Of Railroads and Roller Coasters

Considerations for Perioperative Blood Pressure Management?

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Management of intra- and early postoperative hemodynamics is the "bread and butter" of the operative anesthesiologist's toolkit, a skill that gives many of us great pride. Who hasn't rejoiced at the end of a long case to think to themselves, or better yet to brag to the surgeon, the recovery room nurse, or even a colleague, that the hemodynamics were "railroad tracks" all the way through? On the flip side, how many of us have gone home exhausted after a long case "battling" the "roller coaster" of blood pressure and/or heart rate? Although heart rate has been the subject of great controversy during the 1980s through early 2000s during the peak period of the beta blocker controversy, blood pressure has now assumed the forefront of this scrutiny. The pioneering work of many groups, applying rigorous techniques to the capture and analysis of large amounts of data downloaded from monitoring equipment, has provided numerous observational cohort analyses relating intra-, and more recently, early postoperative data to a variety of clinically important outcomes.

"…[T]he long-standing focus on blood pressure as the only surrogate for perfusion should be tempered…"

In this issue of Anesthesiology, investigators at Erasmus University (Rotterdam, The Netherlands) present data regarding associations between intra- and early postoperative mean arterial pressure and myocardial injury.[1] A unique feature of this study is the availability of postoperative high-sensitivity troponin T measurements as part of an ongoing registry whereby such measurements are "routine." Patients 60 yr of age or older undergoing intermediate to high-risk noncardiac surgery with expected duration of hospitalization of at least 24 h who were admitted to a "high dependency" unit (a unit intermediate in acuity between an intensive care unit and a post-anesthesia recovery unit) were monitored intra- and for 24 h postoperatively frequently (1 to 5 min intra- and 1- to 15-min intervals postoperatively). The association between a variety of calculated metrics of mean blood pressure (absolute thresholds and time-weighted parameters) and myocardial injury (high sensitivity troponin T 50 ng/l or greater) occurring within the first 3 postoperative days were assessed. Myocardial injury was associated with higher prolonged durations of all mean arterial pressure thresholds used, and after adjustment for clinical confounders adjusted odds ratios from 2.18 to 3.26 were observed. Of note, intraoperative hypotension had no independent effect on myocardial injury.

The results and conclusions presented in the article by Liem *et al.*[1] can be viewed and interpreted through different lenses. We present alternate and complementary perspectives on these data. Drs. Le Manach and Collins provide insight into implications of observational study designs and statistics, while Drs. Meyhoff and Aasvang focus on some of the more specific clinical considerations as well as implications for more advanced or remote postoperative clinical monitoring.

Image: J. P. Rathmell.

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Implications of Study Design and Statistics

Interest in the incidence, predictors, and implications of perioperative hypotension have been a major focus of perioperative research over the past decade. Numerous observational studies have demonstrated that intraoperative hypotensive events are associated with postoperative complications (including cardiac, renal, and death), and many investigators have attempted to define blood pressure thresholds associated with such outcomes.[2] Other studies have defined blood pressure metrics (*e.g.*, cumulative minutes, duration, area and time-weighted-averages) to better describe this relationship.[3] Liem *et al.* provide data demonstrating that postoperative hypotension is associated with myocardial injury, but intraoperative hypotension was not.[1] Although intraoperative hypotension occurred in this cohort, the reported profiles were similar in patients whether they experienced postoperative myocardial injury or not. Therefore, knowing the intraoperative blood pressure did not provide information regarding which patients will develop postoperative myocardial injury. Hypotension occurring after surgery was more prevalent in those with myocardial injury.

As with most of the existing studies, establishing a causal relationship between hypotension and the primary outcome was not possible. Observational data are not a substitute to randomized data. One can likely conclude that in most instances, any hypotension is an undesirable condition, but no existing studies (including this current observational study) demonstrate that controlling blood pressure can prevent the undesirable outcomes reported. To accomplish this, an interventional design is required.

While acknowledging the paucity of randomized data, Liem *et al.* used a frequent reporting pattern (as many other authors of similar studies) and claim that postoperative hypotension (*i.e.*, the exposure) was *independently associated* with myocardial injury (*i.e.*, the outcome).[1] Independence from the other variables included in a predictive model is an *assumption* of regression methods. Yet, to verify this assumption is nontrivial in clinical datasets, where multidimensional interactions are frequent. At best, researchers can exclude important collinearity between two variables. It is paramount for the readers to understand that an *independent association* (from any other variables, known or not) between an exposure and an outcome defines a causal relationship (*i.e.*, removing the exposure would prevent the outcome). Even though the nomenclature of regression refers to variables as *independent*, it is a fallacy to declare a variable *independent* and thus suggest causality. A variable's *independence* is an assumption of regression methods, *not a result*. The strongest approach to create an independent exposure is to randomize it. Randomization reduces bias by creating an exposure allocation *independent* from any other variables and allows an efficient mechanism to explore cause–effect relationships and to determine causality. Therefore, claiming *independence* between exposure and outcome suggests to the reader that limiting the exposure would prevent the outcome, with no supporting evidence for the causal nature of the observed association.

One could be tempted to argue that looking at the magnitude of the association, the causal link between hypotension and postoperative outcome doesn't need to be demonstrated and that the level of evidence is enough to justify aggressive perioperative management to prevent hypotension, thus perhaps improving outcome.[4] One could even define a variety of anesthesia care quality metrics based on blood pressure parameters (*e.g.*, blood pressure nadir during surgery, time spent below pre-established thresholds of blood pressure, *etc.*).[3] Further, there is growing enthusiasm for implementing some form of standardized metrics for perioperative blood pressure management based primarily on the large amount of accumulated observational research over the past decade.[5] Although assumptions of the potential benefits are frequent, the interventions required to achieve perioperative blood pressure control are rarely discussed. This concept is not new, and it has been previously implemented in a tentative manner to improve perioperative care based on heart rate control.[6]

In the study by Liem *et al.*, intraoperative hypotension was not statistically associated with postoperative myocardial injury.[1] This suggests that interventions targeting the control of intraoperative blood pressure are not likely to prevent postoperative myocardial injury in this specific population. However, Liem *et al.* do report an association between postoperative hypotension and myocardial injury. Although the causal relationship between this exposure and the outcome cannot be affirmed with this study design, this observation emphasizes the possibility for enhanced monitoring of postoperative blood pressure to identify patients more likely to develop myocardial injury.[1] However, none of the results presented provides direct evidence that simply restoring blood pressure to an arbitrary value would prevent myocardial injury.

Implications for Postoperative Clinical Monitoring

Despite advances in surgical technique and perioperative medicine, surgery still entails risk of life-threatening adverse cardiac outcomes, emphasizing the need for a better understanding of the pathophysiologic mechanisms involved to institute prophylactic or immediate interventions.

The study of high-risk patients by Liem *et al.*, in which blood pressures and high sensitivity troponin T concentrations were prospectively captured, adds to our knowledge by supporting previous findings of the importance of postoperative hypotension on the risk for myocardial injury after major surgical procedures.[4] It combines both the duration and severity of hypotension to risk-stratify patients. One of the key methodologic strengths is the use of invasive blood pressure monitoring with a sampling frequency between 1 and 15 min.

Liem *et al*. focus on events detected in the high dependency unit to explain the observed troponin alterations, which is understandable because frequent or even continuous measurements to detect and correct vital sign deviations are currently only feasible in the intensive care unit, operating room, post anesthesia recovery unit, and other high-dependency units with a high staffing-to-patient ratio and access to monitoring equipment.[1] However, from a physiologic standpoint, there is no reason to assume that deviations only occur in these units.[7] The literature suggests a paucity in our understanding of complications occurring in general wards and especially after discharge.[8] Future studies should also aim outside these highly specialized settings when caring for patients at high risk of cardiovascular and other surgical complications.[9,10] Thus, the few studies on continuous monitoring in the general wards have shown that a large proportion of cases go undetected by the usual manual intermittent measurements with up to 8 or 12 h in-between, or at home, where standards for out-of-hospital monitoring have yet to be established.[4,9–11]

An intriguing aspect of the current study is why severe hypotension lasting for hours was allowed to occur. Were the long durations of low blood pressure refractory or unrecognized? As such, the study does not elucidate the practical approach to treat persistent hypotension. Given the fact that the study took place in a high-dependency unit, low-staffing or inadequate access to treatment modalities (fluid therapy, vasopressors) would not be expected to explain the prolonged duration. This raises the important question of *how* we alert clinical staff about adverse physiologic deviations to ensure timely interventions in a way where alarms do not cause alarm fatigue and other causes for unresponsiveness to alerts.[7] This should be an important research objective, if results such as the ones found by Liem *et al*. are to alter clinical practice.

As such, this study also tells us that the long-standing focus on blood pressure as the only surrogate for perfusion should be tempered, and a more integrated assessment of tissue and myocardial perfusion and oxygenation is needed.[12] The time has come to move beyond single-modality assessments and using a multimodal sensor and patient characteristics approach to form the basis for real-time risk models to identify patients developing severe postoperative complications. This would allow timely and effective interventions, not only in high-dependency units but also extending into the general wards in high-risk procedures and patients, and ultimately at home, allowing for safe and early discharge. Achieving this goal would be the next big step in improving perioperative care, and the study by Liem *et al*. has identified essential information for the blood pressure component of such potential systems.

Hopefully, the perspectives presented above will facilitate the necessary journey toward more enlightened and, most importantly, evidence-based management of perioperative blood pressure, hopefully by a smooth railroad, but more likely we will continue to live with the dreaded roller coaster, to the appropriate destination in one of the "last great frontiers" of anesthetic and perioperative medical practice.

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Competing Interests

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References

1. Liem VGB, Hoeks SE, Mol KHJM, Potters JW, Grüne F, Stolker RJ, van Lier F: Postoperative hypotension after noncardiac surgery and the association with myocardial injury. Anesthesiology 2020; 133:510–22
2. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
3. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE, Miller TE, Mythen MG, Grocott MP, Edwards MR; Perioperative Quality Initiative-3 workgroup; POQI chairs; Physiology group; Preoperative blood pressure group; Intraoperative blood

pressure group; Postoperative blood pressure group: Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122:563–74
4. Sessler DI, Khanna AK: Perioperative myocardial injury and the contribution of hypotension. Intensive Care Med 2018; 44:811–22
5. Meng L, Yu W, Wang T, Zhang L, Heerdt PM, Gelb AW: Blood pressure targets in perioperative care. Hypertension 2018; 72:806–17
6. Abbott TEF, Minto G, Lee AM, Pearse RM, Ackland GL; POM-HR, POMO-O and OPTIMISE study groups: Elevated preoperative heart rate is associated with cardiopulmonary and autonomic impairment in high-risk surgical patients. Br J Anaesth 2017; 119:87–94
7. Haahr-Raunkjær C, Meyhoff CS, Sørensen HBD, Olsen RM, Aasvang EK: Technological aided assessment of the acutely ill patient: The case of postoperative complications. Eur J Intern Med 2017; 45:41–5
8. Aasvang EK, Luna IE, Kehlet H: Challenges in postdischarge function and recovery: The case of fast-track hip and knee arthroplasty. Br J Anaesth 2015; 115:861–6
9. Bojesen RD, Fitzgerald P, Munk-Madsen P, Eriksen JR, Kehlet H, Gögenur I: Hypoxaemia during recovery after surgery for colorectal cancer: A prospective observational study. Anaesthesia 2019; 74:1009–17
10. Duus CL, Aasvang EK, Olsen RM, Sørensen HBD, Jørgensen LN, Achiam MP, Meyhoff CS: Continuous vital sign monitoring after major abdominal surgery: Quantification of micro events. Acta Anaesthesiol Scand 2018; 62:1200–8
11. Khanna AK, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, Lee S, Ti LK, Urman RD, McIntyre R, Jr., Tornero C, Dahan A, Saager L, Weingarten TN, Wittmann M, Auckley D, Brazzi L, Le Guen M, Soto R, Schramm F, Ayad S, Kaw R, Di Stefano P, Sessler DI, Uribe A, Moll V, Dempsey SJ, Buhre W, Overdyk FJ: Prediction of opioid-induced respiratory depression on inpatient wards using continuous capnography and oximetry: An international prospective, observational trial. Anesth Analg 2020 Apr 16 [Epub ahead of print]
12. Foss NB, Kehlet H: Perioperative haemodynamics and vasoconstriction: Time for reconsideration? Br J Anaesth 2019; 123:100–3

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.

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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

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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

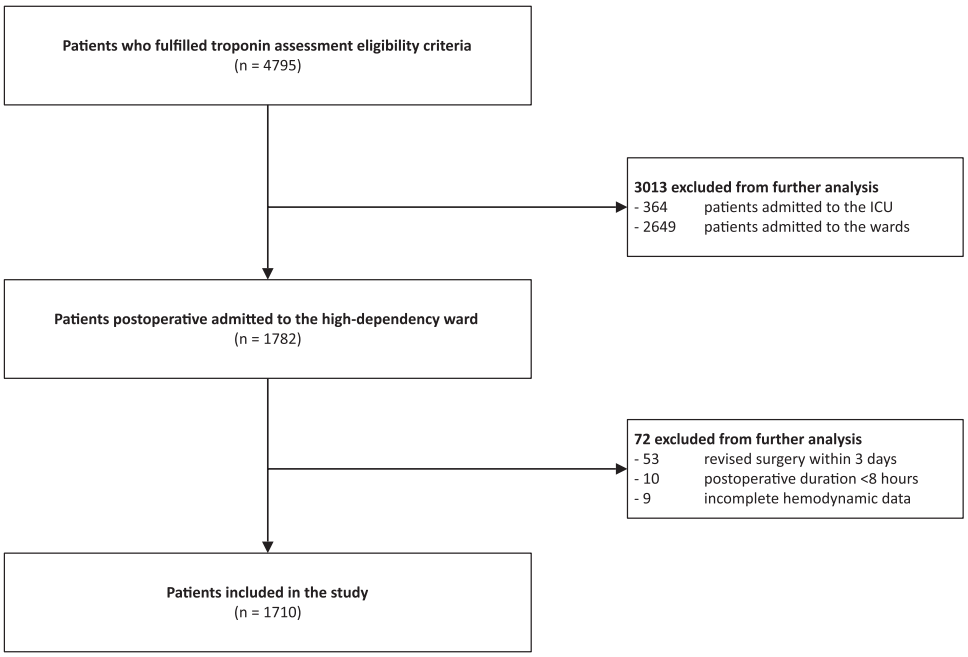

Fig. 1. Patient's flowchart. ICU, intensive care unit.

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,

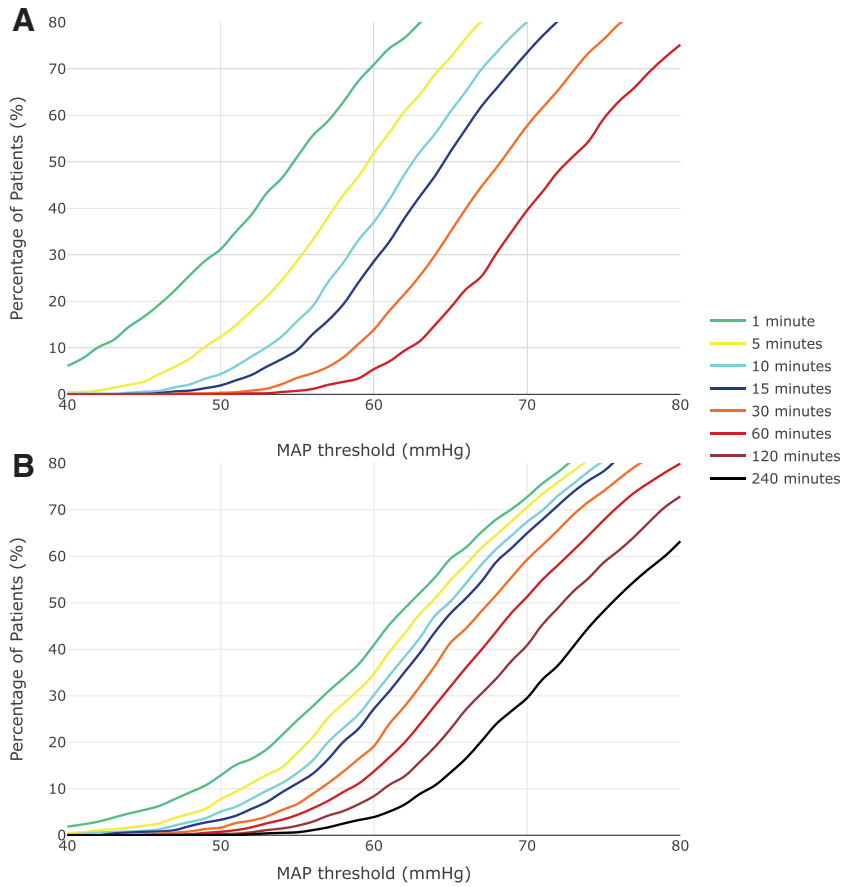

Fig. 2. Incidence of intra- and postoperative hypotension in cumulative minutes. Incidence is presented as percentage of patients who had a cumulative duration in minutes (as indicated by the *colors* in legends) below the mean arterial pressure (MAP) threshold presented on the *x-axis* during the intra- 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

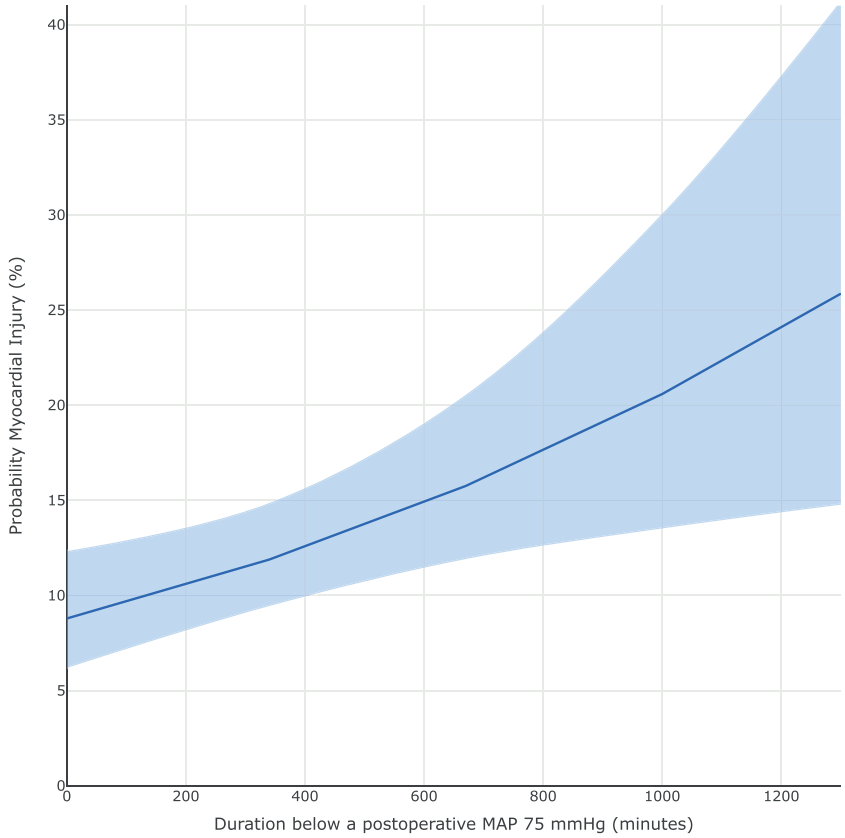

Fig. 3. Postoperative duration below a mean arterial pressure (MAP) threshold of 75 mmHg in minutes and estimated predicted probabilities of myocardial injury. Estimated probabilities of myocardial injury from multivariable logistic regressions adjusted for age, sex, high-risk surgery, emergency procedures, 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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References

1. Waes JA van, Nathoe HM, Graaff JC de, Kemperman H, Borst GJ de, Peelen LM, Klei WA van, Cardiac Health After Surgery I: Myocardial injury after noncardiac surgery and its association with short-term mortality. Circulation 2013; 127:2264–71
2. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2012; 307:2295–304
3. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI, Kurz A, Szczeklik W, Berwanger O, Villar JC, Malaga G, Garg AX, Chow CK, Ackland G, Patel A, Borges FK, Belley-Cote EP, Duceppe E, Spence J, Tandon V, Williams C, Sapsford RJ, Polanczyk CA, Tiboni M, Alonso-Coello P, Faruqui A, Heels-Ansdell D, Lamy A, Whitlock R, LeManach Y, Roshanov PS, McGillion M, Kavsak P, McQueen MJ, Thabane L, Rodseth RN, Buse GAL, Bhandari M, Garutti I, Jacka MJ, Schünemann HJ, Cortes OL, Coriat P, Dvirnik N, Botto F, Pettit S, Jaffe AS, Guyatt GH; Writing Committee for the VISION Study

Investigators: Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2017; 317:1642–51

4. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, Bertran S, Leone M, Pastene B, Piriou V, Molliex S, Albanese J, Julia JM, Tavernier B, Imhoff E, Bazin JE, Constantin JM, Pereira B, Jaber S; INPRESS Study Group: Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: A randomized clinical trial. JAMA 2017; 318:1346–57
5. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. Anesthesiology 2017; 126:47–65
6. van Waes JA, van Klei WA, Wijeysundera DN, van Wolfswinkel L, Lindsay TF, Beattie WS: Association between intraoperative hypotension and myocardial injury after vascular surgery. Anesthesiology 2016; 124:35–44
7. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI: Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: Toward an empirical definition of hypotension. Anesthesiology 2013; 119:507–15
8. Sun LY, Wijeysundera DN, Tait GA, Beattie WS: Association of intraoperative hypotension with acute kidney injury after elective noncardiac surgery. Anesthesiology 2015; 123:515–23
9. Bijker JB, Persoon S, Peelen LM, Moons KG, Kalkman CJ, Kappelle LJ, van Klei WA: Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case-control study. Anesthesiology 2012; 116:658–64
10. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Meguid RA, Hammermeister KE: Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. Anesthesiology 2015; 123:307–19
11. Mascha EJ, Yang D, Weiss S, Sessler DI: Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac durgery. Anesthesiology 2015; 123:79–91
12. Lier F van, Wesdorp FHIM, Liem VGB, Potters JW, Grüne F, Boersma H, Stolker RJ, Hoeks SE: Association between postoperative mean arterial blood pressure and myocardial injury after noncardiac surgery. Br J Anaesth 2018; 120:77–83
13. Roshanov PS, Rochwerg B, Patel A, Salehian O, Duceppe E, Belley-Côté EP, Guyatt GH, Sessler DI, Le Manach Y, Borges FK, Tandon V, Worster A, Thompson A, Koshy M, Devereaux B, Spencer FA, Sanders RD, Sloan EN, Morley EE, Paul J, Raymer KE, Punthakee Z, Devereaux PJ: Withholding *versus* continuing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers before noncardiac surgery: An analysis of the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation prospective cohort. Anesthesiology 2017; 126:16–27
14. Sessler DI, Meyhoff CS, Zimmerman NM, Mao G, Leslie K, Vásquez SM, Balaji P, Alvarez-Garcia J, Cavalcanti AB, Parlow JL, Rahate PV, Seeberger MD, Gossetti B, Walker SA, Premchand RK, Dahl RM, Duceppe E, Rodseth R, Botto F, Devereaux PJ: Period-dependent associations between hypotension during and for four days after noncardiac surgery and a composite of myocardial infarction and death: A substudy of the POISE-2 trial. Anesthesiology 2018; 128:317–27
15. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ: Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. Anesthesiology 2007; 107:213–20
16. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, Plumb J, Mythen MG, Grocott MPW, Edwards MR, Miller TE, Miller TE, Mythen MG, Grocott MP, Edwards MR; Perioperative Quality Initiative-3 workgroup; POQI chairs; Physiology group; Preoperative blood pressure group; Intraoperative blood pressure group; Postoperative blood pressure group: Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122:563–74
17. McEvoy MD, Gupta R, Koepke EJ, Feldheiser A, Michard F, Levett D, Thacker JKM, Hamilton M, Grocott MPW, Mythen MG, Miller TE, Edwards MR, Miller TE, Mythen MG, Grocott MP, Edwards MR; POQI-3 workgroup; POQI chairs; Physiology group; Preoperative blood pressure group; Intraoperative blood pressure group; Postoperative blood pressure group: Perioperative Quality Initiative consensus statement on postoperative blood pressure, risk and outcomes for elective surgery. Br J Anaesth 2019; 122:575–86
18. Liem VGB, Hoeks SE, Grüne F, Mol KHJM, Wesdorp FHIM, Stolker RJ, van Lier F: Prognostic value of postoperative high-sensitivity troponin T in patients with different stages of kidney disease undergoing noncardiac surgery. Br J Anaesth 2018; 120:84–93

19. Cohen AF: [European guideline for the quality of non-commercial clinical trials: Elegant implementation in the Netherlands via the amended Dutch Medical Research Involving Human Subjects Act] Europese richtlijn voor de kwaliteit van niet-commerciele klinische trial. Ned Tijdschr Geneeskd 2003; 147:1493–5
20. Goodyear MD, Krleza-Jeric K, Lemmens T: The Declaration of Helsinki. BMJ 2007; 335:624–5
21. Elm E von, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet 2007; 370:1453–7
22. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA: Intraoperative hypotension and the risk of postoperative adverse outcomes: A systematic review. Br J Anaesth 2018; 121:706–21
23. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction: Third universal definition of myocardial infarction. Circulation 2012; 126:2020–35
24. Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF, Sugarbaker DJ, Donaldson MC, Poss R, Ho KK, Ludwig LE, Pedan A, Goldman L: Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999; 100:1043–9
25. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, De Hert S, Ford I, Gonzalez Juanatey JR, Gorenek B, Heyndrickx GR, Hoeft A, Huber K, Iung B, Kjeldsen KP, Longrois D, Luescher TF, Pierard L, Pocock S, Price S, Roffi M, Sirnes PA, Uva MS, Voudris V, Funck-Brentano C; Authors/Task Force Members: 2014 ESC/ESA guidelines on non-cardiac surgery: Cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: Cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur J Anaesthesiol 2014; 31:517–73
26. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA: Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010; 56:254–61
27. Turan A, Chang C, Cohen B, Saasouh W, Essber H, Yang D, Ma C, Hovsepyan K, Khanna AK, Vitale J, Shah A, Ruetzler K, Maheshwari K, Sessler DI: Incidence, severity, and detection of blood pressure perturbations after abdominal surgery: A prospective blinded observational study. Anesthesiology 2019; 130:550–9