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# Associations between intraoperative hypotension, duration of surgery and postoperative myocardial injury after noncardiac surgery: a retrospective single-centre cohort study

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## Abstract

**Background:** Studies of intraoperative hypotension typically specify a blood pressure threshold associated with adverse outcomes. Such thresholds are likely to be study-biased, investigator-biased, or both. We hypothesised that a newly developed modelling method without a threshold, which is biologically more plausible than a threshold-based approach, would reveal a continuous association between exposure to intraoperative hypotension and adverse outcomes.
**Methods:** Single-centre, retrospective cohort study of subjects ≥60 yr old undergoing noncardiac surgery. We modelled intraoperative hypotension using three different approaches: (1) unweighted, (2) weighted for degree of hypotension (depth), and (3) weighted for duration of hypotension. The primary outcome was myocardial injury, defined as elevated troponin I (>60 ng $L^{-1}$) measured during the first 3 days after surgery. The associations between the three models, postoperative myocardial injury, and mortality (secondary outcome) were reported as penalised adjusted odds ratios (ORs) scaled between the 75th and 25th percentiles.
**Results:** Myocardial injury occurred in 1812/15 452 (12%) procedures, with 554/15 452 (3.6%) procedures resulting in death before discharge from hospital. The unweighted lower blood pressure measure (OR: 0.26, 95% confidence interval [CI]: 0.12–0.53) and the depth-weighted measure (OR: 4.4, 95% CI: 2.6–7.4) were associated with myocardial injury. The duration-weighted measure was not associated with myocardial injury (OR: 0.89, 95% CI: 0.61–1.3). The unweighted measure (OR 0.08, 95% CI: 0.01–0.40) and the depth-weighted measure (OR: 12, 95% CI, 3.8–35) were associated with in-hospital mortality, but not the duration-weighted measure (OR: 1.3, 95% CI: 0.53–3.0).
**Conclusions:** Intraoperative hypotension appears to have a graded association with postoperative myocardial injury and mortality, with depth appearing to contribute more than duration.

**Keywords:** blood pressure; hypotension; myocardial injury; mortality; noncardiac surgery

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**Editor's key points**

- Thresholds for intraoperative hypotension that are associated with adverse outcomes remain unclear.
- Simple threshold-based definitions for intraoperative hypotension associated with adverse outcomes are not as biologically plausible as graded, continuous associations.
- Depth and duration of hypotension exposure were modelled using retrospective data capturing postoperative myocardial injury and mortality.
- Intraoperative hypotension had a graded association with postoperative myocardial injury and mortality.
- Depth of hypotension appears to contribute more than duration.

Intraoperative arterial hypotension is repeatedly associated with postoperative myocardial injury after noncardiac surgery.[1–3] A complicating factor in the interpretation of this association is the dependence on the derivation, and definition, of intraoperative hypotension.[4] There are three main issues in analysing the relationship between hypotension and organ injury: the use of a threshold-based method to model intraoperative hypotension, inadequate incorporation of depth and duration of low blood pressures, and the strong relationship between intraoperative hypotension and the duration of surgery (Supplementary Table S1).[5,6]

Specifying a threshold to define hypotension within the modelling method (i.e. a prespecified threshold) is problematic from a clinical viewpoint, as it assumes that the association with outcome is based on a boundary effect and that we already know at what blood pressure threshold that boundary occurs. Such an association is not very plausible (e.g. an intraoperative mean arterial pressure [MAP] of 65 mm Hg would cause no injury, whereas an MAP of 64 mm Hg would). Moreover, a patient with any MAP <65 mm Hg is more likely to have a prolonged period of lower MAP. A graded association between hypotension exposure and postoperative adverse outcomes makes more sense from a biological perspective: each mm Hg decrease in blood pressure and each minute of exposure may be likely to add to the injury caused by hypotension.

In addition to using a prespecified threshold, current hypotension modelling methods do not include both depth and duration as separate variables, making it difficult to unravel the exact contributions of depth and duration of hypotension exposure. In commonly applied methods, a short but severe dip in blood pressure exhibits the same area-under-the threshold or time-weighted average as a long-lasting blood pressure just below the specific threshold.[3]

Finally, longer surgical times inevitably lead to increased risk of longer exposure to hypotension exposure and adverse postoperative events.[1,2,7,8]

Modelling methods that do not use a prespecified threshold for depth and duration of intraoperative hypotension exposure may provide better insight into mechanisms of postoperative organ injury. We hypothesised that intraoperative low blood pressures have a graded association with postoperative organ injury, rather than an association with a boundary effect. In other words, we believe that there is no critical value at which a low blood pressure 'becomes hypotension'. Therefore, the aim of this study was to develop a new method of modelling intraoperative low blood pressure that allowed to us to study whether the relation between intraoperative hypotension exposure and the occurrence of postoperative myocardial injury is a graded association or a boundary effect.

## Methods

### Study design, setting, and participants

This retrospective cohort study included inpatients aged 60 yr or older who underwent intermediate-to high-risk noncardiac surgery between January 1, 2012 and June 1, 2017 at the University Medical Center Utrecht, Utrecht, The Netherlands. Only patients with at least one postoperative troponin I measurement during the first three postoperative days were included.[2,9] Patients with pre-existing end-stage renal disease (defined as undergoing renal replacement therapy), American Society of Anesthesiologists (ASA) physical status ≥5, duration of anaesthesia <20 min, or when intraoperative blood pressure measurements were not available were excluded. If patients underwent another surgical procedure, then this procedure was considered as a novel patient (3.8% of the patients underwent another intermediate- or high-risk surgery 3 days after the first surgical procedure) (i.e. the analysis was anaesthetic case-based rather than individual patient-based). As this was a retrospective study, the anaesthesia technique and management of intraoperative blood pressure were not standardised. Intraoperative low blood pressure was typically treated with fluids, norepinephrine, phenylephrine, or ephedrine, but these treatments were not included in analysis. The local ethics committee waived the need for informed consent as only routinely collected data were used (University Medical Center Utrecht, Medical Research Ethics Committee, protocol number 16–552).

### Data collection

Intraoperative data from the patient monitor and anaesthesia machine were collected from the electronic anaesthesia information management system (AnStat, CarePoint Nederland BV, Ede, The Netherlands). Data collection started before induction (i.e. immediately after connecting the patient to the monitoring system) (Datex-Ohmeda, Madison, WI, USA; Spacelabs Healthcare, Snoqualmie, WA, USA or both). No comparison of the validity of blood pressure measurements between the devices of different vendors was performed. Demographic, preoperative, and postoperative data were collected from the electronic hospital information system (HiX, ChipSoft, Amsterdam, The Netherlands).

### Exposure variable: intraoperative hypotension

#### *Blood pressure measurements*

The exposure of interest in this study was intraoperative hypotension as modelled with our new modelling method that does not use a prespecified threshold to define hypotension (see: *Modelling intraoperative hypotension exposure*). All arterial blood pressure measurements between the start of induction of anaesthesia and the time of patient emergence were used. Noninvasive oscillometric blood pressure measurements were stored at measurement intervals, typically every 3–5 min. Invasive blood pressure measurements were stored as the

median for each minute. Calibration of invasive blood pressure measurement devices was a routine part of clinical practice, but no data were collected to confirm calibration.

### *Blood pressure data handling*

MAPs of both continuous invasive measurements and noninvasive measurements were extracted. Invasive blood pressure measurements were excluded if these represented <10% of all blood pressure data during the procedure. When both invasive and noninvasive blood pressure measurements were present at a given time point, only the invasive value was included in the analysis, as it is a direct measurement of the MAP rather than an oscillometric estimate. When multiple blood pressure measurements of the same type (multiple invasive blood pressure or noninvasive blood pressure measurements) were available at the same minute value, the average value of these multiple MAPs was calculated. Methods to reduce blood pressure measurement artifacts and interpolate per-minute values for noninvasive interval are described in the Supplementary material.

### *Modelling intraoperative hypotension exposure*

In clinical practice there are many ways that a patient's blood pressure may evolve over the surgical case, resulting in a large variety in patterns of hypotension exposure. We developed three models to reflect the types of hypotensive episodes that may be experienced during a single procedure: (1) a variable to model overall hypotension exposure; (2) a variable to model very low blood pressures; and (3) a variable to model prolonged durations of lower blood pressures. Detailed derivation of these three variables in the new hypotension modelling method is provided in Fig 1 and in the Supplementary material.

## Primary outcome

Postoperative myocardial injury after noncardiac surgery was used as the primary outcome in this exploratory study. According to our local clinical protocol, troponin I levels were routinely measured after surgery in all patients and analysed using a third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, CA, USA) during the first three postoperative days.[2,9] Postoperative myocardial injury was defined as a troponin I level within the first three postoperative days of >60 ng $L^{-1}$, which is above the 99th percentile upper reference limit.[2,9] The secondary outcome was in-hospital mortality during the same admission of the surgical procedure.

## Covariables

Potential confounding variables were obtained from the electronic patient record. A priori, we selected the following confounders: age, sex, ASA physical status, presence of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, non-end-stage renal disease, chronic usage of any preoperative prescription medication, surgical specialty, and priority of surgery (elective surgery, emergency surgery within respectively 2, 8, and 24 h).[9] Because the weighted-hypotension modelling method explicitly models the duration of hypotension in the three lower blood pressure area variables, duration of surgery was only included as a covariable and not as an interaction term with the lower blood pressure area variables.

## Sample size

No sample size calculations were performed, as an *ex ante* prediction of the effect estimates for the associations between the lower blood pressure area variables as calculated by the new intraoperative hypotension modelling method and the outcomes would be very unreliable, and thus not result in a meaningful sample size estimate.

## Statistical analysis

The full statistical models (in R code, R Foundation for Statistical Computing, Vienna, Austria) are provided in the Supplementary material.

Missing data were handled by the multiple imputation method ('aregImpute') function using predictive mean matching from the 'Hmisc' package (release 4.2–0) in R (release 3.5.1; R Foundation for Statistical Computing, Vienna, Austria). Patients without any postoperative troponin I measurements during the first three postoperative days were excluded from the final analyses, but were used for optimisation of the imputation procedure.[10]

Continuous data were presented as medians with interquartile ranges. Categorical variables were expressed as frequencies with percentages. All continuous variables, age, the lower blood pressure area (depth • duration), the depth-weighted lower blood pressure area ($depth^2$ • duration), and the duration-weighted lower blood pressure area (depth • $duration^2$) were transformed using restricted cubic splines with three knots at quantiles 0.10, 0.50, and 0.90 (rcspline.eval function, 'HMisc' package [release 4.2–0]). Using restricted cubic splines for the blood pressure variables is essential to detect a possible boundary effect for the association between low blood pressure and postoperative adverse outcomes.

### *Multivariable regression analyses*

Multivariable analyses for both postoperative myocardial injury and in-hospital mortality were performed as penalised logistic regression analysis (lrm function, 'rms' package [release 5.1–2]) using R (release 3.5.1; R Foundation for Statistical Computing). Penalisation is a shrinkage procedure to avoid multicollinearity and overfitting of the model and consisted of penalised maximum likelihood estimation (pentrace function, 'rms' package [release 5.1–2]) with the following penalties: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24. As continuous variables were transformed using restricted cubic splines, outcome associations for all continuous variables were expressed as penalised, confounder-adjusted scaled odds ratios (ORs) between the 75th and 25th percentile with 95% confidence intervals (CIs). Statistical significance was determined by *P*-value based on penalised adjusted ORs and 95% CIs after bootstrapping ($n$=500 samples) and defined as a two-sided $\alpha$ of 0.05.[11] The performance of the multivariable regression analysis for postoperative myocardial injury using the new hypotension modelling method with the depth- and duration-weighted variables was compared with the same statistical model without the weighted lower blood pressure area variables. For this purpose, index-corrected $R^2$ and C-index values were calculated.

### *Interpretation and representation of the results*

Patterns of hypotension exposure are modelled by the three lower blood pressure area variables, each represented as a restricted cubic spline in the regression model. The

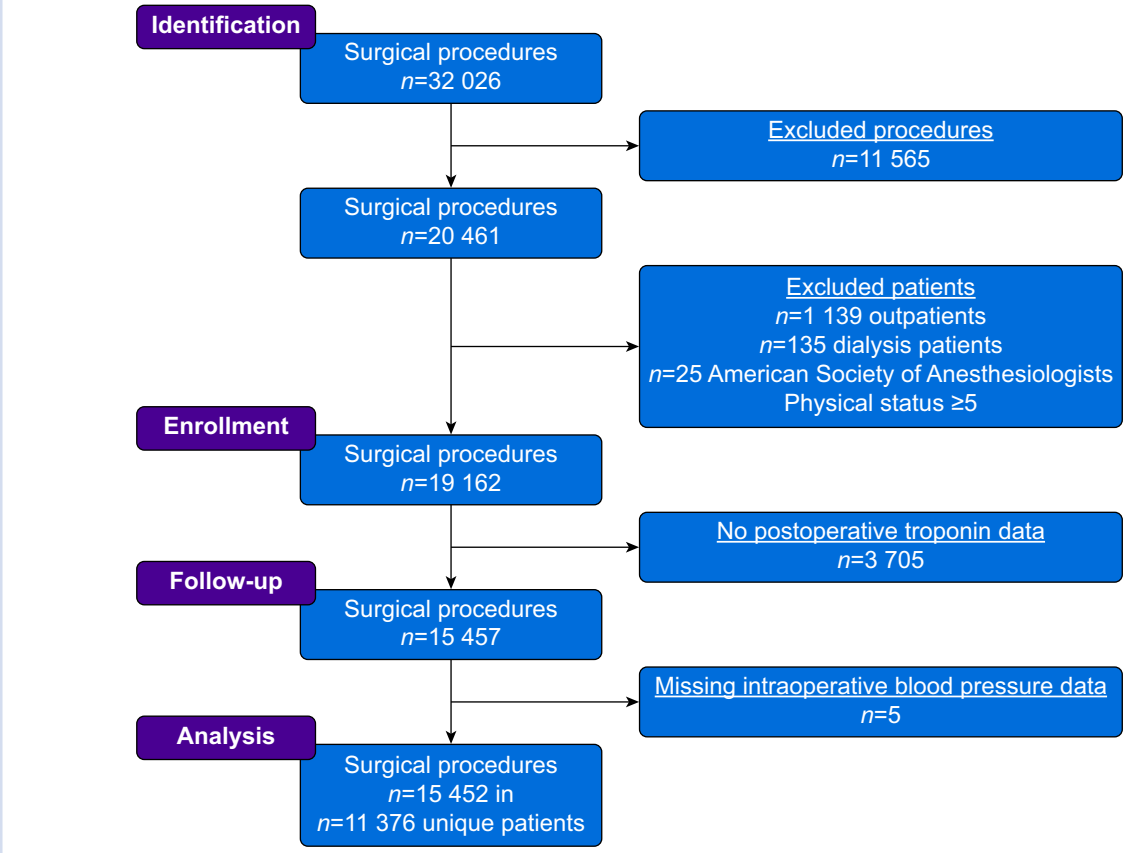


Fig 1. Flow chart of patient and surgical procedure selection.

combination of the new hypotension modelling method with the restricted cubic splines allows the statistical model to estimate a boundary effect without having to use a prespecified hypotension threshold, and differentiate between the effects of depth and duration of hypotension exposure. However, the individual regression coefficients are very difficult to interpret as the hypotension exposure variables are interrelated; such interrelation may yield regression coefficients that alone are not interpretable. Additionally, the values of the lower blood pressure areas have a dependency on the duration of surgery. A partial effect plot was therefore created to visually represent the results of the regression analysis and illustrate the relationship between the blood pressure course as modelled by the three lower blood pressure area variables, the duration of surgery, and the primary outcome. In such a partial effect plot, the presence of a boundary effect would be visible by a sudden increase in risk around a certain blood pressure value, indicating a threshold, rather than a graded risk increase corresponding with a graded increase in hypotension exposure.

## Results

### Study characteristics

A total of 15 452/32 026 (48%) surgical procedures undertaken in 11 376 individuals were suitable for analysis (Fig 2), of which 2563 patients (23%) underwent multiple procedures within the study period (Table 1). Postoperative troponin I measurements were completed in 13 252/15 452 (86%), 12 227/15 452 (79%), 10 197/15 452 (66%) procedures, on postoperative days 0–1, 2, and 3, respectively. Postoperative myocardial injury occurred after 1812/15 452 (12%) procedures. There were 554/15 452 procedures (3.9%) undertaken after which subjects died before hospital discharge.

### Primary outcome: myocardial injury and intraoperative hypotension

Depth-weighted lower blood pressure area (scaled OR 4.4, 95% CI 2.6–7.4), but not duration-weighted lower blood pressure area (scaled OR 0.9, 95% CI 0.6–1.3), was associated with postoperative myocardial injury (Table 2). The scaled OR (calculated after penalisation and adjusting for confounders) indicates that a patient with a depth-weighted lower blood pressure area at the 75th percentile (121 797 mm $Hg^2$ $min^{-1}$) has a 4.4-fold greater risk of developing postoperative myocardial injury than a patient with a depth-weighted lower blood pressure area at the 25th percentile (28 351 mm $Hg^2$ $min^{-1}$). Similarly, the depth-weighted lower blood pressure area (scaled OR 12, 95% CI 3.8–34), but not the duration-weighted lower blood pressure area was significantly associated with in-hospital mortality (Table 2).

### Logistic regression analysis

Partial effect plots illustrate the substantial interaction between the depth and duration of low blood pressure and the

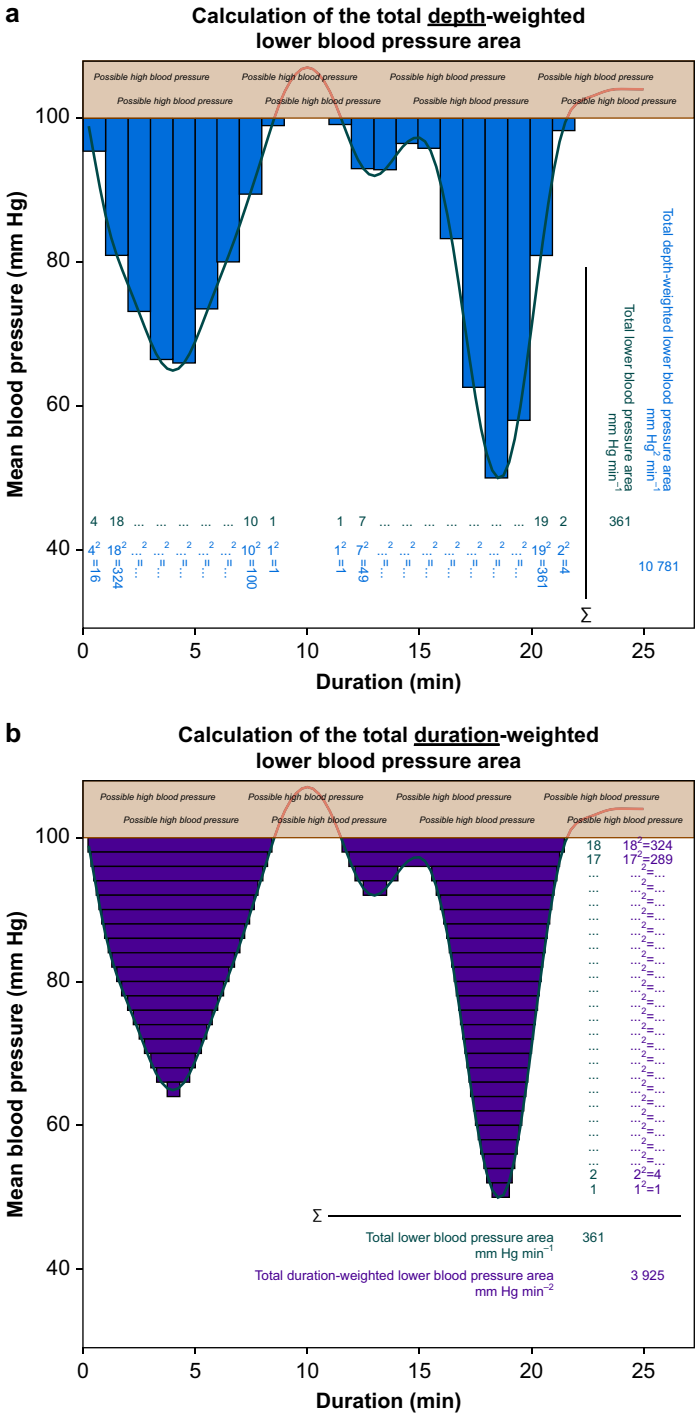


Fig 2. Calculation of the three different lower blood pressure areas. The graph displays the same blood pressure course for a single patient in two panels a and b (blue lines). In both panels, the lower blood pressure area was calculated by taking the integral of the area between the assumed normal blood pressure of a mean arterial pressure (MAP) of 100 mm Hg (light red areas) and all MAP measurements <100 mm Hg during the procedure (expressed as mm Hg $min^{-1}$). The difference between the two panels is the way the integrals were calculated. In panel a, time was partitioned in 1-min intervals and the difference between a current MAP measurement and an MAP of 100 mm Hg was added to the area sum of the previous MAP measurements (a Riemann integral, represented by the yellow vertical bars). In panel b, the MAP values were partitioned into 1-mm Hg intervals and then integrated (a Lebesque integral, horizontal green bars). Both methods yield the same total lower blood pressure area of 361 mm Hg $min^{-1}$ (blue numbers in both panels). The two different types of integrals were necessary to calculate the weighted lower blood pressure areas. For the depth-weighted area, the depth values per minute-interval were squared and summed, resulting in a total depth-weighted lower blood pressure area of 10 781 mm $Hg^2$ $min^{-1}$ (panel a, yellow numbers). For the duration-weighted area, the duration values per mm Hg-interval were squared and summed, resulting in a total duration-weighted lower blood pressure area of 3925 mm Hg $min^{-2}$ (panel a, green numbers). This example illustrates the added value of the weighted areas. The depth-weighted area is much higher than the duration-weighted area, which illustrates that this patient has substantial blood pressure decreases, rather than prolonged moderate hypotension. This fits well with observed blood pressure course (i.e. the blue line).

Table 1 Characteristics of included patients. ASA, American Society of Anesthesiologists; IQR, inter-quartile range. *Number and percentage of missing values related to number of patients. †Number and percentage of missing values related to number of surgical procedures.

| Characteristics of included patients and surgical characteristics | | n=15 452 (%) | Missing values, n (%)* |
|---|---|---|---|
| Age: yr, median (IQR) | | 69 [65–75] | 0 (0) |
| Sex: male, n (%) | | 8671 (56) | 0 (0) |
| **Cardiovascular risk factors and comorbidities** | | | |
| Hypertension, n (%) | | 5959 (39) | 3724 (24) |
| Diabetes mellitus, n (%) | | 2038 (13) | 3853 (25) |
| Renal disease, n (%) | | 1938 (13) | 3781 (25) |
| Cardiac disease, n (%) | | 4352 (28) | 3707 (24) |
| Cardiovascular disease, n (%) | | 1569 (10) | 4552 (29) |
| Chronic medication use, n (%) | | 10 603 (69) | 4121 (27) |
| ASA physical status, n (%) | 1 | 1294 (8.4) | 1712 (11) |
| | 2 | 7952 (51) | |
| | 3 | 4186 (27) | |
| | 4 | 308 (2.0) | |
| **Characteristics of included surgical procedures** | | **n = 15 452** | **Missing values, n (%)†** |
| Median mean blood pressure 5th percentile: mm Hg, median (IQR) | | 64 [58–70] | 0 (0) |
| Median mean blood pressure 50th percentile: mm Hg, median (IQR) | | 80 [73–87] | 0 (0) |
| Area-under-the-normal-blood-pressure: depth • duration, mm Hg $min^{-1}$, median (IQR) | | 2274 [1180–4283] | 0 (0) |
| Depth-weighted area-under-the-normal-blood-pressure: $depth^2$ • duration, mm $Hg^2$ $min^{-1}$, median (IQR) | | 60 644 [28 351–121 797] | 0 (0) |
| Duration-weighted area-under-the-normal-blood-pressure: depth • $duration^2$, mm Hg $min^{-2}$, median (IQR) | | 178 588 [53 188–597 320] | 0 (0) |
| Surgical specialty, n (%) | Ear, nose, throat surgery/oral and maxillofacial surgery | 2887 (19) | 0 (0) |
| | General surgery | 1126 (7.3) | |
| | Gastroenterological and oncological surgery | 1741 (11) | |
| | Gynaecology | 782 (5.1) | |
| | Neurosurgery | 3264 (21) | |
| | Orthopaedic surgery | 1713 (11) | |
| | Plastic surgery | 269 (1.7) | |
| | Trauma surgery | 565 (3.7) | |
| | Urology | 1053 (6.8) | |
| | Vascular surgery | 2052 (13) | |
| Priority of surgery, n (%) | Elective surgery | 11 576 (75) | 0 (0) |
| | Emergency surgery, within 24 h | 1553 (10) | |
| | Emergency surgery, within 8 h | 1718 (11) | |
| | Emergency surgery, within 2 h | 605 (3.9) | |
| Duration of surgery, median (IQR) | | 132 [82–208] | 0 (0) |
| Number of surgical procedures for every patient, n (%) | 1 | 8813 (77) | 0 (0) |
| | 2–5 | 2484 (22) | |
| | 6–15 | 79 (0.7) | |

Table 2 Association between intraoperative area under the normal blood pressure variables and postoperative myocardial injury and in-hospital mortality after noncardiac surgery. Scaled odds ratios represent an increase in the odds comparing the 25th percentile (*index value/category) and 75th percentiles (†reference value/category). Age, depth$^2$ • duration, and depth • duration$^2$ were transformed with restricted cubic splines. Results were adjusted for the following confounders: age, sex, ASA physical status, usage of any chronic preoperative medication, presence of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, non-end-stage renal disease, surgical specialty, and priority of surgery. *P*-value was based on penalised adjusted odds ratios and 95% confidence intervals after bootstrapping ($n$=500). Because of the lack of events in particular groups, not all odds ratios could be calculated. ASA, American Society of Anesthesiologists; CI, confidence interval; N/A, not available; PMI, postoperative myocardial injury.

| | Index value/ category* | Reference value/category† | PMI Adjusted scaled odds ratio (95% CI) | PMI Penalised adjusted scaled odds ratio (95% CI) | P-value | In-hospital mortality Adjusted scaled odds ratio (95% CI) | In-hospital mortality Penalised adjusted scaled odds ratio (95% CI) | P-value |
|---|---|---|---|---|---|---|---|---|
| Area-under-the-normal-blood-pressure: depth • duration, mm Hg min$^{-1}$ | 4283 | 1180 | 0.14 (0.05–0.35) | 0.26 (0.12–0.53) | <0.05 | 0.08 (0.01–0.40) | 0.08 (0.01–0.40) | <0.05 |
| Depth-weighted area-under-the-normal-blood-pressure: depth$^2$ • duration, mm Hg$^2$ min$^{-1}$ | 121 800 | 28 351 | 7.02 (3.74–13.2) | 4.38 (2.60–7.36) | <0.05 | 11.6 (3.82–34.9) | 11.6 (3.82–34.9) | <0.05 |
| Duration-weighted area-under-the-normal-blood-pressure: depth • duration,$^2$ mm Hg min$^{-2}$ | 597 320 | 53 188 | 1.02 (0.62–1.70) | 0.89 (0.61–1.31) | 0.57 | 1.27 (0.53–3.02) | 1.27 (0.53–3.02) | 0.61 |
| Duration of surgery, min | 208 | 82 | 2.11 (1.78–2.52) | 1.99 (1.68–2.36) | <0.05 | 1.49 (1.05–2.10) | 1.49 (1.05–2.10) | <0.05 |
| Age: yr | 75 | 65 | 1.44 (1.31–1.59) | 1.44 (1.31–1.59) | <0.05 | 1.07 (0.91–1.25) | 1.07 (0.91–1.25) | 0.42 |
| Sex | Male | Female | 0.94 (0.84–1.05) | 0.94 (0.84–1.05) | 0.29 | 1.06 (0.87–1.29) | 1.06 (0.87–1.29) | 0.57 |
| Hypertension | | | 1.17 (1.03–1.34) | 1.17 (1.03–1.34) | <0.05 | 1.02 (0.74–1.42) | 1.02 (0.74–1.42) | 0.89 |
| Diabetes mellitus | | | 1.20 (1.02–1.41) | 1.20 (1.02–1.41) | <0.05 | 1.32 (0.95–1.83) | 1.32 (0.95–1.83) | 0.10 |
| Renal disease | | | 1.29 (1.11–1.49) | 1.29 (1.12–1.49) | <0.05 | 1.58 (1.06–2.35) | 1.58 (1.06–2.35) | <0.05 |
| Cardiac disease | | | 1.37 (1.18–1.60) | 1.37 (1.18–1.60) | <0.05 | 0.96 (0.71–1.32) | 0.96 (0.71–1.32) | 0.83 |
| Cardiovascular disease | | | 1.21 (1.02–1.43) | 1.21 (1.02–1.43) | <0.05 | 1.16 (0.71–1.91) | 1.16 (0.71–1.91) | 0.56 |
| Chronic medication use | | | 1.16 (0.79–1.71) | 1.16 (0.79–1.72) | 0.45 | 0.81 (0.40–1.64) | 0.81 (0.40–1.64) | 0.58 |
| ASA physical status | 1 | | 1.00 | 1.00 | | 1.00 | 1.00 | |
| | 2 | | 1.48 (1.07–2.04) | 1.47 (1.07–2.02) | <0.05 | 1.52 (0.81–2.86) | 1.52 (0.81–2.86) | 0.19 |
| | 3 | | 1.91 (1.36–2.68) | 1.90 (1.36–2.66) | <0.05 | 3.50 (1.82–6.74) | 3.50 (1.82–6.74) | <0.05 |
| | 4 | | 3.88 (2.57–5.85) | 3.85 (2.57–5.79) | <0.05 | 8.78 (4.28–18.0) | 8.78 (4.28–18.0) | <0.05 |
| Surgical specialty | General surgery | | 1.00 | 1.00 | | 1.00 | 1.00 | |
| | Ear, nose, throat surgery/oral, and maxillofacial surgery | | 0.37 (0.29–0.47) | 0.38 (0.30–0.48) | <0.05 | 0.23 (0.14–0.38) | 0.23 (0.14–0.38) | <0.05 |
| | Gastroenterological and oncological surgery | | 0.70 (0.57–0.88) | 0.71 (0.57–0.88) | <0.05 | 1.36 (0.96–1.91) | 1.36 (0.96–1.91) | 0.08 |
| | Gynaecology | | 0.42 (0.29–0.61) | 0.42 (0.29–0.61) | <0.05 | 0.12 (0.03–0.51) | 0.12 (0.03–0.51) | <0.05 |
| | Neurosurgery | | 0.55 (0.45–0.67) | 0.55 (0.45–0.67) | <0.05 | 1.00 (0.72–1.39) | 1.00 (0.72–1.39) | 0.98 |
| | Orthopaedic surgery | | 0.57 (0.45–0.72) | 0.57 (0.45–0.72) | <0.05 | 0.58 (0.37–0.90) | 0.58 (0.37–0.90) | <0.05 |
| | Plastic surgery | | 0.25 (0.13–0.50) | 0.27 (0.14–0.51) | <0.05 | N/A | N/A | |
| | Trauma surgery | | 0.78 (0.58–1.06) | 0.79 (0.58–1.06) | 0.12 | 0.98 (0.61–1.59) | 0.98 (0.61–1.59) | 0.94 |
| | Urology | | 0.38 (0.27–0.52) | 0.38 (0.27–0.52) | <0.05 | 0.30 (0.15–0.60) | 0.30 (0.15–0.60) | <0.05 |
| | Vascular surgery | | 0.78 (0.63–0.96) | 0.78 (0.63–0.96) | <0.05 | 0.49 (0.34–0.72) | 0.49 (0.34–0.72) | <0.05 |
| Priority of surgery | Elective surgery | | 1.00 | 1.00 | | 1.00 | 1.00 | |
| | Emergency surgery, within 24 h | | 1.90 (1.58–2.28) | 1.91 (1.60–2.29) | <0.05 | 2.12 (1.51–2.98) | 2.12 (1.51–2.98) | <0.05 |
| | Emergency surgery, within 8 h | | 3.01 (2.59–3.51) | 3.02 (2.59–3.51) | <0.05 | 4.54 (3.48–5.94) | 4.54 (3.48–5.94) | <0.05 |
| | Emergency surgery, within 2 h | | 6.90 (5.59–8.52) | 6.94 (5.62–8.57) | <0.05 | 17.9 (13.3–24.0) | 17.9 (13.32–24.0) | <0.05 |

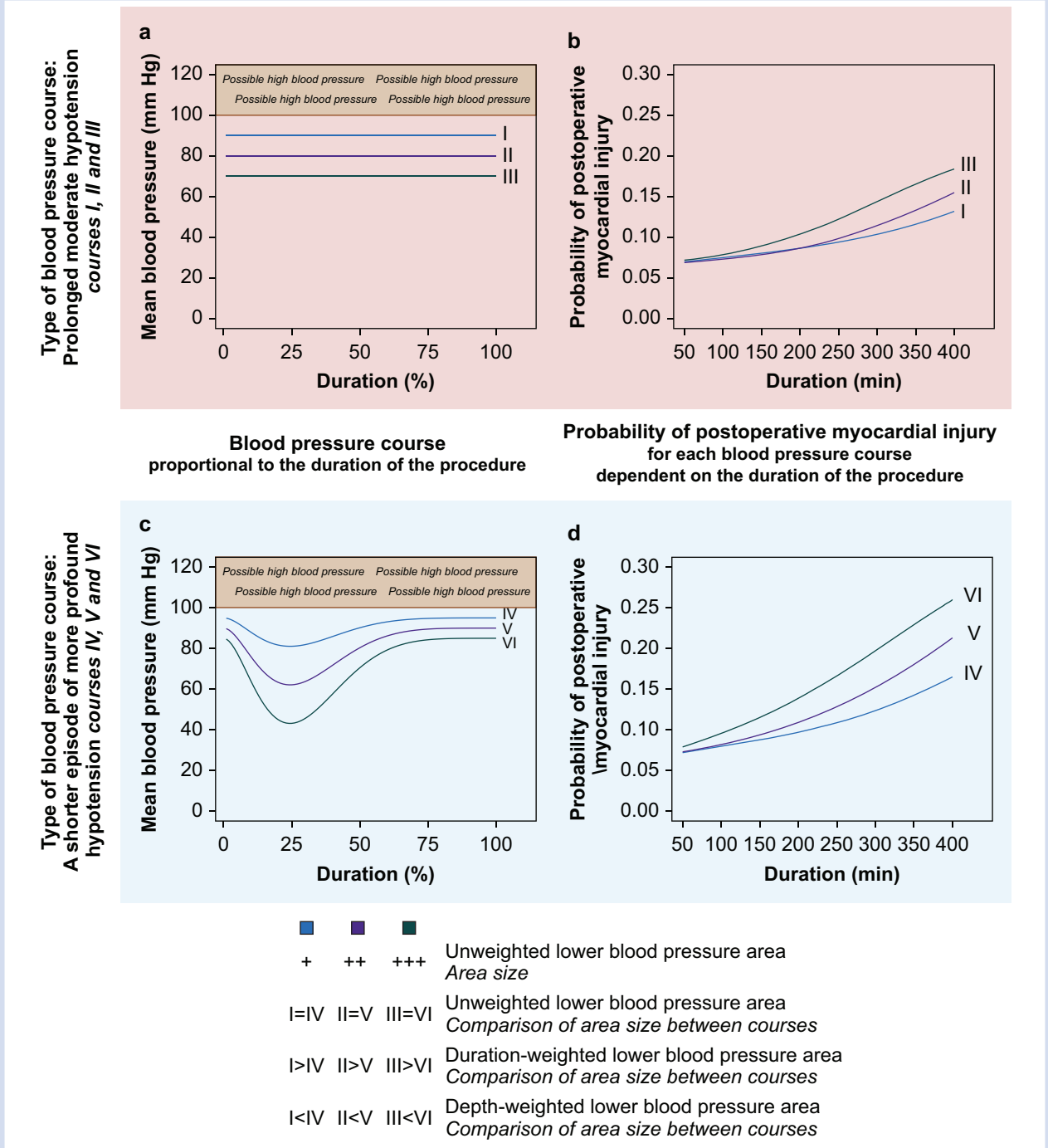


Fig 3. Graded associations between exposure to, and duration of, hypotension and postoperative myocardial injury. (a) Prolonged moderate hypotension. (b) Prolonged moderate hypotension. (c) Shorter episode of more pronounced hypotension, with a variable relative duration of surgery. (d) Shorter episode of more pronounced hypotension. Patients with a more pronounced blood pressure decrease for a shorter duration (panel d: depth-weighted lower blood pressure areas) had a higher associated risk of postoperative myocardial injury compared with patients with prolonged moderate hypotension (panel b: duration-weighted lower blood pressure areas). Substantial intraoperative hypotension (panels b and d; green lines), longer duration of surgery, or both were associated with higher associated risks of postoperative myocardial injury compared with patients with minimal intraoperative hypotension (panels b and d; red lines), shorter duration of surgery, or both.

duration of surgery (Fig 3). The overall model performance of the regression model that included the depth- and duration-weighted lower blood pressure areas was better ($R^2$=0.199; C-index=0.775) than the regression model without weighted variables ($R^2$=0.194; C-index=0.772). The model performance of the new intraoperative blood pressure modelling method was comparable to conventional hypotension modelling methods (Supplementary Table S3).

## Discussion

In this retrospective observational cohort study, our novel intraoperative hypotension modelling method allowed us to explore the impact of weighted depth and duration of hypotension exposure on outcomes, accounting for the duration of surgery. Our results suggest that intraoperative hypotension exposure has a graded association with postoperative myocardial injury and mortality. This offers a plausible alternative explanation to the current paradigm of a blood pressure boundary effect (i.e. a distinct threshold at which low blood pressure becomes hypotension and increases the risk of postoperative myocardial injury or mortality). The depth- and duration-weighted hypotension modelling method in our study is a first attempt to separate the contribution of depth and duration of intraoperative blood pressure and their associations with postoperative adverse events. Our results indicate that the depth of hypotension exposure contributes more to the association with the outcomes than the duration of intraoperative hypotension.

During surgery, low blood pressures are common and often caused by a combination of mechanisms, such as vasodilation, hypovolaemia, or decreased cardiac function.[12] In studies reporting an association between intraoperative hypotension and organ injury after noncardiac surgery,[1,2,7] arbitrarily chosen, or data driven, blood pressure thresholds were analysed. From a physiological perspective, it is questionable whether one blood pressure cut-off 'fits all'.[13] The relationship between intraoperative hypotension and organ injury differs between individuals and between organs. Therefore, individualised intraoperative blood pressure management to prevent organ dysfunction seems more promising than focussing on a single universal blood pressure threshold. A single interventional study[14] reported that targeting an individualised blood pressure reduced postoperative organ dysfunction, compared with targeting a single universal blood pressure threshold (as performed in other interventional studies).[15,16]

Although it is still unclear whether the prevention of intraoperative hypotension improves postoperative outcomes, the question remains which minimum blood pressure is permissible for an individual patient (and for a specific organ) and how to deal with these low intraoperative blood pressures. More insight into the complexity and cohesion of depth and duration of low intraoperative blood pressure might lead to more insight into mechanisms that may help better inform blood pressure management.

We hypothesised that hypotension modelling methods without a prespecified threshold would better resemble the clinical situation and would have a similar or better model performance to statistical analyses that are based on hypotension modelling methods with a threshold. For example, the 5th and 25th lowest MAP percentiles on the first seven postoperative days were significantly associated with occurrence of the composite endpoint of myocardial injury and death after noncardiac surgery.[17] Our study did not indicate a boundary effect (best observed in Fig 3). Moreover, the performance of the statistical models with weighted lower blood pressure areas were comparable (although not superior) to previously described hypotension modelling methods that do not use a prespecified intraoperative hypotension threshold. This suggests that the association between intraoperative hypotension and organ injury may just as well be a graded association rather than a boundary effect, which is a more biologically plausible alternative to current hypotension modelling methods for the prediction of adverse postoperative outcomes.[18]

Our study has several limitations. First, because of the exploratory study design, the *post hoc* percentile-based analysis was applied to data obtained from a single centre, which limits generalisability. Second, although prespecified hypotension thresholds were avoided in the new hypotension modelling methods, an arbitrary MAP=100 mm Hg used to define normal intraoperative blood pressure was necessary, based on previous outcome studies.[9] Without the use of a 'normal' blood pressure cut-off, our hypotension modelling method would assume that higher blood pressure values would always be less harmful than lower blood pressure values. Third, other intraoperative factors (e.g. heart rate, anaemia) were not accounted for. Fourth, the overall model performance was moderate, indicating that our analysis remains limited in explaining the observed variation in outcomes. Fifth, the results were not adjusted for occurrence of postoperative hypotension,[19] which is also associated with myocardial injury after noncardiac surgery.[17,20,21] Sixth, our modelling results are not directly applicable in clinical practice, since weighted lower blood pressure area variables can only be determined after the end of the procedure. Seventh, the new hypotension modelling method results in a complex statistical model for which the individual regression estimates are difficult to interpret. Finally, troponin was not measured after 19% of the procedures, which might have introduced selection bias. However, in a study including a part of this cohort, we previously reported that there were no important differences between patients with and without troponin measurements.[22]

In summary, our novel hypotension modelling method suggests that more extreme lower blood pressure contributes to a greater extent to postoperative myocardial injury and in-hospital mortality than the duration of low blood pressure after noncardiac surgery. Our data suggest that a graded association between low blood pressure and adverse outcomes exists, rather than a boundary effect (i.e. a specific blood pressure threshold).

## Declarations of interest

The authors declare that they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.06.034.

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