SD-MAP (mmHg)†	Units		<0.001
25th percentile	−4.4	1.09 (1.03–1.16)	0.006
Median		1.0 (reference)	
75th percentile	3.0	1.05 (1.01–1.10)	0.033

Secondary Analyses: MAP Exposures	Units	Adjusted Odds Ratio (95% CI)	*P* Value§
10-min sustained minimum MAP (mmHg)			
minimum MAP <70	5 mmHg	0.76 (0.72–0.80)	<0.001
minimum MAP ≥70	5 mmHg	1.02 (0.95–1.10)	0.59
Cumulative minutes of MAP <50 mmHg	10 min	1.23 (1.15–1.30)	<0.001
Cumulative minutes of MAP <55 mmHg	10 min	1.13 (1.09–1.17)	<0.001
Cumulative minutes of MAP <60 mmHg	10 min	1.09 (1.07–1.11)	<0.001
Cumulative minutes of MAP <70 mmHg	10 min	1.04 (1.03–1.05)	<0.001
Cumulative minutes of MAP <80 mmHg	10 min	1.02 (1.01–1.03)	<0.001

Units of comparison to the median vary between the 25th and 75th percentiles for both ARV-MAP and SD-MAP because the relationships with mortality are nonlinear.

* Multivariable logistic regressions adjusting for all baseline factors in table 1 (including 54 CCS categories), surgery duration, and TWA-MAP; † ARV-MAP is the sum of absolute changes in MAP divided by total time; ‡ $P = 0.015$ test for linear trend of ordered categories of ARV-MAP *vs.* mortality, $P = 0.16$ for nominal categories; § Individual logistic regressions adjusting for all baseline factors in table 1 (including 54 CCS categories), surgery duration, and ARV-MAP.

ARV = average real variability; CCS = Clinical Classifications Software for Services and Procedures (part of Healthcare Cost and Utilization Project [HCUP]); MAP = mean arterial pressure; TWA = time-weighted average.

also gave the same conclusions. A sensitivity analysis to the primary results including only the subset of patients (58% of the total sample) for whom history of cardiovascular medications was available (and thus adjusted for as confounding factors) gave very similar results (appendix 1 and table 3), with no differences in trends or conclusions but a slightly stronger relationship between ARV-MAP and 30-day mortality. Finally, using Hansen's version of the ARV-MAP, shown above only to be intuitive for equally spaced data, we found a similarly shaped relationship between ARV-MAP and 30-day mortality (overall *P* value of 0.004); however, odds ratios were weaker, and no difference was found between high ARV and the median.

SD-MAP. In a separate multivariable model, both continuous SD-MAP ($P < 0.001$) and continuous TWA-MAP ($P < 0.001$) were independently associated with 30-day mortality. The interaction between SD-MAP and TWA-MAP was significant using three knots ($P = 0.026$) but not using 4 or 5 ($P > 0.10$), so only the main effects model is reported. As in the univariable model, a U-shaped multivariable relationship between SD-MAP and mortality was found (fig. 3B). However, the relationship between SD-MAP and mortality was small compared with TWA-MAP (fig. 3C). The odds ratio (95% CI) of the 25th percentile *versus* the median SD-MAP (reference) was 1.09 (1.03 to 1.16, $P = 0.006$), and for the 75th percentile was 1.05 (1.01 to 1.10, $P = 0.033$) (table 2).

MAP Thresholds. The confounder-adjusted relationship between minimum MAP sustained for 10 min or more and 30-day mortality was J-shaped with the low point at 75 mmHg (fig. 5A). Minimum MAPs greater than 75 mmHg were associated with only slightly greater mortality. In contrast, the estimated odds of dying by 30 days was 32% higher (95% CI, 25 to 39) for a 5-mmHg reduction in the minimum MAP value sustained for 10 min when that minimum was less than the median of 70 mmHg ($P < 0.001$; table 2). Corresponding odds ratios for a range of minimum MAP value sustained for 10 min compared with 70 mmHg are given in figure 5B. Finally, cumulative time of MAP less than 50, 55, 60, 70, or 80 mmHg was each associated with higher odds of 30-day mortality (all $P < 0.001$; table 2).

For the primary model of ARV-MAP and 30-day mortality and other models, diagnostics in the form of DFBETAs, Pearson residuals, and leverage statistics were good, and no issues were found (see details for primary model in appendix 2 and figs. 6 and 7).

Discussion

Mean arterial pressure variability, measured as the sum of consecutive jumps or drops across a surgery (generalized ARV-MAP), was independently associated with 30-day mortality, consistent with our hypothesis.[8] TWA-MAP was also independently associated with 30-day mortality, consistent with that reported in previous literature.[19] However, the relationship between mean MAP and mortality was much stronger than that for variability and mortality. Interestingly, the relationship between MAP variability and 30-day mortality did not depend on TWA of MAP in any substantial way, such that low variability was weakly associated with higher mortality regardless of the patient's mean MAP for the case. Likewise, TWA of MAP was independently associated with 30-day mortality irrespective of the level of variability.

Several studies have shown that low heart rate variability is a marker of autonomic dysfunction among patients with congestive heart failure[20] or recovering from a myocardial infarction,[21] as well as among patients without clinical evidence of heart disease.[22] Because physiological parameters such as blood pressure and heart rate are autonomic functions, it is possible that decreased variability in blood pressure may be associated with increased mortality and cardiovascular events due to autonomic dysfunction as seen with heart rate. We also saw that blood pressure variability was moderately correlated with TWA-MAP. It thus follows that patients with low TWA-MAP are more likely to have lower variability of MAP, and so the higher mortality for those patients with low variability may reflect the lower mean blood pressure.

Our work differs from previous literature in that we distinguish and isolate blood pressure variability from blood pressure *per se*. For example, Aronson *et al.*[12] found that mean duration of systolic excursion (outside a range of 105–130 mmHg) was weakly associated with 30-day mortality and referred to this exposure as "variability." However, this is not actually a measure of variability but rather of mean pressure. For example, a patient could spend much time with systolic pressure less than 105 mmHg and yet have low variability because all measurements were similar. In other studies, duration of intraoperative hypotension was not associated with mortality[23] or stroke[24,25] under various definitions, but such durations measure extreme values and not specifically the measure-to-measure variability we were interested in. We thus focused on pure measures of variability, that is, those directly assessing changes in consecutive measurements over time, independent of the mean. We adjusted for the mean blood pressure in all models (*e.g.*, Hansen *et al.*[8] adjusted for 24-h blood pressure in their "full" model) as well as a host of other baseline confounding variables, allowing an assessment of the independent contribution of variability *per se*.

Anesthesiologists consider mean, systolic, and diastolic pressures—and each provides valuable information. However, diastolic and especially systolic pressures are subject to considerable distortion depending on vasomotor status, measurement site, and general anesthesia.[26,27] In contrast, MAP generally very nearly equals aortic pressure over a wide variety of clinical conditions and with both oscillometric and radial artery measurements. As might thus be expected, our results were essentially unchanged when analysis was restricted to radial arterial pressures.

There is no recognized standard for measuring blood pressure variability. We considered three measures of mean arterial pressure variability, and our conclusions did not differ

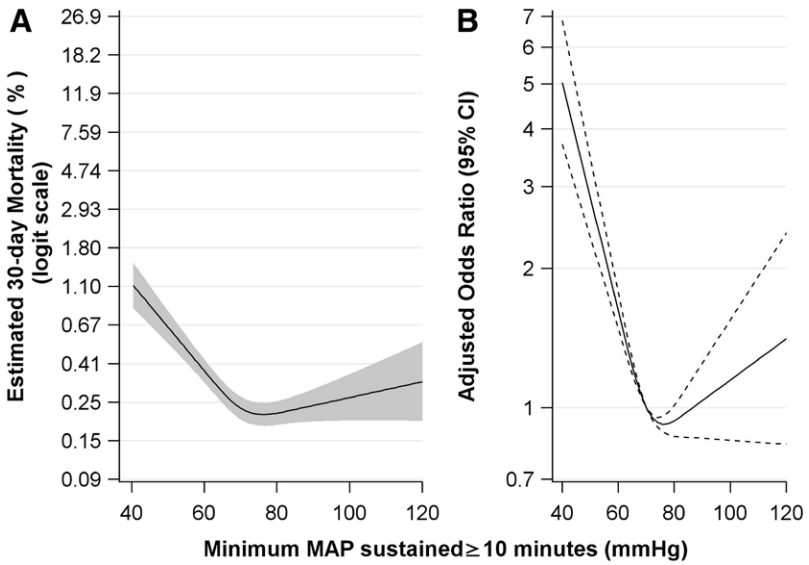

Fig. 5. Multivariable association between minimum 10-min sustained mean arterial pressure (MAP) and 30-day mortality. (*A*) Spline plot of multivariable probability of 30-day mortality as function of 10-min sustained MAP. (*B*) Spline plot of multivariable odds ratios (Y-axis) for relationship between minimum 10-min sustained MAP and 30-day mortality. The reference category for each odds ratio is the median value of the predictor (70 mmHg). There is no variability (and hence no CI) at the median, where odds ratio = 1.0. Curves derived from multivariable logistic regression smoothed by restricted cubic spline with 3 degrees of freedom using 10th, 50th, and 90th percentiles of minimum 10-min sustained MAP as knots.

markedly across the approaches. However, ARV seems preferable to the commonly used SD because it measures consecutive changes in blood pressure, whereas the SD ignores timing of the measurements.[8] We enhance this approach by proposing a generalized version of ARV that remains valid when measurements are recorded at nonequidistant times—as is typical in clinical practice. We also considered a squared version of the ARV to give more weight to more steep jumps but found little difference compared with generalized ARV in the relationship with 30-day mortality. Our generalized ARV thus appears to provide a good estimate of intraoperative variability in blood pressure.

Walsh *et al.*[19] identified 55 mmHg as a number below which the odds of acute kidney injury and myocardial infarction begin to noticeably increase, with the target of 55 mmHg based on the apparently univariable relationship between minimum MAP (single MAP value per patient) and outcome. Our results on MAP should not be directly compared with those of Walsh *et al.* for several reasons, but mainly because we focused on 30-day mortality, whereas they focused on acute kidney injury and myocardial infarction. We observed a U-shaped relationship between TWA-MAP and mortality, such that the odds of mortality decreased as TWA-MAP increased from 40 up to approximately 85 mmHg and then increased for TWA-MAP greater than 85 mmHg. We also found positive relationships between mortality and cumulative minutes of MAP less than 50, 55, 60, 70, and 80 mmHg, such that longer exposure was worse for each threshold. Finally, we found that decreasing the minimum value of MAP that was sustained for more than 10 min was associated with higher odds of mortality when that minimum was less than 70 mmHg, but no association when greater than 70 mmHg. Each of our analyses adjusted for MAP variability and a host of confounding variables and thus represents an estimate of the isolated contribution of MAP level.

In our multivariable modeling of the relationship between blood pressure variability and 30-day mortality, we adjusted for a host of baseline potentially confounding variables, including surgical procedure and a wide range of baseline comorbidities. Although we adjusted for numerous cardiovascular comorbidities, a limitation of our analysis is that we were not able to adjust for history of receiving cardiovascular drugs in the primary analysis due to current limitations of our database. However, adjusting for the reasons for being on the cardiovascular drugs (*i.e.*, the comorbidities) may remove much or most of the confounding due to those drugs on the relationship between blood pressure variability and 30-day mortality. In fact, we were able to verify that adding cardiovascular drugs in a subset of patients (58% of total) for which the information was available only minimally affected our results and did not change any conclusion (appendix 1).

Patients with higher MAP variability had higher levels of many baseline variables known to be risk factors for mortality. Our multivariable models thus included demographics, emergency surgery, medical history, use of an arterial catheter, procedure, ASA-PS, and more. It would be challenging to randomly vary MAP, especially in the most interesting range (approximately <75 mmHg); and it probably would be even more challenging to control blood pressure variability. An analysis of observational data is thus the best practical approach to the questions we addressed in this study. It remains possible that results would differ in other populations or surgical environments. In particular, the observed relative effects might well be clinically important if observed in settings with higher overall 30-day mortality because the absolute differences in mortality across levels of blood pressure variability would be higher. But given the overall limited association between blood pressure variability and mortality, it seems unlikely that blood pressure variability provides much additional predictive information.

In conclusion, MAP and mean pressure variability were nonlinearly related to 30-day mortality in our noncardiac surgery population. After adjusting for TWA-MAP and other important covariables, low blood pressure variability was still associated with higher 30-day mortality, but the differences were not clinically important in our population. Anesthesiologists might thus pay more attention to overall trends in the mean blood pressure for a case than in the minute-to-minute variation.

Appendix 1.

Subset Analysis of Patients for Whom Information on History of Cardiovascular Medications Was Available

Table 3 shows that when we adjusted for history of taking specific cardiovascular medications on the patients in whom this information was available (58% of total), results are almost identical to our primary analysis on all patients—odds ratios are very similar and all conclusions are the same. We conclude that the primary analysis (table 2) did not include any noticeable bias due to data on cardiovascular medications not being available.

Table 3. Subset Analysis of Patients for Whom Information on History of Cardiovascular Medications Was Available (Multivariable Association between ARV-MAP* and 30-day Mortality; N = 60,616)

Factor	Units	Adjusted Odds Ratio (95% CI)†	*P* Value†
ARV-MAP (mmHg/min)†			<0.001
25th (ARV = 1.8)	−0.7	1.18 (1.06–1.31)	0.002
Median (ARV = 2.5)		1.0 (reference)	
75th (ARV = 3.4)	1.1	0.89 (0.83–0.95)	<0.001

Interaction between AVR-MAP and TWA-MAP: $P = 0.43$ (no evidence of interaction). Test for linear trend in mortality for increasing generalized ARV-MAP category (levels not shown): $P < 0.001$; odds ratio, 0.87 (0.81–0.95) for one category increase over quintiles of ARV-MAP.

* ARV-MAP is the generalized ARV of MAP (sum of absolute changes in MAP divided by total time). † Multivariable logistic regressions adjusting for all baseline factors in table 1 (including 55 CCS categories), surgery duration, and TWA-MAP.

ARV = average real variability; CCS = Clinical Classifications Software for Services and Procedures (part of Healthcare Cost and Utilization Project [HCUP]); MAP = mean arterial pressure; TWA = time-weighted average.

Appendix 2.

Model Diagnostics for Primary Analysis Instability Diagnostics on the Regression Coefficients for Average Real Variability of Mean Arterial Pressure and Time-weighted Average of mean Arterial Pressure in the Primary Analysis Model

For the primary analysis model assessing the association between generalized average real variability of mean arterial pressure (ARV-MAP) (see equation 2 in Materials and Methods), we report on observations that might cause instability in the parameter estimates using DFBETAs. The DFBETA diagnostic for an observation is the standardized difference in the parameter estimate due to deleting the observation and can be used to assess the effect of an individual observation on an estimated parameter of the fitted model. For small to medium datasets, values greater than 1 may be considered large. For larger datasets, a conservative calculation indicating large values of DFBETA is an absolute value $> 2/\sqrt{n}$ or 0.006 in our data.

Figure 6, A and B, reports DFBETA values for the linear and nonlinear spline terms for generalized ARV-MAP, respectively, whereas figure 6, C and D, reports the same statistics for time-weighted average mean arterial pressure. Figure 6, A–D, had 1.5, 1.6, 1.7, and 1.7% beyond the

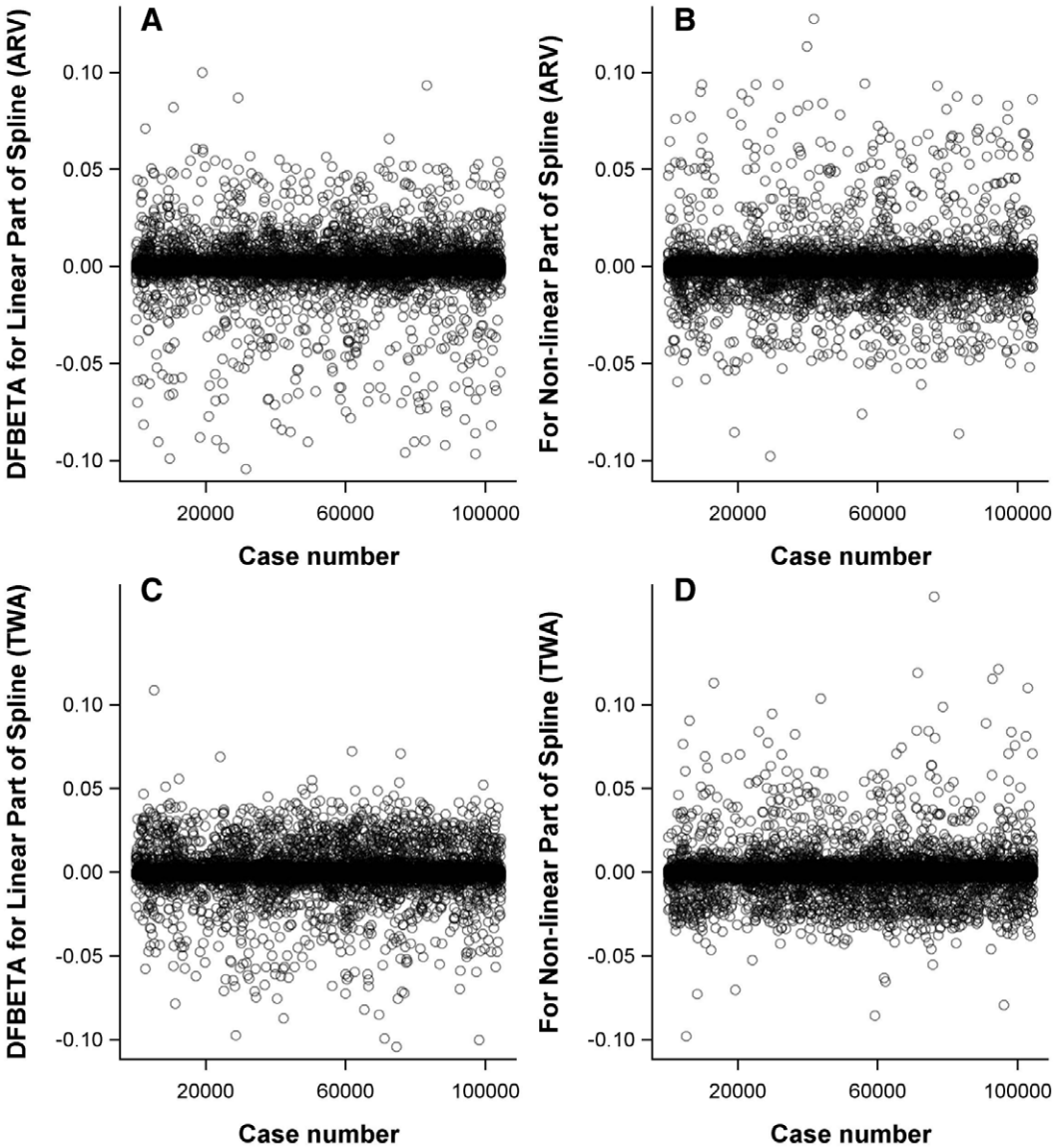

Fig. 6. Instability diagnostics on the regression coefficients for (*A* and *B*) generalized average real variability (ARV) of mean arterial pressure (MAP) and (*C* and *D*) time-weighted average (TWA) of MAP in the primary analysis model as measured by DFBETA. Results indicate that the model fit the data well because there is very little evidence of individual observations affecting parameter estimates for either ARV-MAP or TWA-MAP. Less than 2% of observations in each panel of the figure are beyond the recommended cutoff of DFBETA >0.006.

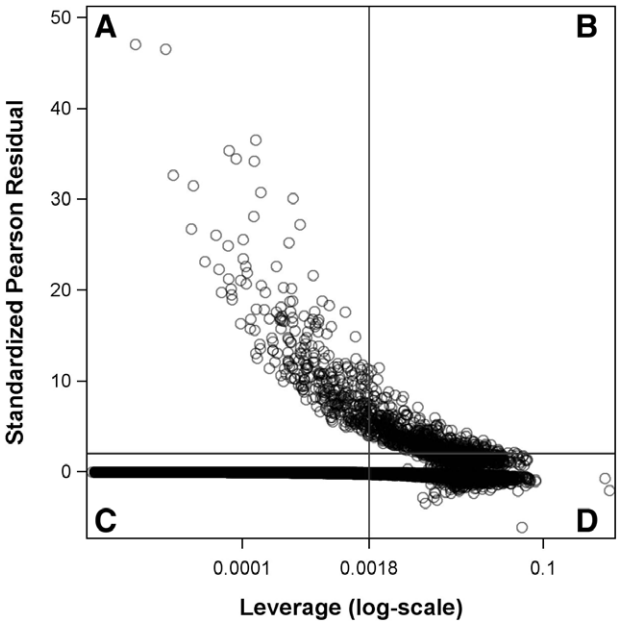

Fig. 7. (*A–D*) Scatterplot of Pearson residuals by leverage: outlier and extreme data point diagnostics for primary analysis model of generalized average real variability (ARV) of mean arterial pressure (MAP) and 30-day mortality. Only a very small percentage of data points (0.3%) were deemed to be both outliers (extreme in Y space, *i.e.,* 30-day mortality) and with high leverage (extreme in the X space, *i.e.,* generalized ARV of MAP), indicating very good model fit for the primary analysis.

recommended cutoff point (*i.e.*, DFBETA > 0.006), indicating that the model fit the data well with relatively very few values that might cause instability in the respective regression parameters.

Outlier and Extreme Data Point Diagnostics for Primary Analysis Model of ARV-MAP and 30-day Mortality

Pearson Residuals

An outlier data value is traditionally defined as a response variable Y (here, 30-day mortality), for which the standardized Pearson residual is greater than 2 in absolute value, shown in the figure with the horizontal line.

Leverage

A conservative definition for an extreme value for an independent variable X (here, the parameter corresponding to the linear portion of the ARV-MAP spline function) for a large dataset is when the leverage calculation is greater than $(2k + 2)/n$, where k is the number of parameters in the model ($k = 96$). In our dataset, a leverage value greater than 0.0018 suggests an extreme value, as shown in the figure by the vertical line. However, experts report that leverage values are not very reliable when the predicted probability is less than 0.10 as is the case for most of our data (Hosmer and Lemeshow[27]).

As displayed in figure 7, only approximately 1% of observations had a Pearson residual outside of ±2, indicating good model fit. Only 0.3% of data points were both outliers and with high leverage, as shown in the figure 7B and representing only 0.5% of observations. Figure 7C (neither abnormal residual nor high leverage) contains 90.2% of all observations. Figure 7A (high Pearson residual but normal leverage) had 0.3% and figure 7D (normal Pearson residual but abnormal leverage) had 8.8% of the data points, respectively.

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Competing Interests

The authors declare no competing interests.

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