Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB
Via Zoom

Tuesday, March 16, 2021
1630-1800 HOURS

PRESENTING ARTICLES:
Dr. Curtis Nickel and Dr. Rosy Fournier

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

ANESTHESIOLOGY

Postoperative Hypotension after Noncardiac Surgery and the Association with Myocardial Injury

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Recent studies have demonstrated associations of postoperative hypotension after noncardiac surgery, defined using varying definitions (categorical or continuous), with adverse outcome including myocardial injury with a varying influence of intraoperative hypotension. The authors have previously reported an association considering mean arterial pressure quartiles assessed by high sensitivity troponin T levels. In this study, they evaluated multiple absolute mean arterial pressure (MAP) thresholds and temporal time-weighted characterizations of hypotension in the first 24 h after surgery in patients admitted to a high-dependency unit with continuous blood pressure monitoring. Myocardial injury was assessed using serial high sensitivity troponin sampling on the first 3 postoperative days.

What This Article Tells Us That Is New

- Postoperative hypotension occurred in from 8 to 48% of patients using MAP thresholds from 60 to 75 mmHg. Myocardial injury (peak high sensitivity troponin T 50 ng/l or greater) was associated with higher prolonged durations for all of the MAP thresholds investigated (50 to 75 mmHg). After adjustment for relevant potential clinical confounders, adjusted odds ratios ranged from 2.18 to 3.26 based on the assessed thresholds and characterizations. In contrast to other studies, intraoperative hypotension had no independent effect on myocardial injury.
- The results may have been influenced by selection of a relatively higher-risk cohort, possible influence of unblinded measurements on clinical decision-making, lack of consideration of clinical processes used to treat intraoperative blood pressure, unavailability of preoperative troponin values, and other potential confounders.

ABSTRACT

Background: Intraoperative hypotension has been associated with postoperative morbidity and early mortality. Postoperative hypotension, however, has been less studied. This study examines postoperative hypotension, hypothesizing that both the degree of hypotension severity and longer durations would be associated with myocardial injury.

Methods: This single-center observational cohort was comprised of 1,710 patients aged 60 yr or more undergoing intermediate- to high-risk noncardiac surgery. Frequent sampling of hemodynamic monitoring on a postoperative high-dependency ward during the first 24 h after surgery was recorded. Multiple mean arterial pressure (MAP) absolute thresholds (50 to 75 mmHg) were used to define hypotension characterized by cumulative minutes, duration, area, and time-weighted-average under MAP. Zero time spent under a threshold was used as the reference group. The primary outcome was myocardial injury (a peak high-sensitive troponin T measurement 50 ng/l or greater) during the first 3 postoperative days.

Results: Postoperative hypotension was common, *e.g.*, 2 cumulative hours below a threshold of 60 mmHg occurred in 144 (8%) patients while 4 h less than 75 mmHg occurred in 824 (48%) patients. Patients with myocardial injury had higher prolonged exposures for all characterizations. After adjusting for confounders, postoperative duration below a threshold of 75 mmHg for more than 635 min was associated with myocardial injury (adjusted odds ratio, 2.68; 95% CI, 1.46 to 5.07, $P = 0.002$). Comparing multiple thresholds, cumulative durations of 2 to 4 h below a MAP threshold of 60 mmHg (adjusted odds ratio, 3.26; 95% CI, 1.57 to 6.48, $P = 0.001$) and durations of more than 4 h less than 65 mmHg (adjusted odds ratio, 2.98; 95% CI, 1.78 to 4.98, $P < 0.001$) and 70 mmHg (adjusted odds ratio, 2.18; 95% CI, 1.37 to 3.51, $P < 0.001$) were also associated with myocardial injury. Associations remained significant after adjusting for intraoperative hypotension, which independently was not associated with myocardial injury.

Conclusions: In this study, postoperative hypotension was common and was independently associated with myocardial injury.

(Anesthesiology 2020; 133:510–22)

Myocardial injury after surgery is common and remains a severe postoperative complication associated with a poor prognosis.[1,2] In the perioperative setting, myocardial injury is usually clinically silent and often unnoticed, yet has identical increased risk in mortality as detected myocardial ischemia.[3] As a potential modifiable factor,[4] intraoperative hypotension has been increasingly investigated and has been suggested as a major contributor to postoperative myocardial injury,[5–7] possibly due to an oxygen supply–demand mismatch from end-organ perfusion disruption. Moreover, intraoperative

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 489. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Preliminary data for this article have been presented at the annual scientific meeting of the Dutch Society of Anesthesiology in Groningen, The Netherlands, September 21, 2018, and at the Anesthesiology Annual Meeting 2019 of the American Society of Anesthesiologists (ASA) in Orlando, Florida, October 20, 2019.

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hypotension has additionally been associated with postoperative acute kidney injury,[5,8] stroke,[9] and mortality.[10,11]

Most studies investigating the effects of intraoperative hypotension and adverse postoperative outcome did not include or account for hypotension during the (early) postoperative period. During surgery, patients are under continuous hemodynamic supervision with adequate blood pressure management opportunities to intervene. On the ward, patients are monitored in 4-to-6-h intervals, where hypotension may be unnoticed, can persist for prolonged episodes, and may potentially be more harmful during this critical phase. Recent studies have confirmed postoperative hypotension to be associated with myocardial injury[12,13] and infarction.[14] Although defining hypotension in the perioperative setting remains challenging with over 140 different definitions[15] and no international consensus to date, postoperative organ injury seems to be a function of both hypotension severity and duration.[16,17] However, papers report limited blood pressure characterizations due to infrequent postoperative blood pressure monitoring and/or a poorly defined measure of postoperative hypotension. Consequently, the current consensus on postoperative hypotension cannot accurately state at which postoperative thresholds harm may occur.[17] It is therefore imperative to explore this potentially modifiable factor in further detail.

The primary aim of this study was to determine whether postoperative hypotension in the first 24 h after noncardiac surgery was associated with myocardial injury. Multiple mean arterial pressure (MAP) thresholds were used to define postoperative hypotension, and different characterizations were investigated. We hypothesized that both the degree of postoperative hypotension severity and longer durations would be associated with myocardial injury.

Materials and Methods

Study Design

This single-center observational cohort study was derived from an ongoing clinical routine troponin registry of noncardiac surgery patients at the Erasmus University Medical Center, Rotterdam, The Netherlands.[12,18] Eligibility criteria were patients aged 60 yr or older undergoing intermediate- to high-risk noncardiac surgery, including elective and emergency procedures with an expected postoperative length of hospitalization of at least 24 h. Patients were included in the period between July 1, 2012, and July 1, 2017. The sample size was based on the available data. When clinically indicated, patients were either continuously monitored on the high-dependency ward (for the remaining day of surgery until the day after surgery), in the intensive care unit, or on the recovery ward before discharge to the wards. Patients who were admitted to the high-dependency ward were selected for analysis. In our hospital, the decision to admit patients to the high-dependency ward after surgery is made several weeks in advance before the surgery itself at the outpatient clinic. Patients are admitted to the high-dependency ward based on either the type of surgical procedure (*e.g.*, intracranial, major abdominal) or significant comorbidity, as judged by the screening anesthesiologist. Patients with a postoperative duration less than 8 h before being discharged to the wards or with a revised procedure within the postoperative period were excluded from analysis (fig. 1). Furthermore, cases were excluded if either perioperative hemodynamic measurements or postoperative high-sensitive troponin T were unavailable. Institutional approval for this study was obtained, and no informed consent was required nor obtained according to local directives for retrospective studies. This study was not registered, was not subject to the Dutch Medical Research Involving Human Subjects Act[19] due to this observational character, and complies with the Helsinki Declaration on research ethics.[20] This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for observational studies.[21]

Data Collection

At the outpatient clinic, patients were screened on medical history, physical examination, laboratory measurements, and an electrocardiogram according to local policy. Baseline characteristics were acquired from medical records and consisted of age, sex, type of surgery, emergency procedures, hypertension, insulin-dependent diabetes mellitus, chronic obstructive pulmonary disease, previous myocardial infarction (MI), coronary artery disease, congestive heart failure, cerebrovascular disease, and peripheral artery disease. Preoperative use of medication was recorded, including β-blockers, statins, angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, calcium channel blockers, diuretics, aspirin, and oral anticoagulants. Additional perioperative laboratory measurements, ward vitals, and admission details were retrospectively extracted from the institution's electronic medical record storage database.

Blood Pressure Measurements

Perioperative blood pressure recordings were extracted from the hospital anesthesia information management system data. The intraoperative period was specified as the documented start of anesthesia until the departure from the operating room. The postoperative period was defined as the departure from the operating room until the patient's discharge from the high-dependency ward to the surgical wards. A maximum of 24 h of postoperative measurements was selected for analysis. Preoperative blood pressures were acquired from all measurements obtained at the wards or from the outpatient clinic noninvasively (oscillometrically). Intraoperative blood pressures were measured and recorded either invasively (arterial line catheter) at 1-min intervals or noninvasively at 1- to 5-min intervals. Postoperative blood pressures on the high-dependency ward were measured invasively or noninvasively and recorded at 1- to 15-min intervals. Based

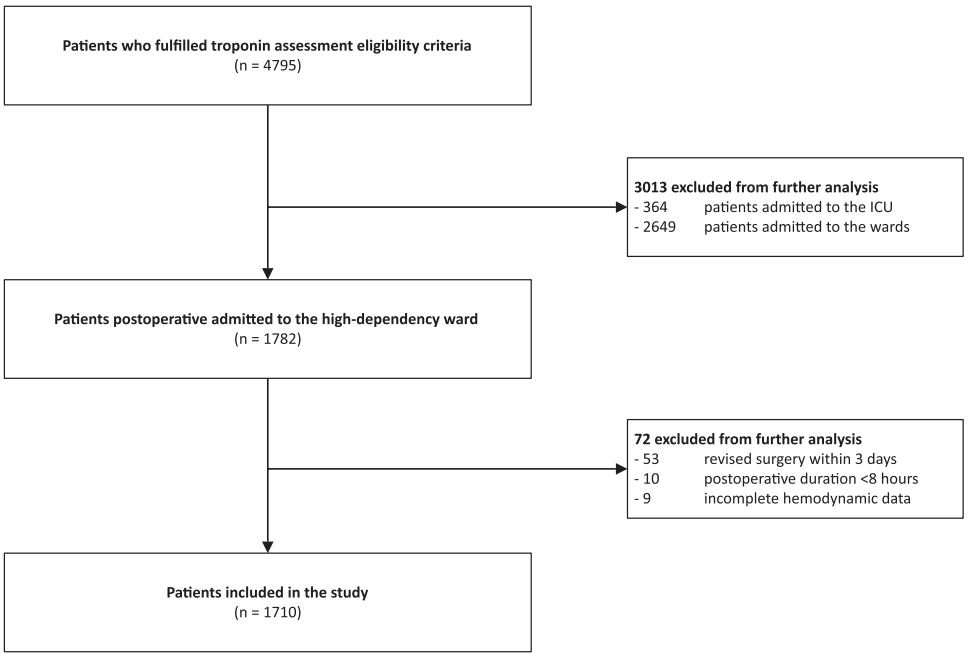

Fig. 1. Patient's flowchart. ICU, intensive care unit.

on a previously published algorithm, the following measurements were considered artifacts and removed from the data accordingly: a systolic blood pressure either less than 20 or greater than 300 mmHg; a diastolic blood pressure either less than 20 or greater than 200 mmHg; a diastolic blood pressure greater than the systolic blood pressure; and a diastolic blood pressure greater than 20 mmHg below the systolic blood pressure.[10] Invasive blood pressure measurements were preferred above noninvasive if both measurements were available. Intervals between blood pressure measurements were linearly interpolated.

MAP Thresholds and Characterizations of Hypotension

Absolute MAP thresholds were used for analyses. Multiple MAP thresholds (50 to 75 mmHg, with 5-mmHg increments)[22] were initially selected to examine postoperative thresholds for myocardial injury and to assess differences between intraoperative and postoperative thresholds.

Different characterizations of blood pressure exposures accounting for time components were calculated for each patient: lowest MAP for multiple cumulative minutes, duration, area, and time-weighted average under MAP thresholds. The lowest MAP was defined as a patient's lowest MAP during the whole intra- or postoperative period for a minimal cumulative duration of 1, 5, 10, 15, 30, 60, 120, and 240 min. Duration was defined as the cumulative length in minutes a patient's MAP had decreased below the threshold. Area under a MAP threshold was defined as the depth underneath the threshold multiplied by duration, expressed as mmHg • minutes, as the severity of hypotension. Additionally, to account for differences in durations of the perioperative periods and assuming measurements are not equidistant, time-weighted average under a MAP threshold, expressed in mmHg, was calculated, defined as area divided by the total duration of the intra- or postoperative period. We defined our main exposure as duration under the selected MAP threshold in minutes with area and time-weighted average under the MAP threshold as additional exposures.

Outcome Measures

Troponin measurements were routinely obtained on postoperative days 1, 2, and 3, unless discharged earlier. High-sensitive troponin T was measured using the Cobas e602 Troponin T hs STAT assay (Roche Diagnostics, Germany). A peak high-sensitive troponin T measurement of 50 ng/l and above during the first 3 postoperative days was defined as myocardial injury after surgery and used as the primary outcome, as previously applied in our similar cohorts[12,18] and within the current clinical practice of our institution.

Furthermore, postoperative MI (which was ruled in or out based on the criteria according to the third universal definition[23]) and 30-day all-cause mortality were assessed after surgery and used as secondary endpoints. Survival status was completed in all patients by means of using the institution's medical records or was ascertained by inquiry from the civil registries.

Statistical Analysis

A data analysis and statistical plan was written after the data were accessed. No statistical power calculation was conducted before the study. Continuous variables are presented as medians with interquartile range or as means and SDs as appropriate. Categorical variables are presented as numbers and percentages. Complete case analyses were performed. Hypotension exposures between patients with and without myocardial injury were compared using the Mann–Whitney U test. Normality for baseline characteristics was assessed visually with histograms and normal quantile–quantile plots. Incidence of intra- and postoperative hypotension is presented as percentages of patients with a cumulative duration below a MAP threshold and were linearly interpolated on the graphs.

Selecting the Postoperative MAP Threshold

To determine the MAP threshold in the postoperative period at which risk of myocardial injury starts to increase, graphs of the estimated probabilities based on the lowest MAP were plotted and inspected using adjusted binomial logistic regression models. In response to peer review, only the two extremes from the preselected cumulative durations (*i.e.*, 1 min and 4 h) were used for inspection to prevent overfitting. Potential confounders were selected and entered (age, sex, high-risk surgery, emergency procedures, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss, and length of surgery) based on known factors associated with perioperative hypotension, postoperative myocardial injury, and cardiovascular and/or mortality risk.[24,25] Restricted cubic splines analyses were applied between the lowest MAP in cumulative minutes and myocardial injury in the models and were retained when they improved the model.

Hypotension and Myocardial Injury

Univariable and multivariable logistic regression analyses were used to assess the association between intra- and postoperative hypotension with myocardial injury. The absolute threshold of 65 mmHg was selected for intraoperative hypotension based on previous studies.[5,8] The threshold for postoperative hypotension was based on examining the plots of the lowest MAP for cumulative minutes and postoperative myocardial injury, as previously explained. One single threshold was selected to define postoperative hypotension for our analyses using three different hypotension exposures (*i.e.*, duration, area, and time-weighted average under MAP) and the association with myocardial injury. Five additional thresholds were selected for comparing the association of the main exposure (duration under MAP threshold) and myocardial injury.

Due to nonlinearity, duration, area, and time-weighted average under the MAP threshold were divided in quartiles with their zero time spent under a threshold as the reference group. Duration under MAP was additionally divided and categorized into less than 0, 0 to 1, 1 to 2, 2 to 4, and greater than 4 h below the threshold. Similar confounders, as described previously, were used for the association between MAP exposures and myocardial injury. Multivariable analyses were first adjusted for potential confounders without and subsequently with intraoperative hypotension to determine if the previous hypotension occurrence would affect postoperative hypotension in the final model. Multicollinearity between the different occurrences of intra- and postoperative hypotension was assessed using variance inflation factor (threshold 5). The interaction between intraoperative hypotension and postoperative hypotension was tested and dropped if not statistically significant. Sensitivity analyses of our primary analysis were performed using the manufacturer's 99th percentile reference value of high-sensitive troponin T (*i.e.*, 14 ng/l) to define myocardial injury.[26] Additionally, in response to peer review, several *post hoc* sensitivity analyses were conducted. These included patients with only invasive blood pressure monitoring and patients with peak troponin elevations on various days after surgery.

Results are reported as odds ratios with their 95% CI. All statistical tests were two-tailed. Significance was set at $P < 0.05$ for comparing between groups and interaction terms. The Bonferroni correction was applied accordingly when comparing three different exposures for postoperative hypotension, resulting in a P value of $0.05/3 = 0.017$ as level of statistical significance. When comparing for five multiple thresholds for postoperative hypotension, a P value of $0.05/5 = 0.01$ as level of statistical significance was used. All statistical analyses were performed using R software version 3.6.0, 2018 (The R Foundation for Statistical Computing, Austria).

Results

The initial study cohort consisted of 4,795 noncardiac surgery patients who met eligibility criteria. Inclusion and exclusion of patients are presented in figure 1. Subsequently, our final study sample comprised a total of 1,710 patients with frequent postoperative hemodynamic monitoring on a high-dependency ward. A total of 1,587 of 1,710 (92%) of the patients had invasive blood pressure monitoring. The median postoperative time (interquartile range) on the high-dependency ward before being discharged to the wards was 21 h (17.7, 22.8).

Baseline Characteristics

Patients' baseline and perioperative characteristics are presented in table 1. This cohort's median age was 70 yr. Over half of the patients had a medical history of hypertension

Table 1. Baseline and Perioperative Characteristics

Patient characteristics	n = 1,710
Age, yr	70 [66, 76]
Male sex, n (%)	984 (58)
Procedural, n (%)	
Emergency	75 (4)
High-risk	439 (26)
General anesthesia	1,671 (98)
Type of surgery, n (%)	
General	308 (18)
Orthopedic	207 (12)
Urological or gynecological	175 (10)
Neurologic	532 (31)
Vascular	307 (18)
Other	181 (11)
Medical history, n (%)	
Hypertension	988 (58)
Insulin dependent diabetes mellitus	194 (11)
COPD	290 (17)
Myocardial infarction	289 (17)
Coronary artery disease	369 (22)
Congestive heart failure	148 (9)
Cerebrovascular disease	305 (18)
Renal failure	122 (7)
Peripheral artery disease	153 (9)
Preoperative medication, n (%)	
β-Blockers	722 (42)
Statins	789 (46)
Angiotensin-converting enzyme inhibitors	418 (24)
Angiotensin-II antagonists	328 (19)
Calcium channel blockers	348 (20)
Diuretics	564 (33)
Aspirin	508 (30)
Oral anticoagulants	259 (15)
Preoperative*	
Hemoglobin, g/dl	14 ± 2
Estimated glomerular filtration rate, ml · min · 1.73 m^{-2}	73 [57, 86]
Heart rate, bpm	74 [66, 82]
MAP, mmHg	96 [89, 104]
Intraoperative	
Length of surgery, min	236 [174, 322]
Estimated blood loss, ml	300 [100, 650]
Postoperative	
Peak high-sensitive cardiac troponin T, ng/l	16 [10, 28]
Myocardial injury, n (%)	238 (14)
30-day all-cause mortality, n (%)	50 (3)

Data are presented as median [25th, 75th percentiles], mean ± SD, or n (%).

*Total missing values of their respective variables were as follows: 1 (0.1%) of preoperative hemoglobin; 7 (0.4%) of preoperative estimated glomerular filtration rate; 1 (0.1%) of preoperative mean arterial pressure (MAP); 1 (0.1%) of 30-day all-cause mortality.

COPD, chronic obstructive pulmonary disease.

and 22% coronary artery disease. The median length of surgery was 236 (174, 322) min, and median blood loss 300 ml (100, 650). The first troponin was routinely measured on the morning after surgery at 6:00 AM. In 36% of the cases, high-sensitive troponin T measurements were available on all 3 postoperative days, 31% of the cases on 2 postoperative days, and 33% on 1 postoperative day. In more than half of our patients (53%), peak high-sensitive troponin T occurred on postoperative day 1, 30% on postoperative day 2, and 17% on postoperative day 3. Overall, postoperative myocardial injury occurred in 238 (14%) patients. Of these, 52 (22%) were defined as MI, and 20 (8%) died within 30 days of all-cause mortality.

Intraoperative and Postoperative Hypotension

Figure 2 shows the incidence of intra- and postoperative hypotension for each MAP threshold in cumulative minutes. There were no differences between intraoperative hypotension exposures in duration, area, and time-weighted average under MAP thresholds in patients with myocardial injury compared to patients without ($P > 0.05$ for all, except for duration under MAP threshold 75 mmHg; table 2). In contrast to the intraoperative period, patients with myocardial injury had longer durations of postoperative hypotension compared to patients without, at all MAP thresholds 50 to 75 mmHg ($P < 0.001$ for all). Likewise, both postoperative hypotension exposures area and time-weighted average under MAP were higher in patients with myocardial injury at all thresholds ($P < 0.001$ for all).

Defining the Postoperative MAP Threshold

Adjusted risk for myocardial injury based on the postoperative lowest MAP for a cumulative duration of 1 min and 4 h are shown in Supplemental Digital Content 1, figure 1(http://links.lww.com/ALN/C392). Probability of myocardial injury increased with decreasing MAP below the threshold of 75 mmHg for both cumulative durations. Longer cumulative durations of the lowest postoperative MAP were furthermore associated with exponentially increased risk of myocardial injury. A MAP threshold of 75 mmHg was hence selected based on the plots, with additional thresholds of 60, 65, 70, and 80 mmHg for comparison.

Primary Analysis

The interaction between intraoperative hypotension and postoperative hypotension was not statistically significant in all models and was subsequently removed from further analyses. Multicollinearities of intraoperative and postoperative hypotension were all minor with a variance inflation factor less than 2. Postoperative duration under a MAP threshold of 75 mmHg was associated with increased risk of myocardial injury after adjusting for potential confounders (fig. 3) and, moreover, remained statistically significant after intraoperative hypotension was added to the model; adjusted odds ratio (95% CI) was 2.68 (1.46 to 5.07) for the fourth quartile (table 3). In contrast, intraoperative hypotension as cumulative duration under the predefined MAP threshold of 65 mmHg was not associated with myocardial injury. Additional characterization of hypotension, area, and time-weighted average under MAP yielded similar unadjusted and adjusted results. After dividing and categorizing duration under MAP in hours, more than 4 h under a MAP of 70 mmHg (adjusted odds ratio, 2.18; 95% CI, 1.37 to 3.51,

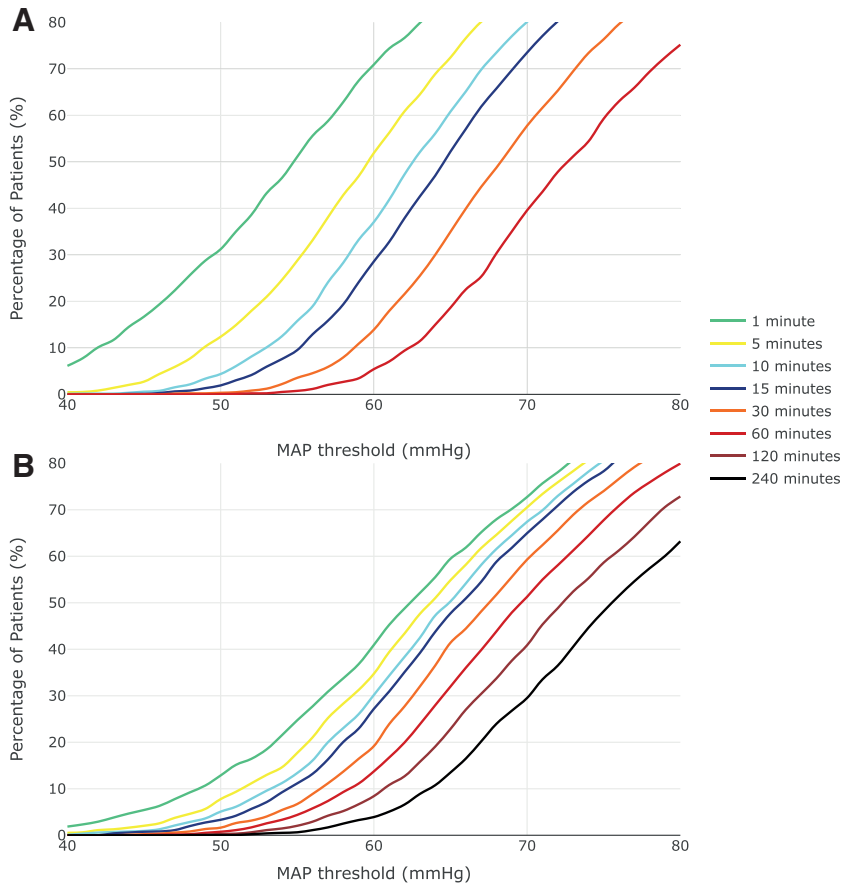

Fig. 2. Incidence of intra- and postoperative hypotension in cumulative minutes. Incidence is presented as percentage of patients who had a cumulative duration in minutes (as indicated by the *colors* in legends) below the mean arterial pressure (MAP) threshold presented on the *x-axis* during the intra- or postoperative period. Percentages were calculated for every MAP threshold and were linearly interpolated on the graphs. (*A*) The total of the intraoperative period, defined as the documented start of anesthesia until the departure from the operating room. (*B*) The total of the postoperative period, defined as departure from the operating room until 24 h on the high-dependency ward or discharge. *E.g.,* A cumulative duration of 60 min below a MAP threshold of 65 mmHg intraoperatively occurred in 19% of the patients, and a cumulative duration of 60 min below a MAP threshold of 75 mmHg postoperatively occurred in 68%.

$P = 0.001$) was associated with myocardial injury (table 4). In our total cohort, patients who suffered myocardial injury were mainly male patients, had a higher incidence of previous cardiovascular history, and were taking more cardiovascular medication (Supplemental Digital Content 2, table 1, http://links.lww.com/ALN/C392). Compared to the total cohort of patients, patients in the lowest postoperative MAP quartile more often underwent major abdominal as well as high-risk procedures. However, they were predominantly not different in previous medical history or use of preoperative medication compared to the total cohort. Within the lowest postoperative MAP quartile, for those patients who suffered postoperative myocardial injury, similar differences can be seen in age, emergency surgery procedures, and cardiovascular medical history. Associations for additional thresholds of 65 and 60 mmHg showed similar patterns. There was no association with myocardial injury for all durations under a MAP of 75 and 80 mmHg ($P > 0.01$ for all). After substitution of the primary outcome with the manufacturer's 99th percentile suggested reference threshold of 14 ng/l, associations were similar.

Additional Analyses

Furthermore, several *post hoc* additional analyses based on reviewer questions were conducted. A sensitivity analysis in patients where peak troponin was measured on day 2 or 3 after surgery as well as a sensitivity analysis in patients where blood pressure was measured with invasive blood pressure monitoring did not influence our main findings. Additionally, we conducted sensitivity analyses where the analyses were replicated separately in patients admitted to the ward or admitted to the ICU. The findings that postoperative hypotension, but not intraoperative hypotension,

Table 2. Differences in Intra- and Postoperative Hypotension Exposures in Patients with Myocardial Injury

Intraoperative				Postoperative			
Exposures	No Myocardial Injury (n = 1,472)	Myocardial Injury (n = 238)	*P* Value*	Exposures	No Myocardial Injury (n = 1,472)	Myocardial Injury (n = 238)	*P* Value*
Lowest MAP, for cumulative min, mmHg				Lowest MAP, for cumulative min, mmHg			
> 1	55 [48, 62]	55 [47, 62]	0.369	> 1	63 [56, 72]	60 [53, 68]	< 0.001
> 3	58 [52, 64]	58 [51, 65]	0.557	> 10	64 [57, 72]	61 [55, 69]	< 0.001
> 5	60 [55, 66]	60 [54, 66]	0.704	> 30	65 [58, 73]	62 [55, 69]	< 0.001
> 10	63 [58, 69]	64 [57, 70]	0.996	> 60	66 [60, 74]	63 [57, 69]	< 0.001
Duration under MAP, mmHg, min				Duration under MAP, mmHg, min			
< 50	0 [0, 1]	0 [0, 2]	0.262	< 50	0 [0, 0]	0 [0, 0]	< 0.001
< 55	1 [0, 5]	1 [0, 8]	0.115	< 55	0 [0, 0]	0 [0, 7]	< 0.001
< 60	5 [0, 16]	5 [0, 20]	0.613	< 60	0 [0, 16]	2 [0, 42]	< 0.001
< 65	16 [4, 44]	14 [4, 46]	0.697	< 65	8 [0, 90]	34 [0, 160]	< 0.001
< 70	42 [14, 96]	32 [11, 95]	0.152	< 70	60 [0, 300]	130 [14, 422]	< 0.001
< 75	81 [34, 160]	56 [26, 136]	0.006	< 75	198 [22, 554]	299 [70, 692]	< 0.001
Area under MAP, mmHg, min*mmHg				Area under MAP, mmHg, min*mmHg			
< 50	0 [0, 3]	0 [0, 6]	0.247	< 50	0 [0, 0]	0 [0, 0]	< 0.001
< 55	1 [0, 22]	2 [0, 37]	0.129	< 55	0 [0, 0]	0 [0, 9]	< 0.001
< 60	17 [0, 79]	20 [0, 105]	0.282	< 60	0 [0, 38]	2 [0, 129]	< 0.001
< 65	79 [10, 228]	74 [9, 288]	0.770	< 65	19 [0, 281]	82 [0, 589]	< 0.001
< 70	228 [64, 581]	205 [59, 642]	0.627	< 70	202 [0, 1270]	457 [34, 1941]	< 0.001
< 75	558 [208, 1228]	424 [155, 1268]	0.153	< 75	874 [55, 3460]	1621 [287, 4794]	< 0.001
Time-weighted average under MAP, mmHg				Time-weighted average under MAP, mmHg			
< 50	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.214	< 50	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	< 0.001
< 55	0.0 [0.0, 0.1]	0.0 [0.0, 0.1]	0.070	< 55	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	< 0.001
< 60	0.1 [0.0, 0.3]	0.1 [0.0, 0.4]	0.078	< 60	0.0 [0.0, 0.0]	0.0 [0.0, 0.1]	< 0.001
< 65	0.3 [0.0, 0.9]	0.3 [0.1, 1.2]	0.215	< 65	0.0 [0.0, 0.2]	0.1 [0.0, 0.5]	< 0.001
< 70	1.0 [0.3, 2.3]	1.1 [0.3, 2.9]	0.379	< 70	0.2 [0.0, 1.1]	0.4 [0.0, 1.7]	< 0.001
< 75	2.5 [0.9, 4.7]	2.4 [0.9, 5.6]	0.820	< 75	0.7 [0.0, 2.9]	1.4 [0.3, 4.0]	< 0.001

Data are presented as median [25th, 75th percentiles].

**P* values from Mann–Whitney U test.

MAP, mean arterial pressure.

was associated with myocardial injury were consistent in these analyses.

Discussion

In this study of patients undergoing intermediate- to high-risk noncardiac surgery, we investigated the association of postoperative hypotension with myocardial injury. Postoperative hypotension ranging from MAP 50 to 75 mmHg for multiple cumulative duration in minutes was common. A postoperative MAP below a threshold of 75 mmHg was found to increase the risk of myocardial injury, with shorter durations at lower thresholds being likewise harmful. After adjusting for potential confounders and intraoperative blood pressure, postoperative hypotension was independently associated with myocardial injury.

This current study confirms former results correlating the lowest MAP on the remaining day of surgery with postoperative high-sensitive troponin T levels[12] and expands on our previous findings by augmenting with frequent blood pressure measurements, multiple thresholds, characterizations for severity, and duration to define postoperative hypotension.

In a substudy of the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION), investigating the effects of withholding angiotensin-converting-enzyme inhibitors and angiotensin-II antagonists in noncardiac surgery, postoperative hypotension was investigated as a secondary objective.[13] Similarly, the substudy of the Perioperative Ischemic Evaluation 2 (POISE-2) trial also investigated postoperative hypotension, but in a period-dependent matter in relation with postoperative MI and death.[14] In both studies, postoperative hypotension was subjectively defined as clinically important hypotension, *i.e.*, when systolic blood pressure dropped to less than 90 mmHg for any duration requiring intervention

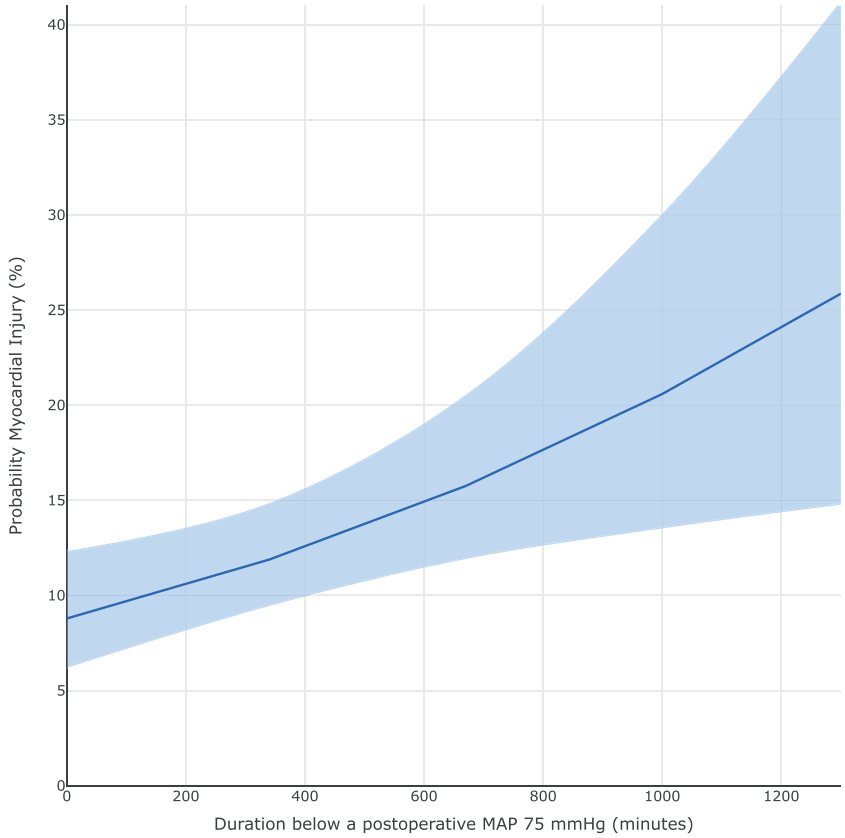

Fig. 3. Postoperative duration below a mean arterial pressure (MAP) threshold of 75 mmHg in minutes and estimated predicted probabilities of myocardial injury. Estimated probabilities of myocardial injury from multivariable logistic regressions adjusted for age, sex, high-risk surgery, emergency procedures, intraoperative hypotension, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss, and length of surgery; one observation deleted due to missingness. There were no significant interactions between postoperative and intraoperative hypotension within the model. Adding restricted cubic splines did not improve the model and were excluded from the final model.

during postoperative day 0 to 3. In the VISION's substudy, postoperative hypotension occurred less often in 19.5% of the patients and was associated with myocardial injury after noncardiac surgery (adjudicated as ischemic of origin, adjusted relative risk, 1.63; 95% CI, 1.4 to 1.8, $P < 0.001$). Postoperative hypotension during the remaining day of surgery occurred in 32% of the patients in POISE-2 and was associated with an increased risk of MI per duration of 10 min (adjusted odds ratio, 1.03; 99.2% CI, 1.0 to 1.05, $P = 0.002$). Differences in the incidence of hypotension with our study can be related to a younger, healthier population of both these cohorts, infrequent routine monitoring, and the use of a less sensitive fourth-generation troponin T assay.

Interestingly, we were unable to assess the association between intraoperative hypotension and postoperative myocardial injury described in previous studies.[5–7] This can be due to selection and treatment bias or due to the fact that the selected threshold of 65 mmHg might have been too high for our cohort (high-dependency ward patients at our center might be more vigorously treated). However, in the substudy of the VISION, the association of intraoperative hypotension and myocardial injury after noncardiac surgery was similarly no longer statistically significant after adjusting for postoperative hypotension (adjusted relative risk, 1.04; 95% CI, 0.9 to 1.2, $P < 0.58$). After adjustment for postoperative hypotension in the POISE-2's substudy, the association of intraoperative hypotension per 10-min increase and MI did not remain (adjusted odds ratio, 1.03; 99.2% CI, 0.9 to 1.1, $P = 0.162$). These results parallel our findings demonstrating the robust association between postoperative hypotension and myocardial injury. Given the likelihood that patients who are hypotensive during surgery are also hypotensive after surgery,[14] previous studies on intraoperative hypotension and myocardial injury might have been confounded by the effect of postoperative hypotension, which was not accounted for. Due to the complexity of the perioperative process influencing the patient's blood pressure, it remains unknown whether the observed hypotension

Table 3. Univariable and Multivariable Associations of Postoperative Hypotension, Defined as Different Exposures, and Myocardial Injury

Minutes under MAP, mmHg	Total (n = 1,710)	Myocardial Injury (n = 238)	Univariable Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	Adjusted Odds Ratio* (95% CI) [Full Model]†	*P* Value
Intraoperative MAP < 65						
Reference (0)	254	39 (15)				
Quartile 1: 1–8	377	52 (14)	0.88 (0.56–1.39)	0.97 (0.57–1.64)	0.90 (0.53–1.55)	0.710
Quartile 2: 9–22	370	49 (13)	0.84 (0.53–1.33)	1.19 (0.70–2.04)	1.15 (0.67–1.98)	0.622
Quartile 3: 23–53	351	44 (13)	0.79 (0.50–1.26)	1.29 (0.74–2.26)	1.12 (0.64–2.00)	0.688
Quartile 4: > 53	358	54 (15)	0.98 (0.63–1.54)	1.64 (0.93–2.93)	1.34 (0.74–2.45)	0.336
Postoperative MAP < 75						
Reference (0)	268	24 (9)				
Quartile 1: 1–86	361	40 (11)	1.27 (0.75–2.18)	1.23 (0.68–2.27)	1.21 (0.67–2.24)	0.533
Quartile 2: 87–312	360	59 (16)	1.99 (1.22–3.35)	1.77 (1.00–3.22)	1.75 (0.98–3.20)	0.062
Quartile 3: 313–635	360	45 (13)	1.45 (0.87–2.48)	1.41 (0.77–2.63)	1.33 (0.72–2.52)	0.371
Quartile 4: > 635	361	70 (19)	2.45 (1.51–4.08)	2.89 (1.60–5.38)	2.68 (1.46–5.07)	0.002
Area under MAP, mmHg*min	**Total (n = 1,710)**	**Myocardial Injury (n = 238)**	**Univariable Odds Ratio (95% CI)**	**Adjusted Odds Ratio* (95% CI)**	**Adjusted Odds Ratio* (95% CI) [full model]**	***P* Value**
Intraoperative MAP < 65						
Reference (0)	254	39 (15)				
Quartile 1: 1–32	366	48 (13)	0.83 (0.53–1.32)	0.96 (0.56–1.65)	0.90 (0.53–1.56)	0.711
Quartile 2: 33–108	362	49 (14)	0.86 (0.55–1.37)	1.21 (0.72–2.08)	1.11 (0.65–1.91)	0.709
Quartile 3: 109–279	364	42 (12)	0.72 (0.45–1.15)	1.13 (0.65–1.97)	0.97 (0.55–1.72)	0.914
Quartile 4: > 279	364	60 (17)	1.09 (0.70–1.70)	1.76 (1.01–3.09)	1.43 (0.81–2.56)	0.224
Postoperative MAP < 75						
Reference (0)	268	24 (9)				
Quartile 1: 1–337	361	42 (12)	1.34 (0.80–2.30)	1.26 (0.70–2.31)	1.24 (0.69–2.29)	0.479
Quartile 2: 338–1,513	360	50 (14)	1.64 (0.99–2.78)	1.53 (0.86–2.80)	1.49 (0.83–2.75)	0.186
Quartile 3: 1,514–4,419	360	58 (16)	1.95 (1.19–3.29)	1.85 (1.04–3.41)	1.80 (1.00–3.34)	0.056
Quartile 4: > 4,419	361	64 (18)	2.19 (1.35–3.67)	2.57 (1.41–4.80)	2.35 (1.27–4.46)	0.008
Time-weighted Average under MAP, mmHg	**Total (n = 1710)**	**Myocardial Injury (n = 238)**	**Univariable Odds Ratio (95% CI)**	**Adjusted Odds Ratio* (95% CI)**	**Adjusted Odds Ratio* (95% CI) [full model]**	***P* Value**
Intraoperative MAP < 65						
Reference (0)	254	39 (15)				
Quartile 1: 0.0–0.1	364	44 (12)	0.76 (0.48–1.21)	0.95 (0.55–1.64)	0.91 (0.52–1.58)	0.733
Quartile 2: 0.2–0.5	364	49 (14)	0.86 (0.54–1.36)	1.19 (0.70–2.04)	1.06 (0.62–1.84)	0.835
Quartile 3: 0.6–1.1	364	44 (12)	0.76 (0.48–1.21)	1.18 (0.68–2.05)	1.04 (0.59–1.82)	0.901
Quartile 4: > 1.1	364	62 (17)	1.13 (0.73–1.76)	1.53 (0.90–2.64)	1.24 (0.71–2.18)	0.454
Postoperative MAP < 75						
Reference (0)	268	24 (9)				
Quartile 1: 0.0–1.3	361	37 (10)	1.16 (0.68–2.01)	1.11 (0.61–2.05)	1.09 (0.60–2.03)	0.771
Quartile 2: 1.4–2.3	360	56 (16)	1.87 (1.14–3.16)	1.76 (0.99–3.20)	1.72 (0.97–3.15)	0.070
Quartile 3: 2.4–3.7	360	55 (15)	1.83 (1.12–3.10)	1.77 (0.98–3.27)	1.70 (0.93–3.17)	0.088
Quartile 4: > 3.7	361	66 (18)	2.27 (1.40–3.80)	2.69 (1.48–5.02)	2.50 (1.36–4.75)	0.004

*Multivariable logistic model adjusted for age, sex, high-risk surgery, emergency procedures, intraoperative hypotension, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss and length of surgery; one observation deleted due to missingness. There were no significant interactions between postoperative and intraoperative hypotension within the models. Bonferroni correction was used to adjust for the three defined exposures for postoperative hypotension. $P < 0.05/3 = 0.017$ was considered as statistically significant. †Full model: model with both intraoperative and postoperative exposures in the model (in quartiles).

MAP, mean arterial pressure.

is refractory, a direct cause of adverse outcomes, a symptom of an underlying disease, or a sign of cardiac decompensation. Regardless of the cause, postoperative hypotension was associated with myocardial injury and remained associated after adding intraoperative hypotension to the models. The recently published Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) study investigated whether individualized blood pressure management during and in the early hours after surgery would lead to less postoperative organ dysfunction.[4] The primary endpoint in this study was the dysfunction of at least one organ system of the renal, respiratory, cardiovascular, coagulation, and neurologic systems during the first 7 days after surgery. In this randomized controlled trial, an individualized strategy (aiming to achieve a systolic blood pressure within 10% of the reference value during and the first 4 h after surgery)

Table 4. Association of Postoperative Hypotension, as Duration under Multiple MAP Thresholds, and Myocardial Injury

Postoperative MAP Thresholds	Duration under MAP Threshold (h)	Total (n = 1,710)	Myocardial Injury (n = 238)	Adjusted Odds Ratio* (95% CI)† [full model]	*P* Value†
MAP < 60 mmHg					
	0	1,010	114 (11)	Reference	
	0–1	466	70 (15)	1.54 (1.05–2.24)	0.027
	1–2	91	23 (25)	2.62 (1.39–4.80)	0.002
	2–4	76	16 (21)	3.26 (1.57–6.48)	0.001
	>4	67	15 (22)	2.10 (0.96–4.39)	0.055
MAP < 65 mmHg					
	0	693	74 (11)	Reference	
	0–1	474	64 (14)	1.45 (0.97–2.19)	0.073
	1–2	153	26 (17)	1.74 (0.96–3.08)	0.062
	2–4	160	23 (14)	1.76 (0.96–3.15)	0.063
	>4	230	51 (22)	2.98 (1.78–4.98)	<0.001
MAP < 70 mmHg					
	0	466	49 (11)	Reference	
	0–1	371	50 (13)	1.25 (0.78–2.02)	0.350
	1–2	174	16 (9)	0.80 (0.40–1.56)	0.529
	2–4	195	28 (14)	1.24 (0.69–2.19)	0.471
	>4	504	95 (19)	2.18 (1.37–3.51)	0.001
MAP < 75 mmHg					
	0	268	24 (9)	Reference	
	0–1	285	32 (11)	1.18 (0.63–2.22)	0.607
	1–2	157	21 (13)	1.63 (0.80–3.31)	0.175
	2–4	178	21 (12)	1.28 (0.63–2.58)	0.487
	>4	822	140 (17)	2.03 (1.19–3.60)	0.012
MAP < 80 mmHg					
	0	153	17 (11)	Reference	
	0–1	191	13 (7)	0.52 (0.22–1.22)	0.136
	1–2	122	18 (15)	1.43 (0.64–3.22)	0.384
	2–4	164	23 (14)	1.30 (0.60–2.86)	0.506
	> 4	1,080	167 (15)	1.38 (0.75–2.69)	0.321

*Multivariate logistic model adjusted for age, sex, high-risk surgery, emergency procedures, intraoperative hypotension, intra- and postoperative heart rate, previous history of hypertension, insulin-dependent diabetes mellitus, coronary artery disease, congestive heart failure, cerebrovascular disease, renal disease, estimated blood loss, and length of surgery; one observation deleted due to missingness. There were no significant interactions between postoperative and intraoperative hypotension within the models. †Bonferroni correction was used to adjust for the five defined MAP thresholds for postoperative hypotension. $P < 0.05/5 = 0.01$ was considered as statistically significant.

MAP, mean arterial pressure.

was associated with decreased incidence in postoperative organ dysfunction (38.1% *vs.* 51.7%; relative risk, 0.73; 95% CI, 0.56 to 0.94, $P = 0.02$). Surprisingly, the incidence of myocardial injury or infarction in this high-risk population was extremely low (0.003%) compared to our study, which might potentially be explained due to their absence of systematic troponin surveillance. If blood pressure management during surgery might prevent perioperative organ injury, it is not unreasonable that postoperative management might also have the potential to improve the patient's postoperative outcome.

One of our study's strengths is exploring multiple MAP thresholds instead of one single cut-off threshold to define postoperative hypotension. Currently, there is no universal accepted definition of perioperative hypotension. The current consensus states both absolute MAP thresholds and relative MAP percentage reduction from baseline to be equally acceptable for the predictive value of myocardial injury when defining hypotension.[16] We chose to report the absolute MAP threshold values for the ease of interpretation in clinical practice. Further strengths are the use of frequent blood pressure monitoring measurements of 1- to 15-min intervals during the postoperative period. Importantly, we were able to quantify multiple characterizations of hypotension, as myocardial injury is a function of both hypotension duration and severity.[16] Both additional severity (area under MAP threshold) and averaged (time-weighted average under MAP threshold) characterizations were comparable with our main characterization of duration below the threshold, confirming the strength of our primary analysis.

In our study, several important limitations need to be considered. First, the recorded frequent postoperative blood pressures were from a high-dependency ward reflecting a higher-risk population, and the data were measured in one single university hospital, which limits generalizability. Second, since blood pressure readings during and after surgery were real-time displayed on the screens and visible

to clinical staff, we cannot account for the fact that some blood pressure recordings were accepted by clinical judgment. Since no validation takes place of the recorded blood pressures, artifacts after applying a data cleaning filter may still be present. Third, we did not account for intravenous fluids, volatile anesthesia, inotropes, and vasopressors, which potentially have a substantial contribution to intraoperative hypotension, though this is also dependent on the institution's protocols and the anesthetists' individual preferences. Fourth, preoperative high-sensitive troponin T as well as the precision of the measurement were unfortunately unavailable; hence, we were unable to validate how many patients had elevated troponin concentrations before surgery. Fifth, although we have adjusted for potential confounders and conducted multiple sensitivity analyses, as with all observational data, our cohort is still accountable for residual confounding and bias. After all possible adjustments, hypotension after surgery is clearly associated with an increased risk for myocardial injury in our cohort. However, given the fact that myocardial injury is still common in patients without severe postoperative hypotension, residual unmeasured confounding should still be expected.

On surgical wards, patients' vital signs are commonly monitored every 4 to 6 h, in which hypotensive episodes may occur more frequently. In a recent prospective blinded observational study of 312 patients, postoperative hypotension after abdominal surgery was measured with a continuous noninvasive monitor and compared to routine vital signs monitoring.[27] In this study, postoperative hypotension was also common and prolonged. More importantly, many of the hypotensive events were not detected by their institution's standard routine monitoring. Given the association between postoperative hypotension and organ dysfunction, and the fact that hypotension is common and easily overlooked on surgical wards, further studies are warranted to understand this critical period. With the implementation of continuous monitoring, physicians may be able to detect those who are most vulnerable. Subsequently, clinical trials could further elucidate what factors contribute to postoperative hypotension and how to treat it effectively to improve outcome.

Conclusions

Postoperative hypotension during the first 24 h after noncardiac surgery on a high-dependency ward is common and associated with myocardial injury when decreasing from a MAP threshold less than 75 mmHg. Multiple characterizations and longer durations of postoperative hypotension were independently associated with myocardial injury at multiple thresholds.

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Competing Interests

The authors declare no competing interests.

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Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study

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See Online for appendix

Summary

Background In non-surgical settings, covert stroke is more common than overt stroke and is associated with cognitive decline. Although overt stroke occurs in less than 1% of adults after non-cardiac surgery and is associated with substantial morbidity, we know little about perioperative covert stroke. Therefore, our primary aim was to investigate the relationship between perioperative covert stroke (ie, an acute brain infarct detected on an MRI after non-cardiac surgery in a patient with no clinical stroke symptoms) and cognitive decline 1 year after surgery.

Methods NeuroVISION was a prospective cohort study done in 12 academic centres in nine countries, in which we assessed patients aged 65 years or older who underwent inpatient, elective, non-cardiac surgery and had brain MRI after surgery. Two independent neuroradiology experts, masked to clinical data, assessed each MRI for acute brain infarction. Using multivariable regression, we explored the association between covert stroke and the primary outcome of cognitive decline, defined as a decrease of 2 points or more on the Montreal Cognitive Assessment from preoperative baseline to 1-year follow-up. Patients, health-care providers, and outcome adjudicators were masked to MRI results.

Findings Between March 24, 2014, and July 21, 2017, of 1114 participants recruited to the study, 78 (7%; 95% CI 6–9) had a perioperative covert stroke. Among the patients who completed the 1-year follow-up, cognitive decline 1 year after surgery occurred in 29 (42%) of 69 participants who had a perioperative covert stroke and in 274 (29%) of 932 participants who did not have a perioperative covert stroke (adjusted odds ratio 1·98, 95% CI 1·22–3·20, absolute risk increase 13%; p=0·0055). Covert stroke was also associated with an increased risk of perioperative delirium (hazard ratio [HR] 2·24, 95% CI 1·06–4·73, absolute risk increase 6%; p=0·030) and overt stroke or transient ischaemic attack at 1-year follow-up (HR 4·13, 1·14–14·99, absolute risk increase 3%; p=0·019).

Interpretation Perioperative covert stroke is associated with an increased risk of cognitive decline 1 year after non-cardiac surgery, and perioperative covert stroke occurred in one in 14 patients aged 65 years and older undergoing non-cardiac surgery. Research is needed to establish prevention and management strategies for perioperative covert stroke.

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Introduction

Although non-cardiac surgery can improve and prolong quality and duration of life, it is associated with complications.[1] The American College of Surgeons National Surgical Quality Improvement Program showed that among 350 031 patients undergoing low-risk non-cardiac surgeries (ie, not including patients undergoing major vascular surgery and neurosurgery), 485 (0·14%) patients had a perioperative overt stroke (ie, acute brain infarct with clinical manifestation lasting >24 h).[2] An international randomised trial[3] that included patients undergoing all types of inpatient non-cardiac surgery showed that 60 (0·7%) of 8351 adults had an overt stroke, and these strokes were associated with a high risk of mortality (32%) and disability (59%).

Covert strokes represent brain infarcts that are not recognised acutely because of unappreciated, subtle, or misclassified manifestations but are detected on brain imaging. In the non-operative setting, covert stroke is more common than overt stroke and is associated with the development of dementia, cognitive decline, decline in psychomotor speed, and an increased risk of subsequent overt stroke.[4–7] These findings in the non-operative setting raise the possibility that prognostically important covert strokes occur after non-cardiac surgery.

Brain MRI with diffusion-weighted imaging enables detection of acute brain infarction that has occurred within the preceding 10 days.[8,9] This technology allows patients to undergo a single brain MRI after surgery to establish the presence of an acute perioperative

Research in context

Evidence before this study

We searched MEDLINE, from database inception until June 20, 2019, using the search terms "stroke", "noncardiac", "non-cardiac", "postoperative", "perioperative" and "surgery", restricted to publications in English, to identify studies in people aged 18 years or older evaluating the epidemiology or the impact of covert stroke after non-cardiac surgery. Less than 1% of adults having major non-cardiac surgery have an overt stroke. Although there are several studies showing that covert stroke is frequent after carotid artery procedures, we did not identify any study outside this population that examined the incidence or effect of covert stroke, with the exception of the NeuroVISION pilot study. We did not identify any study examining the relationship between perioperative covert stroke after non-cardiac surgery with 1-year cognitive decline.

Added value of this study

In this international, prospective cohort study of 1114 participants aged 65 years or older who underwent inpatient, elective, non-cardiac surgery and had brain MRI after surgery, perioperative covert stroke occurred in 7% of participants. Patients who had a perioperative covert stroke showed an increased risk of perioperative delirium, overt stroke, or transient ischaemic attack at 1 year, and cognitive decline (primary outcome) 1 year after surgery, compared with patients who did not have a perioperative covert stroke.

Implications of all the available evidence

Perioperative covert stroke occurs in a substantial number of patients aged 65 years or older and is associated with an increased risk of cognitive decline 1 year after non-cardiac surgery. Research is needed to establish prevention and management strategies for perioperative covert stroke.

brain infarct. The Montreal Cognitive Assessment (MoCA) evaluates multiple cognitive domains, including executive function,[10] and is used for assessing vascular cognitive impairment.[11]

We did the neurological impact of cerebrovascular events in non-cardiac surgery patients cohort evaluation (NeuroVISION) study to inform the relationship between perioperative covert stroke (ie, an acute brain infarct detected on an MRI after non-cardiac surgery in a patient with no clinical stroke symptoms) and cognitive decline 1 year after surgery.

Methods

Study design and participants

NeuroVISION was an international (ie, centres from five continents), prospective, cohort study of a representative sample of adults who underwent elective, non-cardiac surgery to establish the association between perioperative covert stroke and cognitive decline 1 year after surgery. We have previously published details of the study objectives, design, and methods.[12]

Eligible patients were aged 65 years or older; underwent elective, non-cardiac surgery under general or neuraxial anaesthesia; had an anticipated length of hospital stay after surgery of 2 days or more; and provided written informed consent. We excluded patients who underwent carotid artery or intracranial surgery; were unable to undertake neuro-cognitive testing because of language, vision, or hearing impairment; or were diagnosed by a physician with an acute overt stroke (ie, a new focal neurological deficit thought to be vascular in origin with signs and symptoms lasting >24 h) after their index surgery but before their research brain MRI. The complete list of exclusion criteria is shown in the appendix (p 3).

All centres obtained ethical approval before starting patient enrolment and all participants provided written informed consent.

Procedures

Study recruitment was limited by the availability of MRI scanners at five participating centres. At these sites, we used a sampling strategy to ensure proportionate representation of patients who reflected the overall surgical population by randomly assigning the day of the week to start recruitment for specific surgery subtypes, proportional to the prevalence of surgery types at each local centre. At the remaining seven centres, study personnel approached all eligible patients for consent.

Trained research personnel did standardised assessments before the day of surgery. They collected demographic characteristics and clinical information, assessed baseline cognitive function with the MoCA questionnaire, the Digit-Symbol Substitution Test (DSST),[13] and the Trail-Making Test Part B (TMT-B),[14] and completed the Lawton Instrumental Activities of Daily Living Scale.[15]

Trained research personnel screened patients for delirium twice each day during the first 72 h after surgery using the Confusion Assessment Method.[16] To establish clinical outcomes, study personnel followed up patients throughout their hospital stay and contacted them at 30 days after surgery. 1 year after surgery, research personnel interviewed patients in person, collected data for clinical outcomes, and administered the MoCA, DSST, and TMT-B. Patients, health-care providers (eg, treating physicians), research personnel, and out-come adjudicators were masked to brain MRI results.

Patients were scheduled for their brain MRI between days 2 and 9 after surgery. MRI study sequences consisted of axial fluid-attenuated inversion-recovery, gradient-recalled echo or susceptibility-weighted imaging, T2 sequences, and diffusion-weighted imaging with apparent diffusion coefficient mapping. The MRI sequence parameters were set by the site according to their own local stroke protocols, but specific minimum standards were required including use of a 1.5 Tesla machine and maximum slice thickness of 5 mm with no gap. At a central imaging core laboratory, two of four independent experts in neuroradiology (FS, EES, AAD, RA), masked to clinical information, independently assessed each brain MRI for acute infarction, chronic infarction, haemorrhage, and other white matter lesions. Disagreements were resolved by consensus.

	All participants in analyses (n=1114)
Mean age, years	73 (SD 6)
Sex	
Men	629 (56%)
Women	485 (44%)
Medical history	
Hypertension	709 (64%)
Tobacco use	488 (44%)
Diabetes	302 (27%)
Coronary artery disease	169 (15%)
Sleep apnoea	101 (9%)
Depression	88 (8%)
Family history of dementia	68 (6%)
Chronic obstructive pulmonary disease	65 (6%)
Stroke	56 (5%)
Transient ischaemic attack	49 (4%)
Peripheral arterial disease	45 (4%)
Anxiety	37 (3%)
Pulmonary embolism	25 (2%)
In atrial fibrillation just before surgery	71 (6%)
Type of surgery	
Orthopaedic	461 (41%)
Urological or gynaecological	262 (24%)
General	259 (23%)
Vascular	40 (4%)
Low-risk	32 (3%)
Thoracic	31 (3%)
Spinal	29 (3%)
Type of anaesthetic	
General	654 (59%)
Spinal	448 (40%)
Nerve or plexus block	114 (10%)
Local	111 (10%)
Thoracic epidural	49 (4%)
Lumbar epidural	34 (3%)
Preoperative evaluations	
Montreal Cognitive Assessment score	25 (21–27)
Digit-Symbol Substitution Test score	41 (29–55)
Trail-Making Test Part B, time in s	107 (78–171)
Lawton Instrumental Activities of Daily Living score	8 (7–8)

Data are n (%) or median (IQR). Percentages are rounded.

Table 1: **Baseline characteristics**

Outcomes

The primary outcome, cognitive decline, was defined as a decrease of 2 points or more on the MoCA from preoperative baseline to 1-year follow-up. A decrease of 2 points or more on the MoCA is associated with cognitive decline based on a formal neuropsychological test battery.[17,18] Secondary outcomes comprised perioperative covert stroke (ie, research brain MRI finding of an acute infarct in a patient who was not diagnosed with an overt stroke before the MRI); delirium within the first 3 days after surgery; cognitive decline at 1-year follow-up based on DSST and TMT-B; and clinical outcomes, reported and defined in the appendix (pp 4–5). Outcome adjudicators established whether a death was vascular or non-vascular, and whether a patient had an overt stroke, transient ischaemic attack, new atrial fibrillation or flutter, myocardial injury after non-cardiac surgery, and myocardial infarction. Adjudicated events were used for the analyses.

Statistical analysis

We established that a sample size of of 1100 patients would provide 80% power to detect an odds ratio (OR) of 2·18 for the risk of cognitive decline after a covert perioperative stroke, assuming a 30% incidence of postoperative cognitive decline and a 5% incidence of covert stroke. To establish the association between perioperative covert stroke and the primary outcome, we undertook the primary multivariable regression analysis in which the dependent variable was cognitive decline at 1 year (ie, a decrease of ≥2 points on the MoCA from preoperative to 1 year after surgery). Independent variables included perioperative covert stroke and the following variables, which have been shown to be associated with cognitive decline: age; sex; baseline physical impairment as measured by the Lawton scale; a history of stroke, transient ischaemic attack, vascular disease (ie, coronary or peripheral artery disease), and depression or anxiety; and type of surgery (ie, general, vascular, thoracic, urological or gynaecological, orthopaedic, spinal, and low-risk surgery). We used a method of evidence-informed data imputation for patients who did not complete a MoCA at 1 year (appendix p 6).[12,19,20]

The secondary multivariable regression and sensitivity multivariable regression analyses related to cognitive decline on the basis of the MoCA are reported in the appendix (p 7). The secondary analyses of cognitive decline at 1 year on the basis of the DSST and TMT-B are shown in the appendix (p 8).

The secondary analyses assessing the association between perioperative covert stroke and perioperative delirium, and the associations between covert stroke and clinical outcomes were calculated using Cox proportional hazards models unless the proportional hazard assumption was violated. When this assumption was violated, Fisher's exact tests (if any expected cell counts were <5 participants) or χ^2 tests provided a comparison of the cumulative incidences between individuals with and without perioperative covert stroke. All analyses were done using SAS version 9.4.

Role of the funding source

The funders of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report. The corresponding author and the first author of the writing committee had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited patients from March 24, 2014, to July 21, 2017, at 12 academic centres in nine countries (ie, Canada, Chile, China, India, Malaysia, New Zealand, Peru, Poland, and the USA). Of the 1627 patients who were eligible for NeuroVISION, 511 (31%) patients did not participate (appendix p 9). The most common reason for not participating was patient refusal to have an MRI (423 [26%] patients). Two patients were ineligible because they had an overt stroke on postoperative days 2 or 3, before a study MRI could occur.

Of the 1116 patients enrolled in NeuroVISION, we excluded two patients from the analyses who had uninterpretable MRIs. Of 1114 patients included in the analyses, the follow-up for clinical outcomes was complete for 1112 (>99%) patients, and 1001 (90%) patients completed the 1-year MoCA. The most common reason for not completing the 1-year MoCA was death (55 patients).

The mean age of participants was 73 years (SD 6); 629 (56%) were men, 709 (64%) had a history of hypertension, and 56 (5%) had a history of stroke (table 1). Orthopaedic, urological or gynaecological, and general were the most common types of surgeries. The median preoperative MoCA score was 25 (IQR 21–27).

Patients had a brain MRI a median of 5 days (IQR 3–7) after surgery. The postoperative brain MRI results are reported in the appendix (p 11); 78 (7%, 95% CI 6–9) of 1114 patients had imaging findings of an acute perioperative covert stroke. In patients who had a perioperative covert stroke, 10 (13%) of 78 had multiple acute brain infarcts (figure 1). Evidence of a chronic brain infarct was detected in 19 (24%) of 78 of the patients who had a perioperative covert stroke and 239 (23%) of 1036 patients who did not have a perioperative covert stroke. Perioperative covert stroke occurred in all types of non-cardiac surgeries (appendix p 12). Perioperative covert stroke was detected in all centres except one, which recruited three participants (appendix p 13). No significant difference was observed

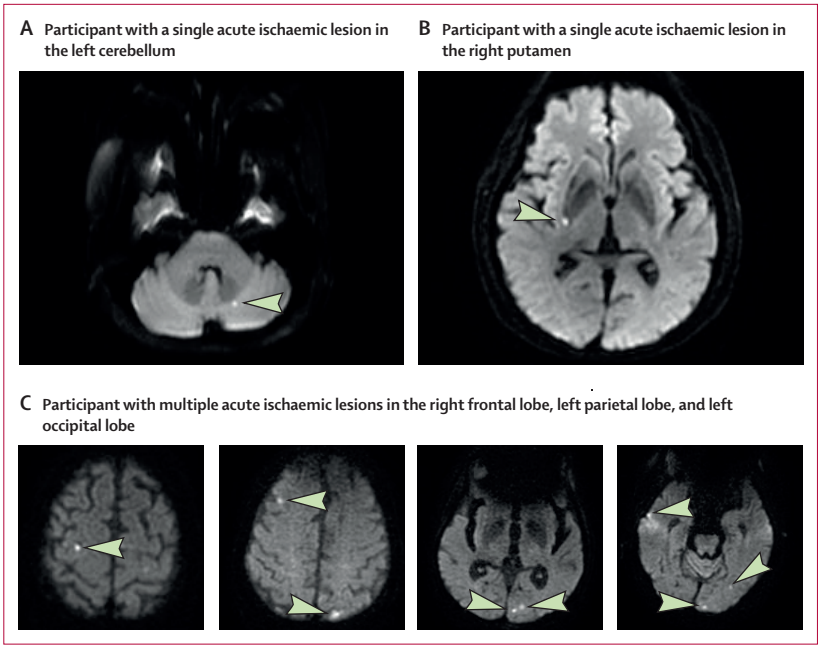

Figure 1: **Examples of acute perioperative brain infarcts in study participants**
Examples are shown on diffusion-weighted imaging sequences.

	Adjusted odds ratio (95% CI)	p value
Perioperative covert stroke	1·98 (1·22–3·20)	0·0055
Age (per 1 year increase)	1·04 (1·02–1·07)	0·0019
Sex		
Men	0·85 (0·63–1·14)	0·27
Women	1 (ref)	..
History of stroke	0·58 (0·28–1·21)	0·14
History of transient ischaemic attack	1·06 (0·53–2·12)	0·87
History of vascular disease†	0·82 (0·56–1·21)	0·32
History of depression or anxiety	0·93 (0·58–1·48)	0·74
Type of surgery		
General	1 (ref)	..
Vascular†	1·26 (0·57–2·78)	0·57
Thoracic	0·77 (0·31–1·89)	0·56
Urological or gynaecological	0·98 (0·66–1·45)	0·92
Orthopaedic	0·64 (0·44–0·93)	0·019
Spinal	0·74 (0·30–1·84)	0·52
Low-risk	1·14 (0·50–2·59)	0·75
Baseline physical impairment‡	0·90 (0·78–1·02)	0·11

Data are odds ratio (95% CI). *Cognitive decline was defined as a decrease of ≥2 points on the Montreal Cognitive Assessment test at 1 year compared with the preoperative baseline. †Vascular refers to coronary artery disease or peripheral arterial disease. ‡Per 1 unit increase of Lawton Instrumental Activities of Daily Living score.

Table 2: **Multivariable analysis to inform primary objective of relationship between covert stroke and 1-year cognitive decline***

in the proportion of patients with covert stroke between centres that used a sampling strategy versus those that approached all eligible patients (44 [6%] of 694 *vs* 34 [8%] of 420; p=0·27).

The primary outcome, 1-year cognitive decline, occurred in 29 (42%) participants who had a perioperative covert stroke and 274 (29%) participants who did not have a perioperative covert stroke. Covert stroke was associated with an increased risk of cognitive decline at 1 year after surgery (adjusted OR 1·98, 95% CI 1·22–3·20; p=0·0055; absolute risk increase 13%; table 2).

We undertook a post-hoc analysis based on the primary multivariable regression model with the inclusion of the type of anaesthetic as an independent variable. The relationship between covert stroke and cognitive decline was consistent with the primary analysis, and type of anaesthetic was not associated with cognitive decline (appendix p 14). We also did a post-hoc analysis based on the primary multivariable regression model adjusted for centre and showed a similar association between covert stroke and cognitive decline, as per the primary analysis (appendix p 15).

	Participants who had a covert stroke (n=78)	Participants who did not have a covert stroke (n=1036)	Hazard ratio (95% CI)	p value
Delirium during first 3 days after surgery	8 (10%)	49 (5%)	2·24 (1·06–4·73)	0·030
Outcomes during the first year after surgery				
Composite of overt stroke and transient ischaemic attack*	3 (4%)	10 (1%)	4·13 (1·14–14·99)	0·019
Overt stroke	2 (3%)	7 (1%)	3·92 (0·82–18·89)	0·066
Transient ischaemic attack	1 (1%)	3 (<1%)	NA	0·15
Dementia	0	1 (<1%)	NA	0·78
Mild cognitive impairment	0	1 (<1%)	NA	0·79

Data are n (%) unless otherwise specified. Percentages are rounded. NA=not applicable. *Patients with an overt stroke before the study MRI were excluded from the study. All overt strokes in these analyses occurred after the study MRI.

Table 3: **Secondary neurological outcomes**

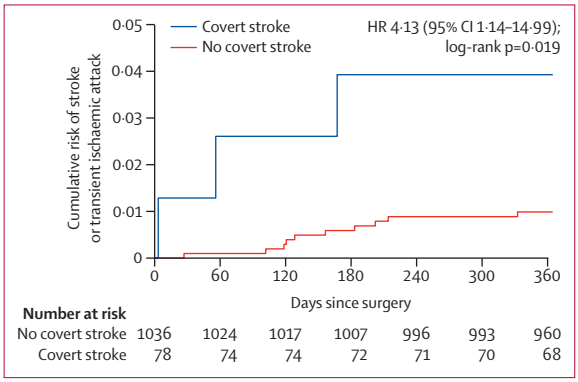

Figure 2: **Kaplan–Meier estimates of the composite outcome of overt stroke and transient ischaemic attack at 1 year**
HR=hazard ratio.

The secondary analyses, and the sensitivity multivariable regression analyses related to cognitive decline based on the MoCA, all showed results consistent with the primary multivariable analysis (appendix pp 16–17). The secondary multivariable regression analyses related to cognitive decline based on DSST and TMT-B as continuous outcomes were consistent with the primary multivariable regression analysis, but TMT-B as a dichotomous outcome was not assciated with occurrence of covert stroke (appendix p 18).

Table 3 reports the secondary neurological outcomes. Delirium in the first 3 days after surgery occurred in eight (10%) of 78 participants who had a perioperative covert stroke and in 49 (5%) participants of 1036 who did not have a perioperative covert stroke; covert stroke was associated with an increased risk of delirium (hazard ratio [HR] 2·24, 95% CI 1·06–4·73; p=0·030, absolute risk increase 6%; appendix p 10).

The 1-year incidence of the composite of overt stroke and transient ischaemic attack was increased in patients who had a perioperative covert stroke (three [4%] participants of 78) compared with patients who did not have a perioperative covert stroke (ten [1%] participants of 1036; HR 4·13, 95% CI 1·14–14·99; p=0·019; absolute risk increase 3%; figure 2).

Secondary non-neurological outcomes and death are reported in the appendix (p 19). Death occurred in six (8%) of 78 patients who had a perioperative covert stroke and in 49 (5%) of 1036 patients who did not have a perioperative covert stroke (HR 1·66; 95% CI 0·71–3·88). Patients who had a perioperative covert stroke did not show an increased risk of non-neurological outcomes and death compared with patients who did not have a perioperative covert stroke.

Discussion

In this international, prospective cohort study of a representative sample of 1114 participants aged 65 years and older who underwent elective, non-cardiac surgery, we showed that 78 (7%, 95% CI 6–9) of 1114 patients had a perioperative covert stroke. Perioperative covert stroke was observed across all types of non-cardiac surgeries. Cognitive decline occurred frequently in individuals without covert stroke (29%) and even more frequently in those with covert stroke (42%). The primary analysis showed that covert stroke was associated with an increased risk of cognitive decline at 1 year. The secondary and sensitivity multivariable regression analyses related to cognitive decline on the basis of the MoCA and DSST all showed consistent results with the primary multivariable analysis. Covert stroke was also associated with an increased risk of perioperative delirium and overt stroke or transient ischaemic attack at 1-year follow-up.

Our study has several strengths. Inclusion of international centres and a sampling strategy to ensure proportionate representation of patients having surgery

supports the generalisability of our results. We masked all the relevant groups to the MRI results. Two independent neuroradiology experts evaluated each MRI, and they were masked to the clinical data.

Our study also had several limitations. 113 (10%) patients did not complete the 1-year MoCA; however, we imputed MoCA scores for these patients. Moreover, our sensitivity analyses without imputation produced consistent results. We excluded patients having emergency surgery and patients younger than 65 years; clinicians should not assume our results apply to these patients. Given that patients had their brain MRI between days 2 and 9 after surgery and brain MRIs with diffusion weighting are able to detect acute strokes that have occurred within the preceding 10 days, some acute strokes might have occurred before surgery. Despite this possibility, the proportion of preoperative acute stroke is likely to be small, as a large population-based study done at the Mayo Clinic Study of Aging showed that of non-surgical patients who underwent MRI evaluation, acute covert stroke was uncommon (ie, six of 2095 patients).[21] The baseline characteristics of the NeuroVISION and Mayo Clinic Study of Aging were similar (appendix p 20).

There were few clinical neurological outcomes, weakening our inferences. Although we showed that cognitive decline occurred in 274 (29%) patients without covert stroke, we did not have a non-surgical control group. Therefore, we do not know whether patients undergoing non-cardiac surgery without a perioperative covert stroke are at increased risk of cognitive decline. Although some studies have suggested non-cardiac surgery can result in cognitive dysfunction, other studies have not supported this association.[22] Moreover, most studies have not had a non-surgical matched cohort.

Study personnel assessed patients for delirium during the first 3 days after surgery and patients underwent their brain MRI a median of 5 days (IQR 3–7) after surgery. Therefore, in most patients, we were not able to establish whether covert stroke preceded delirium. Although the primary analysis adjusted for known confounders of cognitive decline, given the observational nature of our study, there remains the risk of residual confounding.

The NeuroVISION pilot included 100 participants aged 65 years or older who underwent inpatient, non-cardiac surgery at six centres in four countries.[23] The pilot showed an incidence of perioperative covert stroke of 10% (95% CI 6–17), and the CI includes the incidence of covert stroke found in our, substantially larger, NeuroVISION study (ie, 7%).

A systematic review[7] that included 105 non-surgical studies reported that 20% of participants had a previous covert stroke on the basis of their brain MRI results and no history of overt stroke. In NeuroVISION, 5% of participants had a history of overt stroke and 23% of participants had evidence of a chronic infarct on their postoperative brain MRI. This finding suggests that approximately 18% of the NeuroVISION participants had a history of covert stroke, which is in keeping with the results of the non-surgical systematic review.[7] In a non-surgical prospective cohort study,[6] 1015 participants aged 60–90 years who were free of dementia and without a history of overt stroke underwent a baseline brain MRI. Covert stroke was associated with an increased risk of developing dementia and a more rapid decline in cognitive function than patients who did not have a covert stroke. This non-surgical study supports our finding that perioperative covert stroke was associated with an increased risk of cognitive decline.

A non-cardiac surgery study[24] of 551 patients showed no association between perioperative delirium and cognitive dysfunction at 6 months. A prospective cohort study[25] of 98 patients who underwent off-pump coronary artery bypass grafting surgery reported that perioperative brain infarction, detected on MRI, was independently associated with an increased risk of delirium after surgery. Although this study was of patients having coronary artery bypass grafting surgery, the results were similar to our finding of an increased risk of perioperative delirium with covert stroke after non-cardiac surgery.

NeuroVISION showed that 7% of patients had a perioperative covert stroke, which was associated with an increased risk of cognitive decline at 1 year. We selected our primary outcome because previous research has shown that a decrease of 2 or more points on the MoCA is associated with cognitive decline.[17,18] Moreover, the MoCA has shown high correlation when compared with the full 60-min National Institute of Neurological Disorders and Stroke vascular cognitive impairment neuropsychological assessment battery.[26] Supporting the result of our primary outcome, eight secondary and sensitivity multivariable analyses based on the MoCA and DSST showed consistent results. Although the secondary analysis of TMT-B as a dichotomous variable did not show an association with covert stroke, TMT-B as a continuous variable had non-statistically significant worsening of cognitive function with covert stroke ($p=0\cdot064$).

Loss of cognitive function is one of the most feared surgical complications. A random sample survey of households in Alberta, Canada, asked 1216 people about their fears related to undergoing major surgery with general anaesthesia; the most common responses for which participants indicated they were very concerned were brain damage (19%) and memory loss (17%).[27] A study published in 1955[28] to address family concerns related to comments like "he's never been the same since his operation" suggested that surgery might be a factor related to the subsequent diagnosis of dementia. NeuroVISION suggests that perioperative covert stroke might play an important role in explaining cognitive decline after non-cardiac surgery.

A large Danish national cohort study[29] evaluated patients who underwent a hip arthroplasty with matched

controls for age, sex, and region. The study showed that hip replacement was associated with an increased risk of overt ischaemic stroke (adjusted HR 4·69, 95% CI 3·12–7·06) and overt haemorrhagic stroke (adjusted HR 4·40, 2·01–9·62) in the 2 weeks after surgery. Non-cardiac surgery is associated with atrial fibrillation, haemodynamic compromise, hypercoagulability, inflammation, sympathetic stimulation, and bleeding—all of which might be associated with perioperative stroke and covert stroke.[1] Although our finding that covert stroke was associated with an increased risk of stroke or transient ischaemic attack at 1-year follow-up was limited by few events, it suggests the possibility that an embolic cause might underlie our results. Our finding that 13% of patients with a covert stroke had multiple brain infarcts suggests that some of these were embolic. Moreover, a retrospective cohort study[30] of 150 198 patients showed that a patent foramen ovale was associated with an increased risk of perioperative overt stroke (adjusted OR 2·66, 95% CI 1·96–3·63).

A substantial proportion (29%) of the patients who did not have a perioperative covert stroke had cognitive decline 1 year after surgery. This finding suggests the possibility that factors beyond perioperative covert stroke might influence cognitive function after non-cardiac surgery.

One in 14 patients undergoing inpatient, non-cardiac surgery who were aged 65 years and older had a perioperative covert stroke, which was associated with an increased risk of cognitive decline at 1 year. There is a need for research to inform the cause of perioperative covert stroke and establish whether prevention and management strategies avert cognitive decline.

Contributors

MM, PJD, DCa, MTVC, DCo, GG, MDH, SP, MSh, TGS, EES, and CYW contributed to the study design. NRA, RA, FKB, CB, DCa, MTVC, IC, DCo, PJD, AAD, MDH, GM, MM, SP, FS, RDS, MSa, MSh, TGS, AS, EES, JS, WS, DT, and CYW contributed to data collection. QI, SFL, and SIB did the statistical analysis. The steering committee designed the study. The writing committee prespecified the statistical analysis plan before any investigator was unmasked to the study results. The first and last authors (MM and PJD) of the writing committee wrote the first draft of the manuscript, and the writing committee members made critical revisions and decided to submit the paper for publication. The first and last authors (MM and PJD) vouch for the completeness and accuracy of the data. All authors contributed to the interpretation of the data and the critical revisions of the manuscript before seeing and approving the final version.

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Declaration of interests

EES reports personal fees from Portola Pharmaceuticals and Alnylam Pharmaceuticals, outside the submitted work. MDH reports personal fees from Merck, non-financial support from Hoffmann-La Roche Canada Ltd, and grants from Covidien (Medtronic), Boehringer Ingelheim, Stryker Inc, Medtronic LLC, and NoNO Inc, outside the submitted work. MDH has a patent on Systems and Methods for Assisting in Decision-Making and Triaging for Acute Stroke Patients issued to US Patent office number 62/086,077, owns stock in Calgary Scientific Incorporated, a company that focuses on medical imaging software, and is a director of the Canadian Federation of Neurological Sciences, a not-for-profit organisation. PJD reports grants from Abbott Diagnostics, Boehringer Ingelheim, Philips Healthcare, Roche Diagnostics, and Siemens, outside the submitted work. All other members of the writing committee declare no competing interests.

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