Cohort Study Evaluating Preoperative Blood Pressure Values and Risk of 30-day Mortality following Elective Non-Cardiac Surgery

Sudhir Venkatesan MPH[1], Sudhir.Venkatesan@nottingham.ac.uk

Puja Myles PhD[1], Puja.Myles@nottingham.ac.uk

Helen Manning MRCOG[2], hmanning@doctors.org.uk

Abdul M. Mozid MRCP[3], ammozid@hotmail.com

Charlotte Andersson MD[4], ca@heart.dk

Mads Emil Jørgensen MB[5], Mads.Emil.Joergensen@regionh.dk

Jonathan G. Hardman FRCA[6], J.Hardman@nottingham.ac.uk

S. Ramani Moonesinghe MRCP[7], rmoonesinghe@googlemail.com

Pierre Foex FRCA[8], pierre.foex@ndcn.ox.ac.uk

Monty Mythen FRCA[7], m.mythen@ucl.ac.uk

Michael PW Grocott FRCP[9], mike.grocott@soton.ac.uk

Robert D. Sanders FRCA[10], rsanders4@wisc.edu

1. Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom.

2. Department of Obstetrics & Gynaecology, University of Wisconsin, Madison, USA.

3. Department of Cardiology, Bristol Heart Institute, Bristol, United Kingdom.

4. Department of Internal Medicine, Division of Cardiology, Glostrup Hospital, University of Copenhagen, Denmark.

5. The Cardiovascular Research Center, Gentofte Hospital, University of Copenhagen, Denmark.

6. Department of Anaesthesia, University of Nottingham, United Kingdom.

7. Surgical Outcomes Research Centre, Department of Anaesthesia, University College London Hospital, London; National Institute for Academic Anaesthesia's Health Services Research Centre, London, United Kingdom.

8. Nuffield Division of Anaesthetics, Oxford University Hospital, Oxford, United Kingdom.

9. Integrative Physiology and Critical Illness, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton; University Hospital Southampton NHS Foundation Trust; Southampton NIHR Respiratory Biomedical Research Unit, United Kingdom.

10. Anesthesiology & Critical Care Trials & Interdisciplinary Outcomes Network (ACTION), Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, Madison, USA.

Brief Title: Blood pressure and surgical mortality

[+]**Corresponding author**: *Dr Robert D Sanders, Department of Anesthesiology, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, B6/319 CSC Madison, WI 53792-3272 Telephone: 608-263-8100 Fax: 608-263-0575 Madison, USA. Email: robert.sanders@wisc.edu*

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Contributors

RDS and PM designed the research question and study analysis plan with input from the co-authors. SV performed the analysis with input from PM and RDS. SV and PM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All co-authors advised on the analyses. RDS and SV wrote the manuscript with significant input from PM. All authors advised on the manuscript content and contributed to editing and scientific direction. All authors approved the final manuscript.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no competing interests that may be relevant to the submitted work.

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Abstract

Background: Arterial blood pressure (BP) outside of the normal range has important chronic health implications; however, the influence of preoperative BP on postoperative mortality remains controversial.

Objective: To investigate the relationship between preoperative BP and 30-day mortality following elective non-cardiac surgery.

Methods: Cohort study of primary care data from the United Kingdom Clinical Practice Research Datalink (2004-2013). Multivariable logistic regression models, including restricted cubic splines for preoperative numerical BP values, were constructed for 30-day mortality risk. The full model included 29 perioperative risk factors including age, gender, race, comorbidities, medications, and surgical risk. Sensitivity analyses were conducted for elderly patients (>65 years old) and the preoperative timing of BP measurement (within 12 weeks of surgery).

Results: 251,567 adults were included with 589 (0.23%) deaths within 30 days of surgery. After adjustment for all risk factors, preoperative low BP was consistently associated with statistically significant increases in the odds ratio (OR) of postoperative mortality. Statistically significant risk thresholds were identified at preoperative systolic 119mmHg (adjusted odds ratio 1.02 [95% CI 1.01–1.02] compared to reference 120mmHg) and diastolic 63mmHg (OR 1.24 [1.03-1.49] compared to reference 80mmHg). As BP decreased, the OR of mortality risk increased. Subgroup analysis demonstrated that the risk associated with low BP was confined to the elderly with similar risk thresholds identified. Analysis of preoperative values obtained within 12 weeks of surgery showed similar results. Adjusted restricted cubic splines analysis identified that diastolic hypertension was associated with increased postoperative mortality in the whole cohort however this effect was not apparent in the elderly or preoperative subgroups.

Conclusions: In this large observational study we identified a significant dose-dependent association between low preoperative BP values and increased postoperative mortality following elective surgery in the elderly. Preoperative hypotension represents a novel risk factor for postoperative mortality in the elderly.

Perspectives

COMPETENCY IN MEDICAL KNOWLEDGE:

Our data show that preoperative hypotension is associated with increased postoperative mortality in the elderly. This effect was robust to adjustment for confounding and sensitivity analyses, including measurement of BP within 12 weeks of surgery, and is consistent with recent studies suggesting that intraoperative and postoperative hypotension increase the risk of postoperative mortality. Hence preoperative hypotension may offer a cheap and readily available marker of subsequent postoperative risk. Our data did not find clear thresholds for risk associated with systolic hypertension, but rather emphasized the importance of diastolic hypertension, challenging recent guidelines that provide equal weight to both systolic and diastolic BP.

TRANSLATIONAL OUTLOOK: As accumulating data suggest intra- and post-operative hypotension are associated with increased mortality, further research should investigate whether preoperative hypotension acts as a mediator, causally altering postoperative risk, perhaps through predispostion to perioperative hypotension. We suggest that elderly patients with low preoperative blood pressure should undergo judicious control of their hemodynamics in the perioperative period to maintain them at preoperative levels. Future randomized trials should identify appropriate perioperative hemodynamic targets for these vulnerable patients. Further study of the risk imposed by diastolic hypertension is also warranted.

Introduction

Community control of blood pressure (BP) exerts profound effects on cardiovascular outcomes with "J" shaped risk curves indicating risks at either end of the BP spectrum(1-3). The optimal BP remains unclear due to the complexity of the relationship between hypertension, cardiovascular disease, age, and other risk factors(4,5). Excessive reduction of BP may increase cardiovascular risk, especially in the elderly, or patients with diabetes or coronary artery disease(2,4,6), perhaps due to impaired diastolic coronary perfusion(2). Hence recent guidelines recommend relaxed BP targets in these populations. However, the recent SPRINT study challenged these recommendations: lowering systolic BP to a mean value of 121mmHg (versus 136mmHg) was associated with reduced cardiovascular events in the community(7).

While there is strong evidence for the longitudinal control of BP to reduce incident vascular events, guidance for the optimisation of preoperative BP lacks a strong evidence base(8-10). It remains unclear what thresholds are appropriate for the perioperative period where anaesthesia and surgery lead to hemodynamic changes, an exaggerated stress response, hypercoagulability and inflammation. Indeed, the optimal preparation for the physiological strain of anesthesia and surgery is unlikely to be the same as reducing longterm vascular risk in the community. There are significant differences in the mechanisms of injury between incident vascular events in the community and in surgical patients during the perioperative period. Indeed, recent studies stress how perioperative hypotension leads to increased postoperative mortality(11,12). Hence we cannot assume that BP risk thresholds derived from community data will extrapolate to the perioperative period. In particular, the hypothesis that preoperative low BP may be a risk factor for postoperative mortality requires evaluation. Conceptually this hypothesis is supported by evidence that preoperative low BP is a predictor of intraoperative hypotension(13) and intraoperative hypotension is a predictor of postoperative mortality(14,15). Nonetheless recent guidelines do not mention the potential impact of preoperative low BP on postoperative outcomes(10).

Similarly, the contribution of comorbid hypertension to postoperative mortality is unclear despite its prevalence in the community and the established effects on multiple vascular outcomes(5). In 2004, our meta-analysis found an association between the diagnosis of preoperative hypertension and increased postoperative cardiac events; however we were unable to identify numerical BP thresholds associated with increased risk(16). Moreover the diagnosis of preoperative hypertension (or raised pulse pressure(17,18)) is not universally considered important in determining postoperative risk(19,20), as suggested by its omission from the widely used revised cardiac risk index(21). Despite the lack of clarity on this issue, in the UK approximately 1% (~100 patients per day) of elective surgical patients have surgery delayed for further primary care management of BP(10).

To date, no large study has attempted to identify blood pressure thresholds associated with increased postoperative mortality in elective non-cardiac surgery. Herein we analyzed primary care data from an elective non-cardiac surgery cohort to identify preoperative numerical blood pressure thresholds associated with increased postoperative mortality in all patients and in the elderly. Our aim was to identify preoperative risk thresholds beyond which the odds of postoperative mortality increases through analysis of BP as a continuous measure.

Methods

Data source and study design

This research study was approved by the Independent Scientific Advisory Committee for the Medicines & Healthcare products Regulatory Agency, United Kingdom (number 11_034). We extracted longitudinal data from the Clinical Practice Research Datalink – a primary care database including a representative sample of approximately 6% of the UK population. Patients who underwent specific non-cardiac surgical procedures between January 1st 2004 and December 31st 2013 were identified using medical codes (Appendix 1). We retained only adult patients (aged 18 years or above) who had been registered with their General Practitioner for at least one year prior to the date of elective non-cardiac surgery (see STROBE diagram, Supplementary Figure 1).

Patient Involvement

Patients were not involved in the design of this study.

Outcome and Exposure variables

Postoperative mortality, defined as death occurring within 30 days following non-cardiac surgery, was the outcome variable. The latest BP measurement recorded before surgery was the exposure variable.

Covariates

The following comorbidities were adjusted for: atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease and cancer. Additionally, we also adjusted for Charlson's comorbidity score(22) as a weighted indicator of comorbidity burden. Medications adjusted for included statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors. When adjusted for as covariates, drugs were coded as binary variables. Body Mass Index (BMI) was adjusted for by being categorised as <18.5, 18.5-24.99, 25-29.99 and >30. Patients were also categorised as 'current smoker', 'ex-smoker' or 'non-smoker' with alcohol consumption status above or below the recommended UK limits (21 units per week for men and 14 units per week for women). To account for variations in access to care, we adjusted for socioeconomic status (IMD 2010 quintiles) and number of BP measurements recorded in the dataset. The Index of Multiple deprivation (IMD) 2010 is a composite measure of deprivation that assigns a deprivation score to a geographical area based on a number of factors including employment, education, neighbourhood crime rates and access to healthcare facilities. We used the IMD deprivation score assigned to individual subjects' postcode of residence. Finally, we adjusted for the variation in risk posed by the different types of non-cardiac surgical procedures using the operative procedure classes in the validated surgical risk scale(23,24). Each surgical procedure included was given a score from 1 to 5, in increasing order of risk posed by the specific specialty and procedure. Missing data were coded as a dummy variable category.

Statistical analysis

Our primary analysis investigated the association between systolic BP, diastolic BP and pulse pressure with postoperative mortality. To reduce any confounding that the BP reading was associated with the pathology driving the need for surgery, or not reflecting the preoperative period, we conducted additional sensitivity analyses based on time of BP measurement by restricting analysis to BP values recorded between day 8 to 84 (1 to 12 weeks) or day 8 to 365 prior to surgery. For the overall analysis, systolic and diastolic BP measurements were separately modelled as continuous variables using unadjusted and adjusted restricted cubic spline regression analyses (with four knots: systolic 104, 124, 138, and 160mmHg and diastolic 60, 74, 80, and 94mmHg). The location of the knots was determined based on recommended percentiles at 5%, 35%, 65% and 95%(25). Two sets of adjusted logistic regression models were constructed: a fully-adjusted model where the entire covariate list of *a priori* confounders was adjusted for and a parsimonious model where only those covariates that were statistically significantly associated with the outcome (postoperative mortality) were entered in to the model. For the systolic and diastolic BP analyses 120mmHg and 80mmHg respectively were chosen as reference values as these were the population modes in the whole cohort. Pulse pressure was calculated as diastolic BP subtracted from systolic BP with a reference value of 40 mmHg. Model fit was assessed using the Hosemer-Lemeshow (HL) goodness of fit test. Thresholds for risk were set when the 95% confidence intervals (CI) no longer overlapped with 1 (p<0.05). We used the p-value obtained from a likelihood ratio test to separately test for interaction between systolic and diastolic BP and patient age, and heart failure. We also conducted a subgroup analysis (≥65 years and <65 years), as we hypothesized that the extremes of blood pressure would be particularly associated with increased mortality in the elderly(26).

Results

Our study cohort included 251,567 adult patients who underwent elective non-cardiac surgery (Supplementary Figure 1). In total, 52,241 had a systolic BP <120mmHg, 110,488 had a systolic BP 120-139mmHg and 80,207 had a systolic BP ≥140mmHg. Systolic BP measurement was missing in 8,631 cases. A total of 589 deaths were observed (0.23%) within 30 days of surgery. Those who died within 30 days of surgery tended to have more comorbidities than those who survived (Table 1). Absolute risk values associated with different BP strata are available in Supplementary Tables 1-3. For example, mortality was 0.28% in all patients with a preoperative systolic BP under 100mmHg and 2.15% in elderly patients (>65 years old) with a systolic BP under 100mmHg.

Primary analysis

For systolic BP, unadjusted restricted cubic spline analysis showed increased odds of postoperative mortality associated with hypertension (≥123mmHg). Due to the relationship between age and BP, we confirmed a significant interaction with age for both systolic (p<0.001) and diastolic (p=0.011) BP (likelihood ratio test). When adjusting for all covariates including age (full model), low systolic BP (starting at 119mmHg; adjusted odds ratio [OR] [OR] 1.02 [95% CI 1.01-1.02] for 119mmHg compared to reference) was significantly associated with postoperative mortality, with the OR of death increasing with each unit decrease in systolic BP (Figure 1). Systolic hypertension was not associated with increased mortality in adjusted analyses. Table 2 shows the point estimates for specific BP values separated by 20mmHg intervals derived from the cubic splines curve. Results from the parsimonious model were similar to the full model (Supplementary Table 4, Supplementary

Figure 2). For the fully-adjusted model, the HL goodness of fit test produced a X^2 value of 8.25 (p-value: 0.4091) suggesting a good fit.

Similar to systolic BP, low diastolic BP (≤70mmHg) was associated with postoperative mortality in the unadjusted analysis. While this effect persisted in the fully adjusted model, the magnitude of effect observed was smaller and an increase in odds ratio of postoperative mortality was observed at 63mmHg (OR 1.24 [95% CI: 1.03 to 1.49]) which was dose-dependent (Figure 1, Table 2). Similar results were obtained from the parsimonious model (Supplementary Table 4, Supplementary Figure 2). While unadjusted analysis of raised diastolic BP suggested it was not associated with an increase odds of mortality, after adjustment, diastolic hypertension was associated with increased risk in the overall population, with a threshold at >84mmHg (OR 1.07 [95% CI: 1.01 to 1.13]) (Table 2).

Increased pulse pressure (≥50mmHg) was seen to be associated with a statistically significant increase in postoperative mortality in the unadjusted analysis. However, after adjusting for all covariates this effect was attenuated. Rather, pulse pressures from 42 to 58mmHg were associated with a small reduction in OR of postoperative mortality. Furthermore pulse pressures <37mmHg were associated with increased risk (Figure 2, Supplementary Table 4). For the fully-adjusted model, the HL goodness of fit test produced a X^2 value of 12.10 (p-value: 0.1466) suggesting a good fit.

Sensitivity Analyses

We performed a sensitivity analysis with exclusion of BP values <80/40mmHg that may be considered non-physiological, leaving 251,484 patients in the whole cohort and 84,601 in the elderly, and found similar results (Supplementary Table 5; Supplementary

Figure 3 & 4). To identify if preoperative hypotension may reflect heart failure (despite adjusting for the diagnosis of heart failure and prescription of loop diuretics) we tested for an interaction between blood pressure values and congestive heart failure. Indeed heart failure occurred in 1.52% of patients with a systolic <120mmHg and 1.29% of normotensive patients (Supplementary Table 6). However we found no evidence of interaction using the likelihood ratio test (systolic BP p=0.113, diastolic BP p=0.179).

A further sensitivity analysis was conducted based on the timing of BP measurement to exclude indication bias associated with low BP. For example, hypotension may be associated with emergency surgery hence, in addition to restriction our dataset to elective surgery, we excluded BP values obtained within a week of surgery (as longer time intervals between primary care measurement of low BP and surgical admission would appear imprudent). A histogram showing the timing of blood pressure measurements is available in Supplementary Figure 5). Furthermore, we restricted the dataset to within 12 weeks of surgery (day 8 to 84) to reflect preoperative, rather than long-term, measurement. Where BP measurements were made between 1 and 12 weeks preoperatively (n=57,084), systolic BP of ≤119mmHg and diastolic BP of ≤64mmHg were associated with increased OR of postoperative mortality (Figure 2; Table 2). The HL goodness of fit suggested a good fit (systolic BP: X^2 4.67, p-value: 0.7925; diastolic BP: X^2 10.53, p-value: 0.2300). Similar analysis of values from 1-52 weeks before surgery found a similar effect (n=143,462) with systolic BP of ≤119mmHg and diastolic BP of ≤65mmHg were associated with increased OR of postoperative mortality. The HL goodness of fit X^2 6.89 (p-value: 0.5481) also suggesting a good fit.

The impact of preoperative blood pressure in the elderly

An *a priori* planned subgroup, supported by our interaction analysis for age, included patients aged 65 years and above (n=84,633). Of whom 7,924 had systolic BP <120mmHg, 34,531 had systolic BP 120-139mmHg and 41,427 had systolic BP ≥140mmHg (651 had missing systolic values). Unadjusted and adjusted data (fully-adjusted and parsimonious models) demonstrated a dose-dependent increased OR in postoperative mortality associated with systolic and diastolic hypotension (Table 2, Figure 3) supporting our hypothesis that elderly patients harbour the hypotension risk in the cohort. Adjusted associations (fully-adjusted model) with increased mortality were first observed at 119mmHg systolic (OR: 1.02 [95% CI: 1.01-1.03]) and 63mmHg diastolic (OR: 1.24 [95% CI: 1.01-1.53]. Results from parsimonious models are presented in Supplementary Table 4 and Supplementary Figure 2. A pulse pressure of ≤39mmHg was associated with increased OR of postoperative mortality (fully-adjusted model), while measurements from 41 to 66mmHg were associated with a reduced OR of postoperative mortality (Figure 2). HL goodness of fit tests showed good model fit (systolic pressure: X^2 14.13 (p-value: 0.0785); diastolic pressure: X^2 10.78 (p-value: 0.2144); pulse pressure: X^2 14.06 (p-value: 0.0803)). Restricted cubic splines analysis did not identify associations between raised systolic or diastolic BP and increased mortality in the elderly. In patients <65 years old (n=166,934), no association was observed between BP and postoperative mortality.

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Discussion

This cohort study demonstrated a dose-dependent association between preoperative hypotension and postoperative mortality that was consistent across systolic and diastolic BP and sensitivity analyses including the timing of BP measurement. This effect was confined to the elderly, increasing biological plausibility. It is important to note that risk thresholds were identified by statistical difference from the reference ($p<0.05$) at systolic BP of 119mmHg and a diastolic of 63mmHg. At these thresholds the risk associated with the BP value was small but there was a supra-additive increase in the odds of mortality as preoperative BP dropped. Hence every 1mmHg drop in BP below these thresholds is associated with a larger increase in risk. In contrast, raised diastolic, not systolic BP, was associated with an increased odds of mortality in the whole cohort following adjustment. However the effect of raised diastolic BP was not evident in the elderly or when we restricted our analyses to the preoperative period (1-12 weeks prior to surgery). Additionally we observed that low, not raised, pulse pressure values were associated with increased OR of postoperative mortality.

Overall these data have important implications for perioperative risk stratification. The dose-dependent and consistent association of preoperative hypotension in the elderly and postoperative mortality reveals a novel, overlooked perioperative risk factor with increased risk apparent with BP values below 119/63mmHg. This represents a cheap and readily available preoperative marker of postoperative risk.

Preoperative hypotension

Prima facie, the emphasis of our results on hypotension seem to contrast with accumulating data on the community control of BP that emphasizes hypertension (5). However in the perioperative period anesthesia and surgery induce multiple physiological stresses including hemodynamic variation, surgical bleeding, increased myocardial work, pain, alterations in coagulabilty and inflammation that do not occur simultaneously or at a predictable time in the community. As such it seems plausible that preparation for elective surgery should require an alternate strategy to reducing long-term vascular risk. Indeed in the perioperative period hypotension often occurs and is associated with increased postoperative mortality(11,12), hence it is plausible that preoperative hypotension may predispose to perioperative hypotension and subsequently increase odds of death.

The association of preoperative low BP with subsequent postoperative mortality was robust across sensitivity analyses including when purely focused on the preoperative period (8-84 days prior to surgery). This links the events closely in time and increases the biological plausibility for the impact of preoperative hypotension on postoperative mortality. While the mechanisms of this effect remain unclear, the biologically plausibility of a link to perioperative hypotension is strong. We hypothesize that elderly patients with preoperative hypotension are operating at the lower limit of cerebral and other end-organ autoregulation(9) and that this predisposes them to harm from perioperative changes in hemodynamics, inflammation and the stress response, leading to secondary organ injury and increased risk of death. Consistent with this, low preoperative BP is a predictor of intraoperative hypotension(13) and intraoperative hypotension, like postoperative hypotension(11,12), is a predictor of postoperative mortality(14,15). Based on this interpretation, patients with low preoperative BP should have rigorous control of their BP in the perioperative period to maintain it at community levels.

In our sample 9.4% (n=7,924) of elderly subjects had a systolic BP<120mmHg meaning that preoperative hypotension is a prevalent risk factor. One possibility is that low BP represents heart failure in our population. However, in the UK the prevalence of heart failure condition is approximately 1% while in our dataset it was 1.4% suggesting that there is not a deficit in coding of the diagnosis. Hence we consider that our adjustment for heart failure diagnosis and exposure to loop diruretics would account for confounding from this variable. We also conducted an interaction analysis for BP and heart failure did not find a significant effect. Overall we do not consider that heart failure alone explains the association of low preoperative BP and postoperative mortality. An alternative explanation is the prescription of vasoactive medications; 2,329 elderly patients with a systolic BP<120mmHg (29%) had a CPRD diagnosis of hypertension hence over treatment of BP is another possible explanation. Accumulating data suggest that some community vasoactive medications may cause harm when continued into the perioperative period (11,27,28). Randomized trials are required to define the optimal management of community blood pressure medications in the perioperative period.

Preoperative hypertension

Consistent associations of hypertensive BP values with postoperative mortality were lacking. However in adjusted analysis of the whole cohort we identified that raised diastolic BP was associated with increased mortality in a dose-dependent manner. Given the role of diastolic BP in coronary perfusion, the prognostic implications of raised diastolic BP for cardiac events in the community in young to middle age(29), and the prevalence of cardiac events and myocardial injury in the perioperative period (30), future study of the impact of raised diastolic BP on the risk of postoperative cardiac events appears warranted. It is possible that patients with diastolic hypertension may be vulnerable to myocardial injury through impaired coronary perfusion during episodes of perioperative hypotension. Indeed myocardial injury is a major risk factor for postoperative mortality(30). However one small randomized controlled trial of low cardiovascular risk patients did not find a reduction in perioperative risk with acutely lowering diastolic BP to below 110mmHg during a preoperative admission(31). Randomized trials focussed on patients at increased cardiovascular risk seem indicated based on our findings.

Interestingly systolic BP was only associated with increased postoperative mortality in the unadjusted analyses of the whole cohort suggesting that age and other comorbidities, including the secondary consequences of systolic hypertension, exert a greater impact on perioperative risk. Indeed the rise in systolic BP with age leads to accumulation of end-organ vascular disease such as stroke and myocardial infarction that have important known effects on postoperative mortality.

Overall our data indicate that raised diastolic, rather than systolic, BP may influence postoperative risk. It is important to note that recent guidelines(10) emphasized both systolic and diastolic hypertension. Our data directly inform these guidelines as (1) preoperative hypotension, rather than hypertension, is the major hemodynamic factor associated with postoperative mortality and (2) diastolic hypertension exerts greater perioperative impact than systolic hypertension on postoperative mortality. Furthermore our data do not indicate a clear preoperative hypertensive threshold, obtained within 12 weeks of surgery, at which elective surgery is associated with increased mortality. Hence our data do not advocate for the cancellation or delaying of elective surgery for better preoperative control of hypertension as occurs in approximately 1% of elective surgical patients(10).

Strengths and Weaknesses

It is important to recognize that any numerical threshold for BP may be confounded by age, exposure to anti-hypertensive medications, end-organ vascular disease and other comorbidities. Hence we adjusted for many confounders in fully-adjusted and parsimonious models as well as conducting sensitivity analyses for the timing of BP measurement. Not only was the observed effect of preoperative hypotension consistent across models, it fulfils many of the Bradford-Hill criteria including: biological gradient (dose-dependence), plausibility(11,12,14,15), coherence(1-3) (4), strength and temporality.

We concentrated on primary care readings of BP to provide information prior to admission for an operation about perioperative risk and limit the impact of perioperative anxiety. Using primary care data to derive these estimates increases the generalizability of our data to patients undergoing non-cardiac surgery. The available BP data were recorded between one and 12 weeks (and additionally one and 52 weeks) preoperatively in our sensitivity analyses. Future studies should evaluate with greater granularity whether the timing of BP assessment alters the relationship with postoperative mortality. We focussed on mortality as it is the most important marker of severe postoperative complications and has strong clinical relevance however future studies should also include postoperative morbidity endpoints.

Our data are limited in other ways. The observational design of our study – like all large-scale epidemiology studies – is unable to prove causality and is vulnerable to unmeasured confounding. We did not account for perioperative factors other than surgical severity in our analyses as (1) we were interested in defining preoperative risk factors for postoperative mortality (enhancing preoperative risk stratification) and (2) factors such as intraoperative BP management and bleeding risk may be related to preoperative blood pressure values. An important confounder is heart failure which we have explicitly attempted to address through adjustment for loop diuretics and heart failure in our models and through an interaction analysis. However we cannot exclude unmeasured confounding from our results. Future research will have to identify the mechanisms through which preoperative low BP may lead to postoperative mortality as, while our findings have biological plausibility, they do not imply causality. This should include investigation of whether there is a dose-dependent effect of anti-hypertensive drugs on post-operative mortality in patients with preoperative hypotension. Establishing a link between preoperative BP values and intra- and post-operative values, as well as identify preoperative BP risk thresholds that predispose to postoperative morbidity, would further enhance biological plausibility for our finding. Likewise studies should evaluate whether the risk associated with intra- and postoperative hypotension are causally driving mortality or are mediators related to baseline preoperative values.

Conclusions

These data suggest that a previously unrecognized perioperative risk factor, preoperative hypotension, exerts significant effects on postoperative mortality in the elderly. As preoperative blood pressure drops below 119/63 mmHg in the elderly, the OR increase, mandating further study of how to optimize perioperative care of these vulnerable patients. While the SPRINT trial demonstrated that targeting a mean systolic BP of 120mmHg leads to improvement in health over 5 years(7), our data suggest that aggressive lowering of BP below this threshold may be harmful in the setting of surgery in the elderly.

Figure Legends

Figure 1: Unadjusted and fully-adjusted spline graphs for the association between systolic BP, diastolic BP and pulse pressure and perioperative mortality. Fully-adjusted model adjusted for: age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors.

Figure 2: Unadjusted and fully-adjusted spline graphs for the association between systolic BP, diastolic BP and pulse pressure and postoperative mortality in patients in whom BP measurements were recorded between 8 and 84 days prior to surgery. Fully adjusted model adjusted for: age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors.

Figure 3: Unadjusted and fully-adjusted spline graphs for the association between systolic BP, diastolic BP and pulse pressure and postoperative mortality in patients aged ≥65 years. Fully adjusted model adjusted for: age, gender, atrial fibrillation, unstable angina,

valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors.

Supplementary Figure 1: STROBE diagram

Supplementary Figure 2: Parsimonious model spline graphs for the association between systolic and diastolic BP and perioperative mortality in the overall population and in the elderly (≥65 years). Parsimonious models in this case included variables that were statistically significantly (p-value <0.05) with both the exposure and the outcome of interest: age, gender, beta blocker, statin, ACE inhibitors, Ca-channel blockers, thiazide diuretics, loop diuretics, aspirin, other antiplatelet agents, atrial fibrillation, unstable angina, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes, renal disease, cancer, Charlson comorbidity score, BMI, smoking status, alcohol units and surgical risk scale , socioeconomic status (IMD 2010), number of BP measurements.

Supplementary figure 3: Sensitivity analysis excluding observations with systolic BP<80mmHg and diastolic BP<40mmHg. Fully adjusted model adjusted for: age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors.

Supplementary figure 4: Sensitivity analysis excluding observations with systolic BP<80mmHg and diastolic BP<40mmHg in the eldery (≥65 years). Fully adjusted model adjusted for: age, gender, atrial fibrillation, unstable angina, valvular heart disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, diabetes mellitus, renal disease, cancer, Charlson's comorbidity score, smoking, alcohol, surgical risk scale, socioeconomic status (IMD 2010), number of BP measurements, statins, beta blockers, calcium-channel blockers, ACE inhibitors, alpha-2 agonists, loop diuretics, thiazide diuretics, aspirin, other antiplatelet drugs and selective serotonin re-uptake inhibitors.

Supplementary Figure 5: Histogram of BP measurements in the year prior to surgery.

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