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Preoperative outpatient blood pressure variability predicts postoperative mortality, readmission and morbidity after surgery

Marc D. Basson, MD, PhD^a, Marilyn G. Klug, PhD^b, William E. Newman, MD^c, Cornelius Dyke, MD^d

^aDepartment of Surgery, University of North Dakota School of Medicine & Health Sciences and the Fargo VAMC.

^bDepartment of Population Health, University of North Dakota School of Medicine & Health Sciences and the Fargo VA

^cDepartment of Internal Medicine, University of North Dakota School of Medicine & Health Sciences and the Fargo VA

^dDepartment of Surgery, University of North Dakota School of Medicine & Health Sciences and Sanford Health

Abstract

Background: Outpatient blood pressure variability (BPV) predicts hospitalization and death in non-surgical patients independently of hypertension. We hypothesized that preoperative BPV predicts postoperative outcomes.

Methods: We assessed 22,233 veterans undergoing CABG, colectomy, hip replacement, pancreatectomy, carotid endarterectomy or AV-fistula with 10 outpatient BP's over three preoperative years. Calculating BPV as SD of systolic or diastolic BP, we used logistic regression considering demographics, comorbidities, and pre-admission cardiovascular medications to estimate odds ratios for 90-day mortality or readmission, MI, CVA, renal failure, and wound infection, choosing the lowest 5%ile of systolic/diastolic BPV for reference.

Results: Covariate-adjusted ORs for adverse outcomes increased as BPV increased. For instance, the highest 5%ile of systolic BPV had covariate-adjusted ORs of 2.96 and 1.78 for 90-day mortality and readmission. Systolic and diastolic BPV trended together but affected outcomes independently.

Corresponding author: Marc D. Basson, MD, PhD, MBA, Professor of Surgery, Pathology, and Biomedical Science, Senior Associate Dean for Medicine and Research, University of North Dakota School of Medicine & Health Sciences, 1301 North Columbia Road, Stop 9037, Grand Forks, ND 58202, Phone: 701-777-6226, Fax: 701-777-3527, Marc.basson@und.edu.

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Conclusions: Preoperative BPV predicts postoperative outcomes. BPV should be considered in individualized risk assessment and subgroup risk stratification.

Article Summary:

Variability in outpatient blood pressure over three years prior to major surgery is strongly associated with postoperative mortality, morbidity, and readmission independently of hypertension and other risk factors. The importance of this finding is that this previously unsuspected risk factor should be considered in individual patient risk assessment and counseling and in risk stratification for research or quality assurance purposes.

Keywords

visit to visit blood pressure variability; perioperative risk; mortality; morbidity; readmission

Introduction

Blood pressure variability (BPV) is distinct from hypertension and represents the degree of instability in a person's blood pressure over years. BPV may be calculated in a variety of ways, using standard deviation, average change, or greatest change, and based upon systolic or diastolic blood pressure readings.¹ The etiology of elevated BPV is likely to be complex and multifactorial, and may include medication non-compliance, autonomic instability, neurologic abnormalities, vascular wall dysmorphism, diurnal variability, and "white coat syndrome".²⁻⁸ Certain antihypertensive medications are also associated with higher or lower BPV in hypertensive patients.⁹⁻¹¹ Regardless of how it is calculated or what causes it, high outpatient BPV tends to be associated with an increased risk of subsequent hospitalization and/or death over the next few years.^{1, 11, 12} This risk is found whether the patient is hypertensive, normotensive, or relatively hypotensive.¹ It should be noted that in this manuscript we are examining long-term outpatient-obtained blood pressure variability, which may differ in implications and mechanism from any beat-to-beat short- or mid- term variability in blood pressure measurements.

Although the deleterious effects of high BPV are traditionally measured over years in medical outpatients, we recently reported a preliminary analysis in 1,334 patients suggesting that high preoperative BPV might increase the shorter term risk of perioperative death and major complications after coronary artery bypass grafting.¹³ We now therefore hypothesized that patients with high BPV are at higher risk for short term perioperative mortality, readmission, and systemic complications (MI, CVA, new onset renal failure). We tested this hypothesis in a retrospective analysis of a nation-wide cohort of 28,439 patients from the United States Department of Veterans' Affairs system who had undergone one of several common surgical procedures (coronary artery bypass grafting, colectomy, hip replacement, pancreatectomy, carotid endarterectomy, or creation of arteriovenous fistula). Building upon our pilot study, we wanted to confirm the suggestive but not entirely statistically significant results we had obtained in cardiac patients and extend them to other common, non-cardiac operations. We did not study all surgical patients in this study because we feared that our results might be diluted by the inclusion of large numbers of very low risk procedures (e.g. cataract surgery) in which BPV might not have any effect. We calculated BPV as the

standard deviation of either systolic or diastolic blood pressure, using all recorded outpatient blood pressures over three years before the index procedure, requiring at least 10 such recorded measurements for accuracy of calculation. We recorded the incidence of mortality, rehospitalization, MI, CVA, and new onset renal failure, and also recorded the incidence of wound infection as a comparison, since we hypothesized that this would not increase with BPV. We performed logistic regression considering age, gender, BMI, diagnosed hypertension, diagnosed diabetes, preoperative beta blocker use, and preoperative ACE inhibitor use as well as BPV to show that the effects of BPV were independent of these other risk factors. We used logistic regression not just to show that increasing BPV will increase risk of an outcome given a procedure, but to clarify the value of that risk for specific values of BPV. We show this graphically for systolic and diastolic values both independently (using regression with straight lines) and jointly (using different colors for increasing risks). We deliberately did not consider intraoperative or postoperative variables in the prediction of postoperative outcomes because we wanted to focus on information that would be available to a surgeon preoperatively in assessing patient risk. In light of recent suggestions that long acting calcium channel blockers might protect against some of the deleterious effects of having high BPV in medical patients,^{14–18} we also separately analyzed BPV effects in patients who were or were not taking calcium channel blockers preoperatively.

Methods

VINCI (VA Informatics and Computing Infrastructure) is an initiative of the Veterans Administration to facilitate the access of VA-affiliated researchers to VA data while maintaining privacy and data security. Covariates were defined using natural language processing and data was queried within the VINCI workspace by VINCI staff. The resulting report was made available to the investigators for analysis within the secure VINCI workspace. Data was obtained from the VINCI database after approval by the Institutional Review Boards of the University of North Dakota and the Fargo VAMC. 28,439 patients underwent arteriovenous fistula creation, carotid endarterectomy, coronary artery bypass grafting (CABG), colon resection, hip replacement, or pancreatectomy from 2014–2016.

BPV was calculated as the standard deviation (SD) of patients' outpatient systolic and diastolic blood pressures up to 3 years before surgery. Ten covariates were used as potential confounders in the relationship of BPV to the six outcomes: sex, race, age, BMI, diagnosed diabetes or hypertension, length of stay, and use of beta-blockers, ARB/ACE inhibitors or diuretics before admission. These were tested as covariates by using them to predict systolic and diastolic SD in linear regressions and the six outcomes in logistic regressions. Multicollinearity was tested by removing each covariate individually from the model and studying the remained coefficients. As no coefficients changed significantly when a covariate was removed and no covariate had large error, no significant multicollinearity was detected.

To focus the study on a consistent population, we excluded 1,007 patients with extremely high systolic or diastolic SD (>99.5%tile, >38.2 or >20.39 respectively), who had over 380 BPs in the time period (> 98%tile) or over 60 days in the hospital (>98.2%tile). Logistic regressions require complete data so 4,397 patients who were missing number of days in the

hospital and 1,203 without BMI were deleted. A total of 22,233 patients with valid values were analyzed.

As the BPV was not, for this study, defined as a binary variable (strictly ‘low’ or ‘high’ BPV), we chose not to do a case (high BPV) and control (low BPV) study nor a propensity analysis based on two BPV values to control for the covariates, but chose to do logistic regressions to control for potentially confounding covariates and be able to investigate potential interactions of other covariates. The logistic regressions estimated odds ratios for mortality or readmission within 90 days post-procedure, MI, CVA, renal failure, and wound infection with systolic BPV 9 to 24 mmHg in 1 mmHg increments vs. having BPV<9 mmHg (the lowest 5% of the population) (16 odds ratios) while controlling for the covariates, with the 5% threshold for the comparative group being chosen based on sample size.. Ten odds ratios were calculated for diastolic BPV 5 to 13 mmHg relative to BPV<5 mmHg in a similar fashion for the six outcomes.

Using these stepped categories allowed for more continuous view of changes caused by changing BPV than quartiles (odds ratios could be generated at more points), creating a clearer interpretation of the changes than the continuous version of the BPVs as this was based on integers. We did no multiple comparison tests to directly compare one odds ratio to another, but rather used the series of odds ratios to produce estimated regression lines (linear splines) with incremental changes in the BPV predicting odds ratios. The regression lines were used to indicate which odds ratios were significant, the magnitude of change in the odds ratio as BPV changed, and estimability of the risk of the event given a BPV at a certain value. Attributable risk estimated for BPV was the difference between the risk in the top 5%tile and the lowest 5%tile (the absolute risk difference) divided by the top 5%tile. Such techniques have previously been described^{21, 22}.

Three outcomes, MI and mortality or readmission within 90 days post-procedure, had enough patients and significant odds ratios to estimate combined odds ratios based on 1 mmHg increments of systolic BPV ≥ 9 to 24 mmHg and diastolic BPV ≥ 5 to 13 mmHg. The type of procedure (arteriovenous fistula creation, carotid endarterectomy, coronary artery bypass grafting, colon resection, hip replacement, or pancreatectomy) was a potential interactor with BPV and outcomes as the BPV to outcome relationship might change significantly depending on the procedure type being given. Because these were six individual binary variables (as a person may at some time have had two of the procedures), a single procedure variable could not be used. To test for interaction, the coefficients of BPV predicting an outcome (while controlling for the covariates) were estimated while one of the six procedures was not included in the model. Changes in the coefficients of the BPVs were used to investigate whether the procedure that had been dropped exerted a substantial influence on the BPV to outcome relationship. As patients with 90 day readmission were the largest group, we calculated the odds for readmission based on the incremental systolic and diastolic BPV for the procedures of carotid endarterectomy, coronary artery bypass grafting, colon resection, and hip replacement. Regression lines were estimated to fit the curve produced by the odds ratios as the BPV increased.

Like procedure type, use of calcium channel blockers was also a possible interactor. That is, it seemed possible that the relationship between BPV and the outcomes would be different if patients used CCB compared to if they did not. As CCB was a binary variable, regressions of BPV predicting the six outcomes (while controlling for the covariates) was done for CCB users, then for non CCB users. The odds ratios of the BPVs predicting the outcomes were compared between the two CCB groups.

Results

Most patients were male (96%), white (78%), and average 68 years of age (S.D. 9.7). Their average BMI was 30 (S.D. 5.8), 10% had diabetes, and 30% hypertension. The average length of hospital stay was 8.3 days (S.D. 7.7), 21% used beta blocker pre-admission, 19% used ACE/ARB inhibitors, and 12% diuretics. The distribution of BPV within the study population is shown in Figure 1a,b. A wide range of both systolic and diastolic BPV was observed. Systolic blood pressure variability (Figure 1a) ranged from 3–38 mmHg within our cohort (mean 15.9, S.D. 4.8). BPV in the lowest 5% of patients was < 9 mmHg while the highest 5% was 24 mmHg or higher. The first quartile was 13, the median 15, and the third quartile 19. Diastolic blood pressure variability (Figure 1b) ranged from 2–20 mmHg (mean 9.1, S.D. 2.5) with the lowest 5% <5 mmHg and the highest 5% 14 or higher. The first quartile was 7, the median 9, and the third quartile 11. 95% of patients had a systolic BPV ≥ 9 mmHg or a diastolic BPV ≥ 5 mmHg. Systolic blood pressure variability tended to correlate with diastolic blood pressure variability in most patients but not all ($r=.589$, $p<.001$, Figure 1C).

Table 1 shows the description of ten covariates and their coefficients or odds ratios predicting BPV or the six outcomes. Nearly all of the regressions showed the covariates were significant predictors of both the BPV variables and the outcomes. For example, sex was the only variable not related to BPV but it was related to readmission, MI, and CVA. This suggested they be kept in the subsequent analyses as they were potential confounders. Tests for multicollinearity between the covariates showed no excessive multicollinearity was present. Ten covariates were identified as potential confounders (Table 1). All variables but sex proved to be significant predictors of systolic BPV ($B = -0.011$) and diastolic BPV ($B = 1.493$) in our preliminary analysis. Predictors for the six outcomes of mortality and readmission (90 day), MI, CVA, renal failure, and wound infection varied more (six covariates significant for mortality, nine for readmission, seven for MI, five for CVA, five for renal failure, and two for wound infection), but each of these covariates was a significant predictor for one to six outcomes of interest. Therefore, as all ten covariates were significant to some level for BPV and the outcomes, we considered all covariates to be potential confounders and used them with BPV in logistic regressions predicting outcomes.

A series of logistic regressions were then performed using BPV higher than specific integer levels relative to BPV at the lowest fifth percentile. For example the odds of having a systolic BPV 9 or higher relative to having a systolic BPV less than nine was calculated, then the odds of having a systolic BPV 10 or higher relative to less than nine was calculated. The models using these dichotomous versions of BPV included all covariates predicting outcomes. Figure 2 shows the odds ratios found to represent the likelihood of the six

outcomes if the BPV was above a specific value. ORs that are significant ($p < .05$) were then used in a linear regression estimating their relationship. ORs without a line through them were not statistically significant, even if they exceeded one. For systolic standard deviation (Figure 2a), MI shows the greatest increase in OR (slope=0.185). ORs for CVA and readmission also showed a significant increase as the BPV increased. The ORs for renal failure and mortality achieved statistical significance for systolic BPV 14 mmHg and 11 mmHg respectively. The OR for wound infection was not significantly increased for any BPV. Diastolic relationships are shown in the Figure 2b. Mortality and readmission had significant ORs for all values of diastolic BPV, increasing as the BPV increased. No other ORs for CVA, renal failure, wound infection, or MI achieved statistical significance.

Further investigations tested the coexisting relationships of both systolic and diastolic BPV in predicting outcomes (again controlling for the covariates).

Figure 3 shows the contour graphs using systolic and diastolic BPV to simultaneously predict ORs of mortality, readmission, and MI, left to right (appendix A shows three-dimensional versions of this figure). For 90-day mortality (Figure 3a), when the systolic BPV is 10 mmHg or greater, the estimated OR increases 0.9 (from purple to green or 1.9 to 2.8) as the diastolic SD increases. As the systolic SD increases, the effect of the diastolic SD is lessened; when the systolic SD is 20 mmHg or greater the estimated OR only slightly increases from yellow to orange (2.9 to 3.2). This suggests that the systolic SD has more effect on the mortality OR than the diastolic SD, especially at higher systolic SD values. For 90-day readmissions (Figure 3b), the graph of estimated ORs is nearly uniform (the increase in OR is 0.3 as diastolic SD increases for all values of systolic SD), indicating that both the systolic and diastolic SD play similar roles in increasing the OR for readmission. These results are also portrayed in three dimensions in Supplemental Figure 1a and 1b for readers who may find this depiction easier to interpret. For MI (Figure 3c), the diastolic SD had a small (change in OR of 0.3) influence when the systolic SD was 10 mmHg (1.6 to 1.9) and when the systolic SD was higher, an increase in diastolic SD appeared to lower the OR (2.5 to 2.2). Thus, systolic SD but not diastolic SD would appear to significantly impact the OR of MI independently of the other risk factors considered.

As we studied patients undergoing any of six procedures (arteriovenous fistula creation, carotid endarterectomy, coronary artery bypass grafting, colectomy, hip replacement, and pancreatectomy), we considered whether any individual procedure might be driving our results. Deleting any individual procedure from the data set did not affect our results for systolic BPV, while diastolic BPV remained a statistically significant predictor of mortality and readmission regardless of which procedure was dropped, but lost statistical power for the prediction of MI< CVA or renal failure, either because of lower power or a weaker effect. (Table 2)

When outcomes were paired with individual procedure types, only the outcome of readmission had enough observations to estimate logistic regressions for four procedures (pancreas and arteriovenous fistula excluded due to small N). Figure 4 shows the estimated odds ratios from the systolic (Figure 4a) and diastolic (Figure 4b) logistic regressions for these combinations. Odds ratios predicting readmission for patients who underwent coronary

artery bypass grafting were not significant and no linear regression lines were estimated. For carotid, colon, and hip procedures, the risk of readmission increased as the systolic BPV increased. Similar results were found for diastolic BPV, although CABG did not have ORs significantly different from 0 when the BPV was 12 mmHg or larger.

We separately then performed logistic regressions to determine whether the usage of calcium channel blockers influenced the relationships between systolic BPV and the outcomes (Table 3). These regressions were controlled for all covariates. The actual standard deviation was used so the odds ratios are interpreted as the likelihood of an event given an increase of 1mmHg in the systolic or diastolic BPV. The OR for mortality relative to systolic BPV for those on CCB was 1.049 (95% CI 1.010 to 1.091) while those not on CCB was 1.057 (1.041 to 1.073); both significant but not significantly different from each other. Similar results were found for MI and readmissions. For CVA and renal failure, the likelihood of those events was not significantly increased with high BPV for patients on calcium channel blockers but was for patients not taking those drugs. However the pairs of ORs (CCB and non-CCB) were not significantly different from each other.

Discussion

BPV correlated with postoperative adverse outcomes for all adverse outcomes studied except wound infection. High BPV increased risk for postoperative MI, CVA, and renal failure, and most strongly for readmission and mortality. These effects appeared independent of hypertension itself, or of diabetes, age, BMI, or anti-hypertensive medications. In fact, patients in the highest 5%ile for systolic or diastolic BPV had covariate-adjusted relative risks of 3.3 for 90 day mortality and 1.8 for 90 day readmission vs. the lowest 5%ile. Although systolic and diastolic BPV tended to vary together, having both systolic and diastolic high BPV accentuated risk. These observations appeared true across a wide range of procedures. Interestingly, we found no evidence that calcium channel blockers protected against BPV effects.

Abnormally high BPV predicts long term chronic renal failure, diabetes, myocardial infarction, stroke, hospitalization, and death in non-surgical patients.^{1, 10, 12, 23–26} We report here that high BPV correlates with immediate perioperative complication rates, 90 day readmissions, and mortality. The attributable risk to systolic BPV for 90 day postoperative mortality among the top 5%ile vs. the bottom 5%ile was 5.95 (95% CI 5.917–5.953), while a retrospective analysis of a previously published study¹ of the effects of high BPV in a general population (without considering whether they had undergone surgery during the study period) suggests an attributable risk for 90 day mortality of 1.34 (95% CI 1.338–1.342) when the top 5%ile for systolic BPV is compared to the bottom 5%ile. Although the populations from different studies cannot be strictly compared, the effect of BPV on postoperative mortality seems to exceed the effect of BPV in the general population. The only previous report of BPV effects in surgical patients was a pilot study of BPV effects on mortality and morbidity after coronary artery bypass that suggested similar trends but in which statistical significance was severely limited by sample size.¹³

There are other options available for testing data of this type that can answer other hypotheses. Univariate tests would show specific indicators of outcomes but would not control for other variables. Since BPV is likely covariate with other patient variables, it seemed important to be able to take these into account in arguing that BPV was itself a risk factor for poor outcomes. Sensitivity and specificity estimation including receiving operating characteristic curves might be performed to find a single specific value of systolic or diastolic BPV to act as a cutoff, indicating that people with values above that BPV have the best likelihood of an outcome. This, however, is a more limited view as it looks at only one value of BPV, suggesting that below a certain value, BPV is not a risk factor while above a value it becomes a risk factor. In contrast, we examined the continuum of values and then fitted a linear regression line to their associated risks, showing how the risk changes continuously as both the systolic and diastolic BPV change. Other data that was not controlled to specific procedures might also better suit other more general analyses.

Because we calculated BPV on the basis of outpatient BP readings over the previous three years, high BPV is unlikely to reflect the acuity of the illness requiring surgical intervention. BPV may be influenced by autonomic instability²⁷, altered vascular compliance^{2, 6, 7}, diabetes²⁸, neurologic abnormalities^{3, 10}, diurnal variability and anxiety⁸, and medication non-compliance²⁹. Notably, although medication non-compliance may promote BPV, adjusting for non-compliance does not explain BPV effects on cardiovascular outcomes in non-surgical patients.³⁰ Aging may also influence cardiac baroreflex latency and contribute to BPV. In addition, BPV³¹ may be higher in patients receiving anti-hypertensives, particularly ACE inhibitors^{9, 11, 32}, although the effects of BPV persisted in our data set when we controlled for preoperative ACE inhibitors, beta blockers or any anti-hypertensives.

It should be noted that we calculated BPV as the standard deviation of at least 10 measurements over three years. The standard deviation in BP (SD) is a commonly used measure of BPV in the medical literature and was chosen accordingly. Previous work by ourselves and other authors^{1, 19, 20} have explored additional definitions of BPV but found that such additional definitions do not change the central message that greater BPV predicts adverse outcomes. Only patients with 10 outpatient BP's were included. Ten measurements over 3 years is similar to techniques that have been used by others for BPV assessment, including enough measurements over a long enough timeframe to define BPV and still short enough to be manageable, easily measurable and practical enough to be useful, without diluting dilute relatively recent BPV status with data that is several years old when the patient's physiology may have been very different. We previously conducted a sensitivity analysis that validated this definition¹. Most surgeons will not be able to easily and intuitively calculate standard deviations from lists of blood pressure measurements in their electronic medical record. Ideally, the computerized record could itself be set to calculate BPV, just as it does for other calculated parameters such as body mass index. However, we have previously reported that simply scanning a list of blood pressure readings and seeking the greatest change between any two consecutive readings carries similar predictive power and is much easier for a busy physician.¹ Surgeons may also be concerned about the lack of standardization in blood pressure measurement environments and techniques over time, and certainly this can affect blood pressure. However, the data we report here were obtained in a

similar “real world” setting without standardization and nevertheless clearly carry prognostic import.

The mechanism underlying the association between BPV and postoperative morbidity and mortality awaits exploration. How BPV “causes” postoperative surgical morbidity and mortality awaits exploration. Low (rather than high) variability in preoperative heart rate is associated with post-induction hypotension during abdominal surgery.³³ BPV may indicate autonomic instability or vascular wall abnormalities that could affect surgical risk directly.³⁴ Acute preoperative systolic BPV has been associated with the degree of change in blood pressure after tourniquet deflation during knee arthroplasty.³⁵ Conversely, patient-related issues like dementia, anxiety in hospital settings or poor compliance with treatment instructions could certainly affect postoperative outcomes, although non-compliance explains relatively little BPV⁴.

Certainly, all of the conventional limitations of a retrospective analysis of a VA dataset apply to our findings. The VINCI database is a robust and well-recognized data set utilizing VA healthcare data. However, most veterans are male, and administrative data can be flawed. However, our previous pilot study of post-CABG patients¹³ examined a mixed gender private hospital population with similar results, using a prospectively populated patient registry rather than administrative data. More specifically, the VINCI database only captures events within the VA system. Thus, we did not record BP measurements that might have been achieved at outside settings and medication usage outside the VA system might have been missed if medication reconciliation did not pick it up during VA encounters. We might have also missed postoperative complications that occurred outside the VA system, although there is no particular reason to believe that high BPV patients are more or less likely than low BPV patients to seek care for complications outside the VA system. Many BPV studies have analyzed clinical trials of cardiovascular medications in highly selected patients. In contrast, the present study represents “real world” data from across the VA system.

It might also be argued that by requiring patients to have at least 10 outpatient BP readings over three years, we selected patients with high health care utilization who might not represent the population at large. Others have correlated BPV with long term outpatient mortality persisted based on 8 BP readings over 2 years,¹² or even only six BP readings over ten years.³⁶ Indeed, Muntner¹⁰ associated systolic BPV with subsequent mortality in a retrospective analysis of the NHANES study that included patients who had at least three BP measurements over six years. Moreover, three visits to a Veterans Administration facility per year does not seem abnormally high for a typical veteran who gets his care through the VA including primary care, medical specialty consultations, and mental health visits, as well as flu shots and other health encounters. In our original national dataset, 71% of patients had 10 or more BP's over the previous three years.

Diastolic BPV tended to parallel systolic BPV, but this was not uniformly true. Although systolic BPV generally correlated most strongly with postoperative adverse outcomes, multidimensional analyses suggested that systolic and diastolic BPV tended to adversely affect most outcomes independently. Therefore, both may merit consideration in using BPV for perioperative surgical risk assessment.

We studied patients undergoing a broad range of procedures. Although outcome numbers were in many cases too small to demonstrate statistical significance of BPV effects on each specific outcome for each specific procedure (not shown), we could not attribute our observations to any specific procedure. The diversity of procedures studied suggests that these effects may also occur with other major surgical procedures. Whether such effects also occur after anesthesia for minor procedures awaits further study.

Like patients using other antihypertensive agents, patients using calcium channel blockers tend to have higher BPV than patients not using them.³² However, patients receiving amlodipine may have lower BPV than those receiving other anti-hypertensives,^{11, 37, 38} and it has been suggested that amlodipine might treat BPV to improve prognosis in non-surgical patients.^{14, 16, 39} Retrospective analyses suggest that long acting calcium channel blockers may to some extent protect against the effects of high BPV in medical patients, reducing risks of stroke^{40–42} and diabetic foot ulceration in patients without known vascular disease.⁴³ Calcium channel blockers may improve large artery compliance¹⁷ and baroreceptor sensitivity^{15, 18}. We found no evidence that calcium channel blockers protect against the perioperative increased risk of high BPV. This could reflect our inclusion in our study of patients with substantial vascular disease. For instance, although calcium channel blockers protect diabetics without known peripheral vascular disease against the propensity toward foot ulceration associated with high BPV⁴³, they do not protect against major amputation in patients who already have stigmata of more advanced disease such as pre-existing foot ulcers, vascular disease, or neuropathy.⁴⁴ Conversely, the association of BPV with poor outcomes in medical patients is poorly understood, and likely involves different mechanisms. For instance, treating patients with calcium channel blockers does not seem to ameliorate the BPV-associated risk of cognitive decline in high risk elderly patients⁴⁵ Thus, the mechanisms underlying poor surgical outcomes in high BPV patients may differ from those causing poor outcomes in medical patients. Finally, if calcium channel blockers had actually lowered some patients' BPV, any favorable effect of such drugs on surgical outcomes in high BPV patients might have been offset by an "artifactual" lowering of the BPV itself without reducing whatever factors cause both BPV and poor surgical outcomes. Dissecting these disparate possibilities requires further study and perhaps even prospective interventional trials, beyond this investigation.

For outcomes assessments of large populations in quality improvement or clinical trials, we suggest that BPV ought to be considered in stratifying or analyzing results, just like hypertension, diabetes, or other comorbidities. Our data suggests that BPV clearly adds value to the prediction of adverse events even when information about such other comorbidities as diabetes and hypertension is already included in the analysis. We have specifically hesitated to create a hierarchical risk factor scale so as not to minimize recognized risk factors such as diabetes and hypertension. The question of whether high BPV poses a stronger or weaker risk than a different risk factor would seem relevant only if one were to consider knowingly choosing to replace a different risk factor with BPV in an analysis, which seems counterintuitive given the known importance of such other risk factors.

BPV is not currently included in surgical registries like VASQIP, ACSQIP, or the ASTS registry. Although one might argue that BPV may not be modifiable for individual patients preoperatively and so should not be considered in risk assessment or quality assurance, other much better understood risk factors such as hypertension itself or diabetes are often also not really substantially modifiable in the immediate preoperative period for practical purposes. Although we certainly understand more about how hypertension or diabetes affects patients, this should spur us to further exploration of BPV but not prohibit its consideration in risk assessment. The incremental surgical risk for a patient in the highest quartile of BPV seems similar in magnitude to the increased risk in dialysis patients after knee arthroplasty⁴⁶ or malnourished patients undergoing radical cystectomy⁴⁷ and ought to be similarly viewed in assessing patients.

How then should a surgeon respond to finding that a prospective surgical patient has high BPV? We currently lack medical therapy that effectively and specifically treats BPV, as distinct from hypertension, and the institution of calcium channel blockade is not supported by these results. Procedures like colectomy or coronary artery bypass are unlikely to be elective or delayed for prolonged optimization, but accurate risk assessment is nevertheless valuable for counseling patients and may affect surgical and anesthetic choices. Surgeons and patients could consider lesser procedures or even avoiding surgery if their risk is high enough. Like other scarce medical resources⁴⁸, physicians' time must be used efficiently. However, OR efficiency can be viewed in different ways⁴⁹, and noting that one's patient might have thrice the expected mortality would seem inherently worthwhile. In addition, finding a high BPV in a patient submitted for a more elective procedure like hip replacement might motivate a more aggressive search for other risk factors that could be modified to optimize the patient, reducing overall surgical risk. More conventional patient optimization strategies like tightened diabetic control, weight loss, smoking cessation, and other medication optimization might be recommended more forcefully with the recognition of the further risk posed by high BPV.

Further investigation may elucidate why BPV correlates with poor surgical outcomes. However, regardless of the mechanism, these results suggest that high BPV is a risk factor for poor surgical outcomes, including MI, CVA, renal failure, readmission, and death. This should be considered in assessing patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACE inhibitor	acetyl cholinesterase inhibitor
AV fistula	arteriovenous fistula

BMI	body mass index
BP	blood pressure
BPV	blood pressure variability
CABG	coronary artery bypass grafting
CCB	calcium channel blocker
CVA	cerebrovascular accident
MI	myocardial infarction
SD	standard deviation
VA	Veterans' Administration

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Highlights

- High variability in outpatient blood pressure from day to day, distinct from hypertension, is associated with higher risk-adjusted poor surgical outcomes.
- These include postoperative readmission, myocardial infarction, CVA, renal failure, readmission, and 90 day mortality.
- Systolic and diastolic variability trended together but had independent effects.
- This previously unsuspected risk factor should be considered in preoperative risk assessment and stratification.

Figure 1.

(A) The distribution of systolic blood pressure variability within the study population is shown. The vertical axis depicts the percentage of the population that had systolic BPV greater than or equal to the value shown. 5% of patients had a BPV less than 9mmHg while the uppermost 5% of patients had a systolic BPV >24mmHg. Mean systolic BPV was 15.9. (B) The distribution of diastolic blood pressure variability within the study population is shown. The vertical axis depicts the percentage of the population that had diastolic BPV greater than or equal to the value shown. 5% of patients had a diastolic BPV less than 5mmHg while the uppermost 5% of patients had a diastolic BPV >14mmHg. Mean diastolic BPV was 9.1 mmHg. (C) The correlation of systolic and diastolic BPV is illustrated. Systolic BPV correlated with diastolic BPV ($r=0.589$, $p<0.001$), although we did observe patients in whom systolic and diastolic BPV were disparate.

Figure 2.

Odds ratios from systolic (A) and diastolic (B) BPV associated with six outcomes are depicted by symbols as indicated in the key. Linear splines were added to show trends in statistically significant odds ratios. Equations represent the functions determining these splines.

Figure 3.

Contour graphs of estimated change OR for mortality (A), readmission (B), and MI (C) as systolic and diastolic BPVs change. Odds ratios are represented as color spectra, with the lowest odds ratios in dark purple and the highest odds ratios in bright red. Vertical lines are drawn at systolic BPV of 10 and 20 mmHg to specifically indicate the change in odds ratio (color) as the diastolic BPV increases for each of these systolic BPVs. The actual values for the range and change in odds ratio for each of these systolic BPV values are recorded at the top of each vertical line. The equation at the lowest right represents the function that determines the odds ratio based upon systolic and diastolic BPVs. The equation presents significant coefficients for systolic and diastolic variables and their interaction.

Figure 4.

Odds ratios of outcomes for carotid endarterectomy (Carotid), colon resection (Colon), hip replacement (Hip), and coronary revascularization (CABG) plotted against systolic (A) and diastolic (B) BPV are depicted by symbols as indicated in the key. Linear splines were added to show trends in statistically significant odds ratios. Equations represent the functions determining these splines.

Table 1.

Covariates predicting BPV and outcomes for 22,233 patients.

		Systolic	Diastolic	Mortality	Readmission	MI	CVA	Renal	Wound
		15.94 (4.81)	9.10 (2.48)	858 (3.86%)	5,945 (26.87%)	668 (3.00%)	539 (2.42%)	477 (2.15%)	197 (0.89%)
	Descriptive	B	B	OR	OR	OR	OR	OR	OR
Male	21,331 (95.94%)	-0.002	-0.011	1.493	0.784*	2.731*	1.588*	1.352	1.242
Black	3,504 (15.76%)	0.061*	0.064*	0.960	1.231*	0.607*	0.607*	1.149	0.954
Other	1,476 (6.64%)	0.003	-0.003	0.982	0.969	1.467*	1.029	1.877*	0.594
Age	67.55 (9.71)	0.173*	-0.023*	1.066*	1.011*	1.007	1.021*	1.007	0.978*
BMI	29.58 (5.74)	-0.065*	-0.031*	0.962*	0.993*	1.013	1.010	1.024*	1.020
Diabetes	2,268 (10.20%)	0.069*	0.024*	1.173	0.293*	1.429*	0.841	1.035	0.837
Hypertension	6,722 (30.23%)	0.059*	0.054*	0.468*	0.914*	1.118	1.082	1.012	0.929
Length of Stay	8.29 (7.67)	0.033*	0.050*	1.054*	1.038*	1.062*	1.046*	1.049*	1.076*
Beta Blk Pre-adm	4,727 (21.26%)	0.072*	0.049*	1.282*	1.116*	1.294*	1.343*	1.714*	0.699
ARB/ACE Inhibitors	4,154 (18.68%)	0.073*	0.055*	0.853	0.937	1.464*	1.148	1.087	0.953
Diuretics	2,599 (11.69%)	0.070*	0.049*	1.392*	1.397*	0.788	0.856	1.307*	0.992

Mean (standard deviation) or N (%) are shown as descriptives. Females (4.06%), white race (77.60%), no diabetes (89.8%), hypertension (69.77%), beta blockers pre-admission (78.74%), ARB/ACE inhibitors (81.32%), and Diuretics (99.31%) were used as reference values in the regressions.

* p < .05.

Systolic and diastolic BPV were entered as continuous variables and their slope coefficients were standardized. Slope Coefficients are standardized. Standardized slope coefficients (B) of the covariate predicting systolic or diastolic BPV are shown in columns 2 and 3. Only 'other' race (referenced to white race) was not significant in multiple linear regressions. The ORs of the relationships between the covariates and the six outcomes from multiple logistic regressions are shown in the following columns. All variables were significantly associated with at least one outcome.

Table 2.

Significance of systolic and diastolic BPV predicting outcomes when only one of five procedures is removed from the data (when controlling for covariates in logistic regression). (Shaded parameters indicate statistical significance.)

Outcome	Procedure Removed	N Event/Total N	Systolic BPV		Diastolic BPV	
			St Beta	p	St Beta	p
Mortality	av Fistula	807 / 21,123	.1373	<.001	.1358	<.001
	CABG	748 / 18,569	.1389	<.001	.1422	<.001
	Carotid	829 / 18,704	.1566	<.001	.1501	<.001
	Colon	425 / 15,447	.1457	<.001	.1721	<.001
	Hip	638 / 15,301	.1215	<.001	.1140	<.001
	Pancreas	843 / 22,021	.1422	<.001	.1444	<.001
Readmission	av Fistula	5,525 / 21,123	.0609	<.001	.0711	<.001
	CABG	5,065 / 18,569	.0704	<.001	.0811	<.001
	Carotid	5,373 / 18,704	.0850	<.001	.0861	<.001
	Colon	3,889 / 15,447	.0644	<.001	.0815	<.001
	Hip	4,126 / 15,301	.0828	<.001	.0793	<.001
	Pancreas	5,887 / 22,021	.0726	<.001	.0811	<.001
MI	av Fistula	654 / 21,123	.1417	<.001	.0195	.384
	CABG	165 / 18,569	.1275	.003	.0291	.510
	Carotid	630 / 18,704	.1393	<.001	.0105	.648
	Colon	592 / 15,447	.3021	<.001	.0042	.861
	Hip	633 / 15,301	.1039	<.001	-.0012	.959
	Pancreas	666 / 22,021	.1195	<.001	.0085	.703
CVA	av Fistula	531 / 21,123	.0718	.003	-.0108	.666
	CABG	281 / 18,569	.1323	<.001	.0588	.074
	Carotid	386 / 18,704	-.0063	.833	-.0768	.012
	Colon	460 / 15,447	.0754	.004	-.0140	.607
	Hip	501 / 15,301	.0461	.073	-.0078	.762
	Pancreas	536 / 22,021	.0626	.011	-.0127	.611
Renal Failure	av Fistula	414 / 21,123	.0434	.123	-.0353	.218
	CABG	286 / 18,569	.0953	.004	.0711	.029
	Carotid	460 / 18,704	.0887	<.001	-.0020	.941
	Colon	344 / 15,447	.0726	.011	-.0110	.721
	Hip	409 / 15,301	.0665	.018	-.0129	.684
	Pancreas	472 / 22,021	.0724	.005	.0002	.993
Wound Infection	av Fistula	195 / 21,123	.0066	.877	.0165	.684
	CABG	181 / 18,569	-.0395	.388	-.0218	.631
	Carotid	194 / 18,704	.0085	.841	.0083	.839
	Colon	47 / 15,447	.0807	.325	.0566	.478

Outcome	Procedure Removed	N Event/Total N	Systolic BPV		Diastolic BPV	
			St Beta	p	St Beta	p
	Hip	176 / 15,301	-.0483	.293	-.0317	.467
	Pancreas	192 / 22,021	-.0196	.651	-.0044	.914

Table 3.

Odds of outcomes from controlled logistic regressions of systolic BPV among CCB users and among CCB non-users.

Outcome	CCB	BPV OR	LL	UL
Mortality	Yes	1.049 *	1.010	1.091
(N=106; 752)	No	1.057 *	1.041	1.073
MI	Yes	1.049 *	1.010	1.091
(N=84; 584)	No	1.045 *	1.001	1.091
CVA	Yes	1.020	0.970	1.073
(N=61; 478)	No	1.025 *	1.006	1.045
Renal	Yes	1.019	0.974	1.065
(N=74; 403)	No	1.029 *	1.008	1.051
Readmission	Yes	1.029 *	1.012	1.047
(N=784; 5,191)	No	1.028 *	1.021	1.035

*
p<.05

2,558 (12%) used CCBs, 18,923 (88%) did not

OR from logistic regression of BPV predicting the outcome and are interpreted as the likelihood of an outcome given an increase of 1mmHg in the systolic or diastolic BPV. The table presents these ORs for patients who were recorded to be receiving CCB and patients who were not recorded to be receiving CCB. Covariates used were length of stay, sex, race, age, BMI, diabetes or hypertension diagnosis, and pre-admission use of beta-blockers or ACE inhibitors.