Association between Intraoperative Hypotension and Myocardial Injury after Vascular Surgery

Judith A. R. van Waes, M.D., Wilton A. van Klei, M.D., Ph.D., Duminda N. Wijeysundera, M.D., Ph.D., Leo van Wolfswinkel, M.D., Ph.D., Thomas F. Lindsay, M.D., Ph.D., W. Scott Beattie, M.D., Ph.D.

ABSTRACT

Background: Postoperative myocardial injury occurs frequently after noncardiac surgery and is strongly associated with mortality. Intraoperative hypotension (IOH) is hypothesized to be a possible cause. The aim of this study was to determine the association between IOH and postoperative myocardial injury.

Methods: This cohort study included 890 consecutive patients aged 60 yr or older undergoing vascular surgery from two university centers. The occurrence of myocardial injury was assessed by troponin measurements as part of a postoperative care protocol. IOH was defined by four different thresholds using either relative or absolute values of the mean arterial blood pressure based on previous studies. Either invasive or noninvasive blood pressure measurements were used. Poisson regression analysis was used to determine the association between IOH and postoperative myocardial injury, adjusted for potential clinical confounders and multiple comparisons.

Results: Depending on the definition used, IOH occurred in 12 to 81% of the patients. Postoperative myocardial injury occurred in 131 (29%) patients with IOH as defined by a mean arterial pressure less than 60 mmHg, compared with 87 (20%) patients without IOH ($P = 0.001$). After adjustment for potential confounding factors including mean heart rates, a 40% decrease from the preinduction mean arterial blood pressure with a cumulative duration of more than 30 min was associated with postoperative myocardial injury (relative risk, 1.8; 99% CI, 1.2 to 2.6, $P < 0.001$). Shorter cumulative durations (less than 30 min) were not associated with myocardial injury. Postoperative myocardial infarction and death within 30 days occurred in 26 (6%) and 17 (4%) patients with IOH as defined by a mean arterial pressure less than 60 mmHg, compared with 12 (3%; $P = 0.08$) and 15 (3%; $P = 0.77$) patients without IOH, respectively.

Conclusions: In elderly vascular surgery patients, IOH defined as a 40% decrease from the preinduction mean arterial blood pressure with a cumulative duration of more than 30 min was associated with postoperative myocardial injury. **(Anesthesiology 2016; 124:35-44)**

MYOCARDIAL infarction after surgery remains one of the leading causes of postoperative complications in more than 100 million global surgeries annually. Moreover, patients who suffer from (silent) postoperative myocardial injury are at an increased risk of mortality.[1,2] Myocardial injury is detected by increased cardiac biomarker levels in 12 to 19% of older patients after intermediate-risk to high-risk noncardiac surgery[1,2] and in up to 27% of patients after vascular surgery.[3–5] The prevention and treatment of myocardial injury may reduce these adverse events. Despite major undertakings, efforts to reduce this important public health issue have so far proved largely unsuccessful. The side effects related to prophylactic suppression of the compensatory sympathetic effects of surgery or the inhibition of platelet

What We Already Know about This Topic

- Myocardial injury in the perioperative period is associated with morbidity and mortality and is an area of increasing interest
- Intraoperative hypotension may be associated with myocardial injury

What This Article Tells Us That Is New

- In a cohort study of elderly vascular surgery patients, intraoperative hypotension defined as a 40% decrease from preinduction mean arterial pressure for greater than 30 min is associated with an increased risk of postoperative myocardial injury
- The work highlights the degree and duration of perioperative hypotension as important variables associated with myocardial injury in a high-risk surgical population

Corresponding article on page 4. 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). An abstract of this article has been presented as a poster at the Annual Meeting of the American Society of Anesthesiologists, October 11, 2014, New Orleans, Louisiana.

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function have been shown to outweigh the benefits in several major clinical trials.[6–8] In these trials, perioperative hypotension was reported to be associated with postoperative myocardial infarction. The majority of this hypotension occurs during surgery and represents a potentially modifiable risk factor.[8]

The predominant theory suggests that the etiology of postoperative myocardial injury is due to ischemia.[9,10] Postoperative myocardial ischemia is most commonly seen in patients with diffuse coronary artery disease and predominately the result of an imbalance between myocardial oxygen supply and demand. Hypotension has historically been believed to contribute to this ischemic imbalance by causing a decreased oxygen supply.[11] Intraoperative hypotension (IOH) has also been implicated in ischemia–reperfusion injury to the heart, brain, and kidneys and is associated with death.[6,12–16]

Because IOH may be modifiable, it would be imperative to understand whether there exists a threshold below which myocardial injury increases. Several definitions of IOH have already been studied, and the association between hypotension and the degree of associated tissue injury varies widely and mostly depends on the definition of hypotension.[17] In the Perioperative Ischemic Evaluation (POISE) trials, hypotension was poorly defined, *i.e.*, a systolic blood pressure less than 90 mmHg.[6,8] In cohort studies, intraoperative mean blood pressure levels below 50 and 55 mmHg and a 40% decrease in mean arterial blood pressure were reported to be associated with myocardial injury.[12,18] The results of these cohort studies must be interpreted cautiously because blood sampling for cardiac biomarkers was only performed in high-risk patients or in those with clinical evidence of myocardial ischemia, which may have led to an unresolved ascertainment bias.[19]

The primary objective of the current investigation was to determine whether IOH, as defined by four different blood pressure thresholds, is associated with the occurrence of postoperative myocardial injury. Vascular surgery patients were the population of interest because they have a high degree of epicardial coronary artery disease, are thought to be less able to tolerate hypotension, and are also known to have an increased risk of postoperative myocardial injury. We used intraoperative clinical care data from two university hospitals where blood pressure was measured frequently and selection bias was minimized because biomarkers were assessed routinely after surgery in all patients.

Materials and Methods

Patients

This two-center cohort study included consecutive patients undergoing vascular surgery at the University Health Network Hospital Toronto (UHNT), Toronto, Ontario, Canada, between January 1, 2010, and December 31, 2011, and at the University Medical Center Utrecht (UMCU), Utrecht, the Netherlands, between January 3, 2011, and December 15, 2011. Patients were eligible if they were aged 60 yr or older and were undergoing vascular surgery under general anesthesia or a combination of regional and general anesthesia. In patients who underwent surgery more than once, only the first surgery was included in the analyses. A reoperation was included as a novel case if this surgery took place during another hospital admission and at least 30 days after the first surgery. Patients were excluded if intraoperative blood pressure measurements or postoperative troponin measurements were not available. The local ethics committees from both centers waived the need for informed consent (UHNT Research Ethics Board, protocol number 06-0193-AE; and the UMCU Medical Research Ethics Committee, protocol number 12-425). All data were anonymized before analysis.

Data Collection

All preoperative data were obtained from electronic medical records, including patient characteristics, preoperative physical status, comorbidities, type of procedure, and postoperative troponin levels. Intraoperative data including blood pressure measurements, heart rate, and blood loss were collected from the anesthesia information management systems. In these systems, each minute of heart rate and invasive blood pressure measurements is averaged, and then the data are stored. Noninvasive blood pressure measurements are generally stored every 3 to 5 min.

Intraoperative Hypotension

In this study, we have used four previously defined thresholds for IOH: two absolute mean arterial pressure (MAP) thresholds (MAP less than 50 mmHg and MAP less than 60 mmHg) and two thresholds relative to the preinduction MAP (a decrease of 30% or more and a decrease of 40% or more).[14,17] The baseline MAP used in calculating the relative change was defined as the mean MAP of all available blood pressure measurements in the operating theatre before induction of anesthesia. The time of induction was calculated using an algorithm that was previously described by Bijker *et al.*[14] We excluded patients in whom blood pressures before induction of anesthesia were not available in those analyses where IOH was defined as a relative decrease from the preinduction MAP. When both invasive and noninvasive blood pressure measurements were available, the invasive blood pressure measurements were used. During minutes when no blood pressure measurement was recorded or the measurement was considered to be an artifact, the previous (nonartifact) measurement was used. An episode of IOH with a duration of only 1 min (*i.e.*, a single-data point) was considered to be a possible artifact and therefore excluded from the analysis.

For each patient, the cumulative duration of hypotension was calculated, defined as the total number of minutes that the MAP was below the threshold during the surgical procedure. The number of episodes of IOH was counted, in which an episode was defined as an uninterrupted period of time

that the MAP was below the threshold. To take the severity of the hypotension into account, the total area under the curve (AUC) of IOH was calculated, defined as the depth below the threshold MAP multiplied by the duration of hypotension.

Outcome

The primary outcome was postoperative myocardial injury, defined as an increased cardiac troponin I above the 99th percentile with a 10% coefficient of variation within 3 days after surgery.[11] According to the clinical care protocol in both hospitals, cardiac troponin I was measured routinely after surgery. In the UHNT, troponin was measured immediately after surgery and once daily on the first 2 postoperative days; measurements were continued to 5 days after surgery in case of increase in troponin levels. Troponin was analyzed using the Dade Behring Dimension assay (Siemens Healthcare Diagnostics, USA). In the UMCU, troponin was measured once daily on the first 3 days after surgery, and follow-up of increased troponin levels was carried out at discretion of the attending cardiologist. Troponin was analyzed using the enhanced AccuTnI assay (Beckman Coulter, USA). For each patient, the highest value of all troponin measurements was used in the analysis. Secondary outcomes included the occurrence of postoperative myocardial infarction and all-cause mortality within 30 days. Myocardial infarction was defined according to the universal definition as a troponin value above the clinical cutoff level and symptoms of ischemia, signs of ischemia on the electrocardiogram, imaging evidence of new myocardial loss, new wall motion abnormalities, or identification of an intracoronary thrombus.[11]

Statistical Analysis

Baseline characteristics were compared between patients with and without IOH as defined by a MAP of 60 mmHg. Categorical variables were compared using chi-square test, and continuous variables were compared using the Student's *t* test or Mann–Whitney *U* test, as appropriate. Data on blood loss were missing in 110 (12%) patients. Data analysis was performed after multiple imputations of these missing data. Five data sets were imputed by the method of fully conditional specification.[20]

We compared the cumulative duration of IOH between patients with and without postoperative myocardial injury using the chi-square test. Multivariable regression analysis was used to determine the association between the duration of IOH and myocardial injury for each of the four definitions of IOH. We used Poisson regression analysis to obtain relative risks (RR).[21] In this, the duration of IOH was categorized into six categories (less than 1, 2 to 5, 6 to 10, 10 to 20, 20 to 30, and more than 30 min), because the relationship between IOH and myocardial injury was expected to be nonlinear. We used restricted cubic spline analysis to assess the linearity of this relationship. The association was adjusted for possible confounders in a multivariable model, including age, sex, emergency surgery, preoperative use of β-blockers, calcium channel blockers, renin–angiotensin system inhibitors and diuretics, intraoperative blood loss, mean intraoperative heart rate, center and the six variables from the revised cardiac risk index, *i.e.*, high-risk surgery, history of myocardial infarction, history of cerebrovascular disease, heart failure, diabetes, and renal failure.[22] Emergency surgery was defined as surgery required within 72 h after the indication for surgery was set. Preoperative medication use (β-blockers, calcium channel blockers, and renin–angiotensin system inhibitors) was defined as regular (chronic) use of medication before surgery, irrespective of whether those medications were continued of discontinued on the day of surgery. High-risk surgery was defined as intrathoracic, intraabdominal, or suprainguinal vascular surgery. Preoperative renal failure was defined as a preoperative serum creatinine more than or equal to 177 μM/l. Because four different definitions of IOH were tested, Bonferroni correction was used to adjust for multiple comparisons, resulting in a 98.8% CI (*P* value of 0.05/4 = 0.0125) as level of statistical significance.

We performed sensitivity analyses where the duration of surgery was added to the multivariable model because we considered duration of surgery a potential residual confounder. First, the opportunity to detect IOH is greater in patients with longer durations of surgery. Second, the duration of surgery may also be associated with a higher risk on developing myocardial injury because longer durations of surgery may indicate more complicated procedures.[18] The final sensitivity analyses were conducted to assess the degree of the hypotension. In these analyses, the AUC of IOH was substituted in the multivariable model instead of the duration of IOH to determine whether this would alter the results. The analysis was performed using SPSS software (release 20.0 for Windows; SPSS, Inc., USA) and R software (release 2.14.1 for Windows; https://cran.r-project.org/bin/windows/, accessed January 15, 2012).

Results

In total, 1,010 vascular surgery patients were eligible for inclusion: 689 patients from the UHNT and 321 patients from the UMCU. Figure 1 shows the inclusion of patients. The 104 (10%) patients who were excluded because troponin

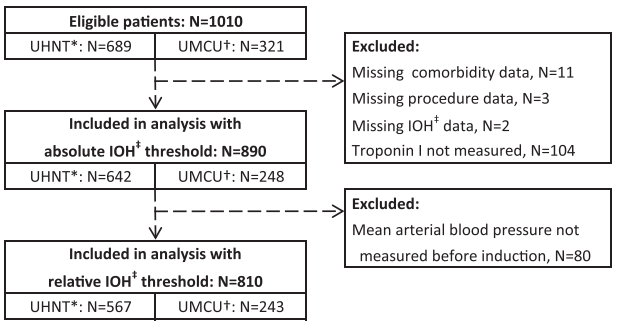

Fig. 1. Flowchart of patient inclusion. * UHNT = University Health Network Toronto; † UMCU = University Medical Center Utrecht; ‡ IOH = intraoperative hypotension.

Table 1. Baseline Characteristics, Stratified for IOH defined as a MAP < 60 mmHg

	No IOH (N = 440)	IOH (N = 450)	*P* Value
Center			
UHNT	297 (67.5)	345 (76.7)	0.002
UMCU	143 (32.5)	105 (23.3)	
Male	307 (69.8)	311 (69.1)	0.83
Mean age (SD)	73.4 (7.9)	73.7 (7.8)	0.61
RCRI factors			
High-risk surgery	273 (62.0)	293 (65.1)	0.34
History of myocardial infarction	72 (16.4)	95 (21.1)	0.07
History of heart failure	28 (6.4)	24 (5.3)	0.51
History of cerebrovascular disease	104 (23.6)	87 (19.3)	0.12
Renal failure (preoperative)	35 (8.0)	36 (8.0)	0.98
Diabetes	54 (12.3)	36 (8.0)	0.04
Peripheral vascular disease	239 (54.3)	277 (61.6)	0.03
Preoperative medication use			
β-Blocker	228 (51.8)	263 (58.4)	0.05
Calcium channel blocker	144 (32.7)	125 (27.8)	0.11
Renin–angiotensin system inhibitor	167 (38.0)	174 (38.7)	0.83
Diuretics	129 (29.3)	141 (31.3)	0.56
Statin	257 (58.4)	252 (56.0)	0.47
ASA class			
1	5 (1.1)	2 (0.4)	0.17
2	65 (14.8)	62 (13.8)	
3	169 (38.4)	152 (33.8)	
≥ 4	201 (45.7)	234 (52.0)	
Emergency surgery	119 (27.0)	146 (32.4)	0.08
Procedure			
Open aortic surgery	13 (3.0)	59 (13.1)	< 0.001
(T)EVAR	99 (22.5)	115 (25.6)	
Carotid surgery	98 (22.3)	51 (11.3)	
Peripheral bypass surgery	46 (10.5)	87 (19.3)	
Other	184 (41.8)	138 (30.7)	
Mean duration of surgery, min (SD)	166 (88)	215 (127)	< 0.001
Mean preinduction MAP, mmHg (SD)*	106 (16)	100 (16)	< 0.001
Mean of average heart rate, beats/min (SD)	67 (13)	67 (13)	0.81
Median estimated intraoperative blood loss, ml (IQR)†	100 (0–300)	150 (0–500)	0.05
Postoperative myocardial injury	87 (19.8)	131 (29.1)	0.001
Postoperative myocardial infarction	12 (2.7)	26 (5.8)	0.08
Death within 30 d	15 (3.4)	17 (3.8)	0.77

Figures are numbers of patients (%), unless indicated otherwise. * N = 392 and N = 418, respectively, because in 80 patients, the preinduction MAP was not available; hence, the relative decrease of MAP could not be calculated. † N = 377 and N = 403, respectively, because blood loss data were not available in 110 patients.

ASA = physical status classification by the American Society of Anesthesiologists; IOH = intraoperative hypotension; IQR = interquartile range; MAP = mean arterial pressure; RCRI = Revised Cardiac Risk index; (T)EVAR = (thoracic) endoscopic vascular aneurysm repair; UHNT = University Health Network Toronto; UMCU = University Medical Center Utrecht.

was not measured were healthier at baseline compared with the patients in whom troponin was measured. These patients used less β-blockers preoperatively, were involved in fewer high-risk procedures, and had less IOH.

The remaining 890 (86%) patients were on average 73 yr old, two third underwent high-risk surgery, almost 50% were classified as American Society of Anesthesiologists physical status IV, and approximately one third underwent emergency surgery (table 1). In 80 (9%) patients, no preinduction blood pressure data were available; hence, these patients were only included in the analysis where IOH was defined by an absolute threshold (*i.e.*, MAP less than 50 and less than 60 mmHg). Of the 810 patients in whom preinduction blood pressure data were available, the mean preinduction MAP was 103 (SD, 16) mmHg.

Primary Outcome

Postoperative myocardial injury occurred in 131 (29%) patients with IOH as defined by a MAP less than 60 mmHg, compared with 87 (20%) patients without IOH ($P = 0.001$; table 1). The incidence of IOH was 51 and 12% when using a MAP of 60 and 50 mmHg to define IOH, and 81 and 52% when IOH was defined as 30% or more and 40% or more decrease from the preinduction MAP, respectively.

Table 2. Occurrence and Characteristics of IOH, Using Four Different Thresholds of the MAP to Define IOH

	No Myocardial Injury (N = 672)	Myocardial Injury (N = 218)	*P* Value
Number of patients with IOH (%)			
MAP < 60 mmHg	319 (47.5)	131 (60.1)	0.001
MAP < 50 mmHg	65 (9.7)	38 (17.4)	0.002
≥ 30% decrease from preinduction MAP*	489 (78.5)	163 (87.2)	0.03
≥ 40% decrease from preinduction MAP*	312 (50.1)	111 (59.4)	0.08
Median number of episodes of IOH (IQR)			
MAP < 60 mmHg	2 (1–4)	3 (1–5)	0.06
MAP < 50 mmHg	1 (1–2)	1 (1–2)	0.23
≥ 30% decrease from preinduction MAP*	5 (2–9)	4 (2–9)	0.71
≥ 40% decrease from preinduction MAP*	3 (1–6)	4 (2–7)	0.009
Median duration of IOH, min (IQR)			
MAP < 60 mmHg	10 (5–27)	18 (7–36)	0.005
MAP < 50 mmHg	5 (3–12)	7 (4–13)	0.24
≥ 30% decrease from preinduction MAP*	47 (16–113)	66 (13–147)	0.11
≥ 40% decrease from preinduction MAP*	18 (6–43)	37 (11–77)	< 0.001

* N = 623 and N = 187 patients without and with myocardial injury, respectively, because in 80 patients, the preinduction MAP was not available; hence, the relative decrease of MAP could not be calculated.

IOH = intraoperative hypotension; IQR = interquartile range; MAP = mean arterial pressure.

IOH as defined by a mean arterial blood pressure less than 60 mmHg occurred in 54 and 42% of patients from the UHNT and the UMCU, respectively. The incidence of IOH stratified for different categories of the mean intraoperative heart rate is given in Supplemental Digital Content 1, table 1, http://links.lww.com/ALN/B217. The median cumulative duration of IOH varied between 6 and 49 min depending on the used definition and was longest if IOH was defined as 30% or more decrease from the preinduction MAP. The median number of episodes of IOH varied between 1 and 5, depending on the used definition.

By using a MAP of 60 or 50 mmHg, IOH occurred in 60 and 17% of patients in whom postoperative myocardial injury occurred, compared with 48 ($P = 0.001$) and 10% of patients ($P = 0.002$) without myocardial injury, respectively. Patients with postoperative myocardial injury had longer durations of IOH compared with patients without postoperative myocardial injury (table 2).

The unadjusted risk of postoperative myocardial injury in patients with IOH was higher compared with patients without IOH for each definition of IOH. Restricted cubic spline analysis showed that this association was not linear (Supplemental Digital Content 1, fig. 1, http://links.lww.com/ALN/B217). When IOH was defined as 40% or more decrease from the preinduction MAP, the unadjusted RR of myocardial injury was 1.9 (98.8% CI, 1.3 to 2.8, $P < 0.001$) for a cumulative duration of IOH of more than 30 min (table 3). By using this definition, IOH with a duration of more than 30 min occurred in 60 of 187 (32%) patients with postoperative myocardial injury compared with 107 of 623 (17%) patients without myocardial injury. The baseline MAP of patients with IOH using this definition (118 mmHg; SD, 13) was higher compared with patients without IOH (95 mmHg; SD, 15; fig. 2).

After adjustment for possible confounding factors and multiple comparisons, IOH with a cumulative duration of more than 30 min was significantly associated with myocardial injury when IOH was defined as a MAP less than 60 mmHg (RR, 1.7; 98.8% CI, 1.1 to 2.6, $P = 0.004$), when IOH was defined as 30% or more decrease from the preinduction MAP (RR, 1.8; 98.8% CI, 1.1 to 3.1, $P = 0.005$), and when IOH was defined as 40% or more decrease in MAP (RR, 1.8; 98.8% CI, 1.2 to 2.6, $P < 0.001$; tables 3 and 4). Postoperative myocardial injury was also associated with age, a history of myocardial infarction, preoperative renal failure, preoperative β-blocker use, and emergency surgery (table 3). When IOH was defined as a MAP of less than 50 mmHg, the adjusted RR of myocardial injury was 1.5 (98.8% CI, 0.4 to 6.7, $P = 0.47$) for a duration of IOH of more than 30 min (table 4). In the light of the significant associations for the other definitions of IOH, we also would expect a significant association when IOH was defined as a MAP of less than 50 mmHg with a duration of more than 30 min, but given its wide CI, this association may not be significant due to the low number of patients with IOH for this definition. IOH defined as 30% or more decrease from the preinduction MAP and as a MAP less than 50 mmHg with a duration of 6 to 10 min also seemed to be associated with myocardial injury. However, restricted cubic spline analysis showed that this association only appeared significant as a result of the chosen cutoff points, but that it was not consistent for longer durations of IOH (table 4; Supplemental Digital Content 1, fig. 2, http://links.lww.com/ALN/B217).

The sensitivity analysis in which the duration of surgery was added to the multivariable model resulted in a significant association with myocardial injury only when IOH was defined as 40% or more decrease from the preinduction MAP with a duration of more than 30 min (RR, 1.7; 98.8%

Table 3. Association between the Duration of IOH, Defined as a 40% Decrease in Mean Arterial Blood Pressure Compared with the Preinduction Blood Pressure and Postoperative Myocardial Injury

	Unadjusted Analysis			Adjusted Analysis		
	RR	98.8% CI	*P* Value	RR	98.8% CI	*P* Value
Duration of IOH (min)						
≤ 1	Ref			Ref		
2–5	1.1	0.6–1.8	0.75	1.3	0.7–2.2	0.27
6–10	0.6	0.2–1.5	0.14	0.8	0.4–1.6	0.33
11–20	1.4	0.8–2.4	0.14	1.3	0.8–2.4	0.21
21–30	1.4	0.7–3.0	0.23	0.8	0.4–1.7	0.53
> 30	1.9	1.3–2.8	< 0.001	1.8	1.2–2.6	< 0.001
Female	1.2	0.9–1.7	0.19	1.1	0.8–1.6	0.40
Age (per 10 yr)	1.2	1.0–1.5	0.004	1.3	1.1–1.5	0.001
Diabetes	1.0	0.6–1.7	0.97	0.9	0.5–1.6	0.64
History of myocardial infarction	1.9	1.4–2.6	< 0.001	1.9	1.4–2.6	< 0.001
History of heart failure	1.7	1.1–2.9	0.006	1.3	0.8–2.1	0.20
History of cerebrovascular disease	0.7	0.5–1.1	0.09	1.0	0.6–1.5	0.97
Preoperative renal failure	2.2	1.4–3.2	< 0.001	1.8	1.1–2.7	0.001
Preoperative medication use						
β-Blocker	1.7	1.2–2.4	< 0.001	1.6	1.2–2.3	0.001
Calcium channel blocker	0.9	0.6–1.3	0.48	0.9	0.7–1.3	0.53
Renin–angiotensin system inhibitor	0.8	0.6–1.1	0.12	0.8	0.6–1.1	0.07
Diuretics	1.5	1.1–2.0	0.004	1.3	0.9–1.8	0.04
High-risk surgery	0.9	0.6–1.2	0.36	1.1	0.8–1.5	0.60
Emergency surgery	1.9	1.4–2.6	< 0.001	1.6	1.1–2.2	0.001
Mean heart rate (per 10 beats/min)	1.3	1.2–1.4	< 0.001	1.3	1.2–1.5	0.001
Intraoperative blood loss (ml)						
< 500	Ref			Ref		
500–1,000	1.5	0.9–2.4	0.06	1.5	1.0–2.4	0.02
1,000–2,000	2.1	1.3–3.4	0.005	1.8	0.9–3.6	0.02
> 2,000	1.6	0.7–3.7	0.02	1.4	0.7–2.7	0.18
Center: UHNT	0.8	0.6–1.1	0.10	0.6	0.4–0.9	0.001

IOH = intraoperative hypotension; RR = relative risk; UNHT = University Health Network Toronto.

CI, 1.1 to 2.5, *P* = 0.002; Supplemental Digital Content 1, table 2, http://links.lww.com/ALN/B217). When IOH was defined as a MAP of less than 50 mmHg, a MAP of less than 60 mmHg, or 30% or more decrease from the preinduction MAP with a duration of more than 30 min, the RR of myocardial injury was 1.6 (98.8% CI 0.4 to 6.0, *P* = 0.38), 1.5 (98.8% CI 0.9 to 2.3, *P* = 0.03), and 1.7 (98.8% CI 1.0 to 2.8, *P* = 0.02), respectively (Supplemental Digital Content 1, table 3, http://links.lww.com/ALN/B217). This finding supports the significant association between IOH defined as 40% or more decrease from the preinduction MAP with a duration of more than 30 min that was found in the primary analysis but attenuates the associations that were found for the other definitions.

The results of the sensitivity analysis in which the AUC of IOH was included in the multivariable model instead of the duration of IOH were comparable with the results of the primary analysis, albeit that the association was significant when IOH was defined as a MAP less than 50 mmHg (RR, 3.4; 98.8% CI, 1.3 to 9.2, *P* = 0.002), when IOH was defined as 30% or more decrease in MAP (RR, 1.7; 98.8% CI, 1.0 to 2.8, *P* = 0.007), and when IOH was defined as 40% or more decrease in MAP (RR, 1.8; 98.8% CI, 1.2 to 2.7, *P* < 0.001), but not when IOH was defined as a MAP less than 60 mmHg (RR, 1.5; 98.8% CI, 0.9 to 2.5, *P* = 0.06; Supplemental Digital Content 1, tables 4 and 5, http://links.lww.com/ALN/B217). This result supports the association between IOH defined as a 30% or more decrease and 40% or more decrease in MAP and myocardial injury that was found in the primary analysis.

Secondary Outcomes

Postoperative myocardial infarction as defined by the universal definition was diagnosed in 26 (6%) patients with IOH as defined by a MAP less than 60 mmHg compared with 12 (3%) patients without IOH (*P* = 0.08; table 1).[11] Using this definition of IOH, death within 30 days occurred in 17 (4%) patients with IOH compared with 15 (3%) patients without IOH (*P* = 0.77; table 1).

Discussion

This two-center cohort study in elderly high-risk vascular surgery patients found that a relative decrease in MAP 40% or more from the preinduction blood pressure is associated

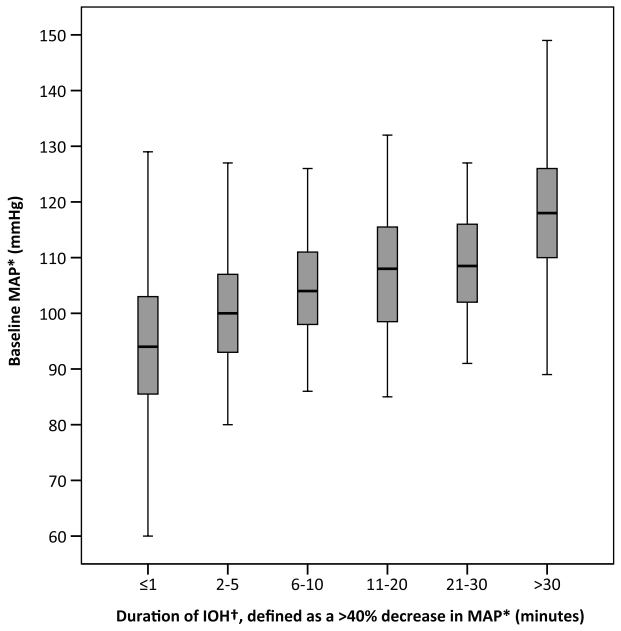

Fig. 2. Baseline mean arterial blood pressures for different durations of intraoperative hypotension, defined as a more than 40% decrease in mean arterial blood pressure. * MAP = mean arterial blood pressure; † IOH = intraoperative hypotension.

with postoperative myocardial injury if the decrease persists for more than 30 cumulative minutes. As an example, this drop in blood pressure is a preoperative pressure of 160/100(120) mmHg falling to 105/55(72) mmHg during anesthesia and sustained below this level for more than 30 min in total. In this study, this degree of blood pressure change occurs in one fifth of the patients. A MAP less than 60 mmHg and a relative decrease in MAP of 30% or more from the preinduction blood pressure with a duration more than 30 min may also be associated with myocardial injury, but these associations did not remain statistically significant after further adjustment for the duration of surgery, or when the AUC of IOH was studied. Furthermore, we found no statistically significant association between IOH and myocardial injury if the cumulative duration was less than 30 min.

We investigated the association between IOH and postoperative myocardial injury by combining data from two hospitals that measure cardiac biomarkers routinely after surgery. One of the strengths of this study is that cardiac troponin was measured as part of a postoperative care protocol, thus increasing generalizability and reducing misclassification or selection bias. Further strengths of our study include the adjustment for more possible confounders than in previous studies. Of note, this analysis was adjusted for preoperative use of cardiovascular medications (β-blockers, rennin–angiotensin system inhibitors, calcium channel blockers, diuretics), intraoperative blood loss, heart rate, and also for the duration of surgery in a sensitivity analysis. In addition to the duration of IOH, we also assessed the depth

Table 4. Association between the Duration of IOH and Myocardial Injury for Four Different Definitions of Hypotension

Definition of IOH	Duration of IOH (min)	RR	98.8% CI	*P* Value
MAP < 50 mmHg	≤ 1	Ref		
	2–5	1.3	0.8–2.2	0.21
	6–10	2.0	1.1–3.6	0.003
	11–20	1.0	0.4–2.2	0.89
	21–30	2.0	0.8–5.1	0.08
	> 30	1.5	0.4–6.7	0.47
MAP < 60 mmHg	≤ 1	Ref		
	2–5	1.1	0.7–1.7	0.52
	6–10	0.9	0.5–1.6	0.58
	11–20	1.5	1.0–2.3	0.02
	21–30	1.5	1.0–2.5	0.02
	> 30	1.7	1.1–2.6	0.004
≥ 30% decrease from preinduction MAP	≤ 1	Ref		
	2–5	1.7	0.8–3.6	0.10
	6–10	2.8	1.6–5.1	< 0.001
	11–20	1.8	1.0–3.5	0.02
	21–30	0.9	0.4–2.2	0.81
	> 30	1.8	1.1–3.1	0.005
≥ 40% decrease from preinduction MAP	≤ 1	Ref		
	2–5	1.3	0.7–2.2	0.27
	6–10	0.8	0.4–1.6	0.33
	11–20	1.3	0.8–2.4	0.21
	21–30	0.8	0.4–1.7	0.53
	> 30	1.8	1.2–2.6	< 0.001

The results are adjusted for age, sex, comorbidities, preoperative medication use, heart rate, and intraoperative blood loss.

IOH = intraoperative hypotension; MAP = mean arterial pressure; RR = relative risk.

of the hypotension by including the AUC of IOH. Although the AUC cannot distinguish between a short period of severe hypotension and a long period of mild hypotension (*e.g.*, 5 mmHg below the MAP threshold for 20 min results in the same AUC as 20 mmHg below the MAP threshold for 5 min), we included it in a sensitivity analysis as a measure of the severity of IOH.

Several limitations of the study must be addressed. First, factors that may accompany hypotension and may influence the occurrence of myocardial injury, like heart rate variability, pulse pressure variation and hemoglobin level, were not taken into account. Furthermore, specific triggers of hypotension, *e.g.*, anesthetic overdose or acute severe bleeding, and specific treatments of hypotension such as fluid administration and the use of vasopressors and inotropics were not studied. In a retrospective observational study such as this study, it is challenging to properly model all the factors that influence intraoperative hemodynamics while occurring and being treated simultaneously, and the interactions between these factors. However, to fully understand the etiology of hypotension and myocardial injury, these factors should be studied as well. Therefore, although the results of this study indicate that hypotension may be associated with myocardial injury, this should not be interpreted as a definitive answer.

Moreover, the obtained RRs should not be interpreted as absolute figures, but rather as an indication that longer durations of IOH, *i.e.*, longer than approximately 30 min, are associated with myocardial injury. Second, although troponin measurements were part of a routine postoperative care protocol in both centers, troponin was not measured in 10% of patients because of nonadherence to the protocol. In addition, some patients did not have troponin measured consecutively on all 3 postoperative days; hence, myocardial injury may have been underestimated. Third, the results were not adjusted for preexisting troponin increases because troponin was not measured before surgery. This may be an important deficiency because it is now known that troponin is increased in a variety of patients.[23–27] In addition, this analysis did not adjust for postoperative events, such as sepsis, stroke, acute renal failure, and pulmonary embolism, which have all been linked to troponin increases.[10,27–31] Furthermore, the analysis was adjusted for chronic medication use but did not take into account that certain drugs may have been discontinued before surgery. Fourth, IOH as defined by a MAP of 50 mmHg occurred in only a few patients, which may reflect adequate intraoperative care, but could have resulted in a less-stable statistical regression model of myocardial injury. Fifth, we did not measure the association between hypotension and injury in other vital organs in addition to the myocardium, although IOH may cause injury to the brain and kidneys as well.[12,13,32] Our analysis does not consider the possibility that the hypotension may have been refractory to treatment, especially because the hypotension expressed in this study occurred in a fully monitored setting staffed by experienced anesthesiologists. Sixth, the multivariable model shows a significant association between center and myocardial injury, which may indicate important differences between the two centers and may have influenced the results. Finally, like in all retrospective observational analyses, residual confounding may exist.

IOH is believed to lead to diffuse myocardial ischemia through an imbalance between oxygen supply and demand of the myocardium.[11] Recently, the POISE-2 trial showed that hypotension was an independent predictor of myocardial infarction. Although hypotension was defined by a relatively high blood pressure threshold, *i.e.*, a systolic blood pressure less than 90 mmHg, hypotension occurred less frequent compared with our study. This may be explained by the healthier study population in POISE-2 trial compared with our study population and differences in definitions of IOH (Supplemental Digital Content 1, table 6, http://links.lww.com/ALN/B217). In addition, the duration of hypotension was not taken into account in POISE-2 trial.[8] The association between IOH and postoperative myocardial injury was also studied by Alcock *et al.* in a smaller cohort of patients. Using a systolic blood pressure less than 100 mmHg to define IOH, IOH was associated with postoperative myocardial injury, but this association was not adjusted for perioperative β-blocker use or intraoperative blood loss.[32] Kheterpal *et al.*[18] reported that high-risk patients experiencing a cardiac adverse event were more likely to experience an episode of a MAP less than 50 mmHg or a 40% decrease in MAP. Walsh *et al.* found an association between a MAP less than 55 mmHg and postoperative myocardial injury in a large cohort of surgical patients.[12] However, both the studies by Walsh *et al.* and Kheterpal *et al.* were limited by the fact that myocardial injury was measured selectively, and all missing data were assumed to be negative. This problem is illustrated by the reported incidence of the outcome (0.2 and 2.3%, respectively), which was much lower than reported in other studies.[2,33,34] Another study has estimated that this selective monitoring of troponin indeed will underestimate the incidence (more than 10%) of myocardial injury threefold.[3] Furthermore, the reported effect measure by Walsh *et al.* was not adjusted for perioperative use of cardiovascular medications that are also associated with IOH.[6,35,36] Recently, Mascha *et al.*[37] studied the association between intraoperative blood pressure variability and mortality in a large cohort of noncardiac surgery patients. They reported that low MAP variability was associated with 30-day mortality, but that the differences were not clinically important after adjustment for the average MAP. Furthermore, they reported that the cumulative time of MAP less than 50, 55, 60, 70, or 80 mmHg was each associated with higher odds of death.

The occurrence of IOH could be merely a marker of other intraoperative events and comorbidities that are associated with an increased risk of developing postoperative myocardial injury.[10,19] It should be noted that our study was performed in older patients undergoing mainly high-risk vascular surgery, a population where coronary artery disease is common. The influence of IOH on the development of myocardial injury may be more pronounced in the presence of coronary artery disease through an imbalance between myocardial oxygen supply and demand; hence, the results from this study are not directly generalizable to a younger and healthier population. Conversely, our results do not imply that durations of IOH of less than 30 min are generally safe, because previous studies have shown that shorter durations of hypotension are associated with renal dysfunction.[12,37] In this study, an association between preoperative use of β-blockers and postoperative myocardial injury was observed, even after adjustment for confounding (table 3). Although this association may be well biased by residual confounding, IOH may be an intermediate factor between β-blocker therapy and myocardial injury[38,39] and should be subject to further investigation.

In conclusion, this study shows that a MAP of 40% below the preinduction MAP with a cumulative duration of more than 30 min and irrespective of duration of surgery was associated with the occurrence of postoperative myocardial injury. Importantly, we could not demonstrate an association between IOH durations of less than 30 min and myocardial injury. Of note, in interpreting the results of this

study, it should be considered that several hemodynamic factors and specific treatments that may accompany hypotension and may influence the occurrence of myocardial injury were not accounted for in this study.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. van Waes: Department of Anesthesiology, University Medical Center Utrecht, Q04.2.313, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. j.a.r.vanwaes@umcutrecht.nl. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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