

Intraoperative Hypotension and 1-Year Mortality after Noncardiac Surgery

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Background: **Intraoperative hypotension (IOH) is frequently associated with adverse outcome such as 1-yr mortality. However, there is no consensus on the correct definition of IOH. The authors studied a number of different definitions of IOH, based on blood pressure thresholds and minimal episode durations, and their association with 1-yr mortality after noncardiac surgery.**

Methods: **This cohort study included 1,705 consecutive adult patients who underwent general and vascular surgery. Data on IOH and potentially confounding variables were obtained from electronic record-keeping systems. Mortality data were collected up to 1 yr after surgery. The authors used two different techniques to reduce the influence of confounding variables, multivariable Cox proportional hazard regression modeling and classification and regression tree analysis.**

Results: **The mortality within 1 yr after surgery was 5.2% (88 patients). After adjustment for confounding, the Cox regression analysis did not show an association between IOH and the risk of dying within 1 yr after surgery (hazard ratio around 1.00 with high *P* values for different definitions of IOH). Additional classification and regression tree analysis identified IOH as a predictor for 1-yr mortality in elderly patients. When the blood pressure threshold for IOH was decreased, the duration of IOH at which this association was found was decreased as well.**

Conclusions: **This observational study showed no causal relation between IOH and 1-yr mortality after noncardiac surgery for any of the definitions of IOH. Nevertheless, additional analysis suggested that for elderly patients, the mortality risk increases when the duration of IOH becomes long enough. The length of this duration depends on the designated blood pressure threshold, suggesting that lower blood pressures are tolerated for shorter durations. The effect of IOH on 1-yr mortality remains debatable, and no firm conclusions on the lowest acceptable intraoperative blood pressures can be drawn from this study.**

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IN recent years, there has been an increased interest in a possible causal effect of intraoperative hypotension (IOH) on adverse outcomes after noncardiac surgery, such as myocardial infarction, stroke, slow graft function after liver or kidney transplantation, and even 1-yr mortality.[1–6] However, almost 50 different definitions of IOH were used in the recent anesthesia literature, resulting in widely varying incidences of IOH when applied to actual patient data.[7] Obviously, these different incidences of IOH influence the estimated association between IOH and adverse outcome. Therefore, it is not surprising that several studies did not show an association between IOH and adverse outcomes.[8,9] A recent meta-analysis even provided support for the notion that "moderate" hypotension during orthopedic surgery might improve outcome by reducing blood loss and transfusion requirements.[10]

The ability of a particular patient to tolerate episodes of hypotension also depends on other factors, such as the indication for surgery, age, and comorbidity. If blood pressure becomes low enough for a duration that is long enough, organ perfusion will be compromised. This in turn might result in end-organ damage or death. However, what exactly constitutes "too low" or what is "too long" is unknown.

We hypothesized that the association between IOH and 1-yr all-cause mortality depends on a series of selected threshold values for IOH and associated durations of IOH episodes. To explore this hypothesis, a series of frequently used IOH definitions—comprising different threshold values and minimal episode durations of IOH—were studied for their associations with 1-yr mortality in a cohort of general and vascular surgery patients.

Materials and Methods

Study Design

This study was an observational cohort study. Patients were selected from a previously conducted prospective cohort study: the Outpatient Preoperative Evaluation by Nurses study.[11] In brief, all consecutive adult patients (aged 18 yr or older) who visited the outpatient preoperative

evaluation clinic of the University Medical Center Utrecht, The Netherlands, between February 2002 and February 2003 for general or vascular surgery were selected for the current study. They underwent surgery in the period from February 2002 to August 2003, during general, spinal, epidural, or combined general–epidural anesthesia.

The study protocol was approved by the local hospital ethics committee (University Medical Center Utrecht). The committee waived the need for written informed consent because patients were not subjected to any investigational actions and only patient information relevant to usual care was obtained. According to the Dutch law on personal data protection, patient confidentiality was guaranteed.

Data Collection

Preoperative data were collected at the outpatient preoperative evaluation clinic and included data on patient demographics, medical history, physical examination, and American Society of Anesthesiologists physical status. Intraoperative data were obtained from the electronic anesthesia record-keeping system. This anesthesia record-keeping system stores data from the anesthesia ventilator and monitor, such as ventilator settings, blood pressure, heart rate, and oxygen saturation every minute (when available), as well as data that are entered manually during anesthesia, such as administration of medications, time of intubation, and infusions. In general, noninvasive blood pressure was measured at least every 5 min. When blood pressure was measured both invasively and noninvasively, invasive measurements were used for the current analysis. The blood pressure data were extracted from the anesthesia record-keeping system using a dedicated program (LabView version 8; National Instruments Corporation, Austin, TX). For each patient, this program retrieved the patient characteristics and a data array containing all blood pressure data from the anesthesia record-keeping system. The baseline blood pressure was defined as the mean of the blood pressure reading on the outpatient preoperative evaluation clinic, and all blood pressure readings in the operating room before induction of anesthesia. This required the exact time of induction of anesthesia. Because induction of anesthesia was entered manually in the anesthesia record-keeping system, often after induction and intubation actions are completed, this event was considered to be a less reliable estimate of the induction of anesthesia. Therefore, induction of anesthesia was defined, according to an algorithm described in a previous study, as the moment of administration of induction medication or 3 min before the first appearance of continuous expired carbon dioxide registration, whichever came first.[7] In case of spinal or epidural anesthesia, the time of puncture was taken as the induction time.

Intraoperative Hypotension

Intraoperative hypotension was defined as the duration that the blood pressure was below an *a priori* designated threshold value. The thresholds were selected from a previously conducted review study according to those most commonly used in the literature.[7] We selected four systolic blood pressure thresholds (100, 90, 80, and 70 mmHg), four mean blood pressure thresholds (70, 60, 50, and 40 mmHg), and four thresholds relative to baseline blood pressure (a decrease of 10, 20, 30, and 40%) for both systolic and mean blood pressures: in total, 16 thresholds. Blood pressures below these thresholds were considered IOH when the duration of low blood pressure (*i.e.*, the minimal episode duration) was at least 1, 5, or 10 min: thus, in total, 48 (16×3) definitions. For each patient, the duration of IOH was calculated for each of these 48 definitions. Therefore, IOH was expressed as a continuous variable representing the number of minutes that the blood pressure was below the threshold value for longer than the minimal episode duration.

Outcome

We studied all-cause mortality within 1 yr after surgery. Time until death (in days) was calculated from the day of surgery, with patients who survived 365 days considered censored observations. Patients lost to follow-up were censored on the last known date they had visited the hospital. Mortality data were collected by using the hospital information system, using the Dutch civil registration system, and contacting the patient's general practitioner.

Potential Confounders

The association between IOH and 1-yr mortality was adjusted for possible confounders. These included age, sex, body mass index, smoking, comorbidity, type of surgery, duration of surgery, and cumulative exposure to administered anesthetics.[6] Smoking was defined as present or absent, disregarding pack-years and the number of cigarettes smoked daily. Comorbidity was measured by the American Society of Anesthesiologists physical status and by a history of heart disease, hypertension, diabetes, and stroke. Type of surgery was defined as vascular, major general surgery (intracavitary procedures), or minor general surgery (superficial or minimally invasive procedures).[6] Duration of surgery was expressed in minutes from induction of anesthesia to end of surgery. The cumulative exposure to anesthetics included volatile and intravenous anesthetics. The cumulative exposure to volatile anesthetics (sevoflurane or isoflurane) was assessed as the area under the inspiratory concentration curve. The cumulative amount of intravenous anesthetics (propofol) was assessed as the area under the simulated effect site concentration curve. The effect site concentrations were simulated using the Marsh parameter set with an effect compartment time constant (ke0) of 0.291.[12,13]

Statistical Analysis

Unadjusted Kaplan–Meier curves were plotted for patients with and without hypotension starting with the IOH definition of a systolic blood pressure below 80 mmHg (threshold value) for at least 1 min (episode duration). Differences between Kaplan–Meier curves were tested with log-rank tests. The hazard ratio for duration of IOH was estimated with Cox proportional hazards regression analysis. The association between duration of IOH and 1-yr mortality was adjusted for age, sex, and other confounding variables. Variables were considered confounders if an association between the variable and the presence of IOH (yes/no) was found. We expected that healthier patients could tolerate greater degrees of hypotension than patients with severe comorbidity. We took this assumed heterogeneity in effect into account by studying interactions between IOH and other patient characteristics. Continuous variables (*i.e.*, duration of IOH, age, duration of surgery, and cumulative exposure to anesthetics) were tested for nonlinearity using restricted cubic spines.[14] The proportional hazards assumption was checked using scaled Schoenfeld residuals.[15] The complete analytical approach was repeated for the other 15 IOH threshold values. Finally, these 16 analyses were also performed for the two other minimal episode durations of 5 and 10 min, resulting in 48 (16×3) analyses.

Another method to study heterogeneity is classification and regression tree (CART) analysis, a nonparametric statistical technique that assigns individuals to mutually exclusive groups based on a set of selected predictor variables. CART analysis selects cutoff values for the variables at which they differentiate best between different patient groups (here with and without 1-yr mortality). This allowed for exploring at which duration of IOH the 1-yr mortality risk was increased most. Furthermore, CART analysis is more flexible than regression analysis and makes no assumptions about the underlying mathematical relations. Finally, this method may identify interactions that may not have been found using traditional methods.

All of the variables selected for the Cox proportional hazards modeling were also available for selection in the CART analysis. The CART analysis was also repeated for a range of IOH threshold values. To estimate hazard ratios with 95% confidence intervals (CIs) for the different CART nodes, we grouped the cohort according to the CART node characteristics and used these in a Cox proportional hazards model.

Analyses were performed with R (release 2.7.1; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (release 15.0; SPSS Inc., Chicago, IL).

Results

After application of the inclusion and exclusion criteria, a cohort of 1,705 general and vascular surgery patients was selected. Nine patients (0.5%) were lost to follow-up. The demographic and intraoperative patient characteristics are presented in table 1. The mortality rate within 1 yr after surgery was 5.2% (n = 88). Most patients (22%) died of cancer (table 2).

Figure 1 shows the Kaplan–Meier curves for patients with and without IOH, defined according to four systolic blood pressure thresholds (100, 90, 80, and 70 mmHg) and a minimal episode duration of 1 min. With decreasing threshold values for IOH, the divergence of the curves increased. The log-rank tests showed significant differences in risk of mortality for all four definitions of IOH (P values 0.05, 0.001, < 0.001, and < 0.001, respectively).

The proportional hazards and linearity assumptions were not violated. Therefore, Cox proportional hazards analysis was used and all continuous variables were modeled linearly. The crude hazard ratio of duration of IOH (systolic blood pressure below 80 mmHg for at least 1 min) was 1.013 (95% CI, 1.007–1.019; table 3). When adjusted for all confounders, an effect of duration of IOH on the outcome could not be found (hazard ratio, 1.00; 95% CI, 0.989–1.011; table 3). With this definition of IOH, only age (hazard ratio, 1.042; 95% CI, 1.023–1.061), American Society of Anesthesiologists physical status (overall P value < 0.05), history of hypertension (hazard ratio, 2.406; 95% CI, 1.407–4.112), and duration of surgery (hazard ratio, 1.008; 95% CI, 1.004–1.012) were associated with 1-yr mortality. Cumulative exposure to sevoflurane showed a hazard ratio of 0.998 (95% CI, 0.995–1.000). No statistically significant effects for interaction were found. It should be noted that these results were not corrected for multiple testing.

Table 4 shows the results for all other selected thresholds for IOH and the three minimal episode durations. None of the 48 adjusted hazard ratios were statistically significant. Therefore, a correction for multiple testing was deemed unnecessary. To graphically represent the hazard ratio as a function of the threshold values for low blood pressure, the associations between a wider range of low blood pressure thresholds and 1-yr mortality were calculated for all three minimal episode durations. Although not statistically significant, the risk of dying within 1 yr after general or vascular surgery seems to increase when the threshold value of IOH was below a systolic blood pressure of 80 mmHg or a mean blood pressure of 60 mmHg or when there was a decrease in both systolic and mean blood pressure of 40–45% from baseline (fig. 2).

The CART analysis included the duration of IOH in the tree when IOH was defined as a mean blood pressure below 50–75 mmHg for patients older than 46 yr. Two trees are presented in figure 3 with hypotension defined as a mean blood pressure below 50 mmHg and 60 mmHg for at least 1 min. With a mean blood pressure below 60 mmHg, IOH was included in the tree with a cutoff value

Table 1. Characteristics of the Cohort (n = 1,705)

	Total Cohort (n = 1,705)	Intraoperative Hypotension*		
		Present (n = 652)	Absent (n = 1,053)	*P* Value
Mean age (SD), yr	52 (15.8)	57 (14.2)	49 (15.9)	< 0.05‡
Male sex	880 (51.6)	324 (49.7)	556 (52.8)	0.21§
Mean BMI (SD), kg/m^2	25 (4.8)	25 (4.9)	25 (4.8)	0.60‡
Smoking	509 (29.9)	195 (29.9)	314 (29.8)	0.97§
ASA physical status				
I	647 (37.9)	186 (28.5)	461 (43.8)	< 0.05§
II	872 (51.1)	374 (57.4)	498 (47.3)	
III or IV	186 (10.9)	92 (14.1)	94 (8.9)	
History of				
Cardiac disease	258 (15.1)	115 (17.6)	143 (13.6)	< 0.05§
Hypertension	380 (22.3)	177 (27.1)	203 (19.3)	< 0.05§
Diabetes mellitus	143 (8.4)	67 (10.3)	76 (7.2)	< 0.05§
Stroke	118 (6.9)	45 (6.9)	73 (6.9)	0.94§
Type of surgery				
Minor general	1,200 (70.4)	366 (56.1)	835 (79.3)	< 0.05§
Major general	303 (17.8)	187 (28.7)	116 (11.0)	
Vascular	199 (11.7)	99 (15.2)	100 (9.5)	
Median surgery duration (25th–75th percentile), min	112 (73–163)	151 (100–217)	91 (65–134)	< 0.05‖
Type of anesthesia				
General	1,226 (71.9)	457 (70.1)	769 (73.0)	< 0.05§
Regional	201 (11.8)	17 (2.6)	184 (17.5)	
Combined	278 (16.3)	178 (27.3)	100 (9.5)	
Cumulative exposure to anesthetics,† (25th–75th percentile)				
Median AUC for sevoflurane	111 (61–201)	151 (74–274)	95 (55–160)	< 0.05‖
Median AUC for isoflurane	96 (44–167)	141 (73–197)	66 (27–125)	< 0.05‖
Median AUC for propofol	310 (179–454)	321 (190–510)	305 (175–441)	0.18‖
1-yr mortality (KM estimate)	88 (353.7)	53 (346.2)	35 (358.4)	< 0.05#

Values are number (%) unless otherwise specified.

* Intraoperative hypotension was defined as a systolic blood pressure below 80 mmHg for at least 1 min. † Cumulative exposure to anesthetics for patients receiving propofol (n = 446) was expressed as the area under the effect site concentration curve; for patients receiving volatile anesthetics (sevoflurane, n = 863 or isoflurane, n = 356), this was expressed as the area under the inspiratory concentration curve. *P* values were derived with ‡ independent samples Student *t* test for normally distributed variables, § chi-square test for categorical variables, ‖ Mann–Whitney U test for nonnormally distributed variables, and # log-rank test for survival distributions.

ASA = American Society of Anesthesiologists; AUC = area under the curve; BMI = body mass index; KM = Kaplan–Meier.

of 30 min, whereas a mean blood pressure below 50 mmHg resulted in a cutoff value of only 5 min. Therefore, at the lower end of the blood pressure threshold range, the duration at which IOH was included in the classification and regression tree was shorter (table 5). The CART analysis with IOH defined by systolic blood pressures yielded less clear results. IOH defined as systolic blood pressure below 70 mmHg was included in the tree with duration dichotomized at 3 min; IOH defined as systolic blood pressure below 95 mmHg was included with a dichotomized value of 104 min. The systolic blood pressure threshold values between 70 and 95 mmHg were not selected with the CART analysis.

Table 2. Causes of Death (n = 88)

Cause of Death	Within 30 Days (n = 23)	Within 1 Year (n = 88)
Malignancy	0 (0)	19 (22)
Sepsis/infection/multiple organ failure	3 (13)	13 (15)
Cardiac*	7 (30)	11 (13)
Pulmonary†	4 (17)	9 (10)
Rebleed	4 (17)	4 (5)
Stroke	2 (9)	2 (2)
Kidney failure	0 (0)	2 (2)
Ischemic bowel	1 (4)	1 (1)
Unknown	2 (9)	26 (30)

Values are number (%).

* Cardiac causes of death included myocardial infarction, ventricular fibrillation, asystole and heart failure. † Pulmonary causes of death included pulmonary embolus, acute respiratory distress syndrome, and pneumonia.

Discussion

In this observational study, we studied the association between the duration of intraoperative hypotension and the risk of dying within 1 yr after general or vascular surgery. To this aim, a variety of frequently used definitions of IOH were used. Eighty-eight of 1,705 patients (5.2%) died within 1 yr after surgery.

Using regression techniques, a trend of higher mortality risk within 1 yr after surgery was found for threshold values below a systolic blood pressure of 80 mmHg, below a mean blood pressure of 60 mmHg, or for a decrease in both systolic and mean blood pressure of

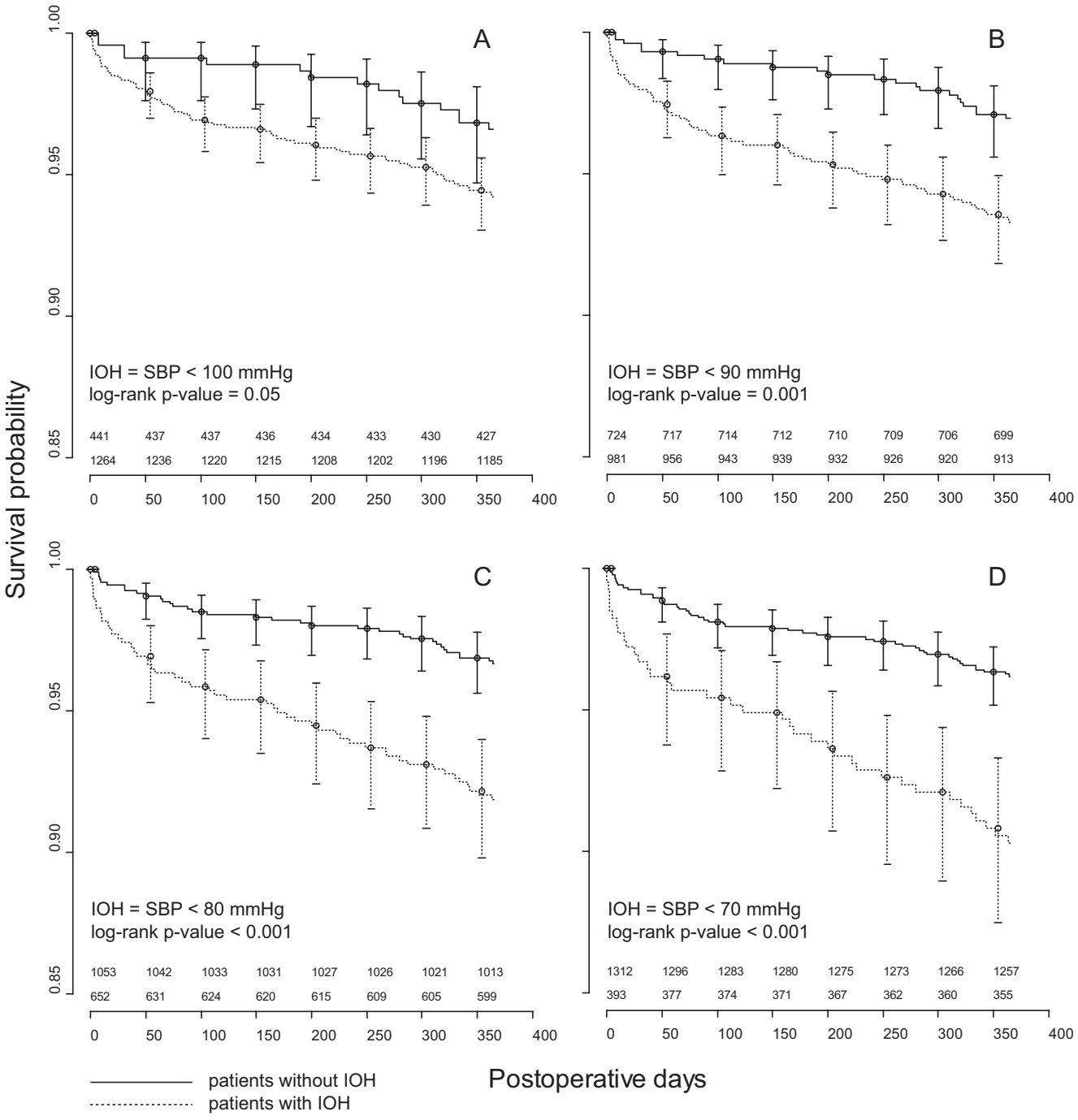

Fig. 1. Kaplan–Meier curves for all-cause mortality of the cohort (n = 1,705 patients). Intraoperative hypotension (IOH) was defined as a systolic blood pressure (SBP) below 100 mmHg for at least 1 min (*A*), an SBP below 90 mmHg for at least 1 min (*B*), an SBP below 80 mmHg for at least 1 min (*C*), or an SBP below 70 mmHg for at least 1 min (*D*). The differences in survival probabilities were compared using log-rank tests. *Above the x-axis*, the numbers at risk are presented at 50-day intervals. The *upper row* corresponds with the *upper curve*, and the *lower row* corresponds with the *lower curve*. The *horizontal bars* indicate 95% confidence intervals at 50-day intervals.

40–45% from baseline (fig. 2). The unexpected decrease in hazard ratios to 1 and even below 1 at the extremes (low absolute blood pressure or high relative blood pressure thresholds) are unstable estimates that can be explained by the very low number of patients at these low blood pressure extremes. These hazard ratios are therefore not reliable, which is illustrated by the wide CIs in figure 2. Therefore, conclusions on lowest acceptable blood pressure thresholds cannot be drawn from these results.

The CART analysis included duration of IOH in the tree for IOH defined as a mean blood pressure threshold value between 50 and 75 mmHg. For the lower threshold values in this range, shorter durations of IOH were associated with 1-yr mortality than among the higher

Table 3. Crude and Adjusted Association (Using Cox Proportional Hazards Analysis) of IOH Defined as a Systolic Blood Pressure Lower than 80 mmHg for at Least 1 Minute, and 1-Year Mortality

Effect of IOH	Hazard Ratio for IOH (95% CI)*	*P* Value
Crude		
IOH	1.013 (1.007–1.019)	< 0.05
Adjusted		
IOH + age	1.015 (1.008–1.021)	< 0.05
Previous step + sex	1.015 (1.008–1.021)	< 0.05
Previous step + ASA physical status	1.015 (1.008–1.021)	< 0.05
Previous step + history of cardiac disease	1.015 (1.008–1.021)	< 0.05
Previous step + history of hypertension	1.014 (1.008–1.021)	< 0.05
Previous step + history of diabetes mellitus	1.014 (1.008–1.021)	< 0.05
Previous step + type of surgery	1.011 (1.004–1.018)	< 0.05
Previous step + duration of surgery	1.001 (0.988–1.010)	0.81
Previous step + type of anesthesia	1.001 (0.988–1.010)	0.80
Previous step + cumulative exposure to anesthetics	1.000 (0.989–1.011)	0.99

* Hazard ratios express the association between duration of intraoperative hypotension and death within 1 yr after noncardiac general or vascular surgery.

ASA = American Society of Anesthesiologists; CI = confidence interval; IOH = intraoperative hypotension.

thresholds, where longer durations of hypotension were tolerated. Again, no conclusions on causality can be drawn because of the type of this analysis, as residual confounding may still exist. However, these results do seem to provide support for the widely accepted clinical reasoning that in elderly patients, decreasing blood pressures are tolerated for increasingly shorter durations.

Some limitations of the study need to be addressed. First, because this study was observational, adjustment for confounding variables was required. Multivariable regression analysis is appropriate for the adjustment of observed confounders. All variables that were associated with IOH and mortality were included in the regression model. In addition, we performed a CART analysis. Unfortunately, such an analysis does not allow the analyst to force confounders into the tree, and residual confounding is particularly present in this analysis. Nevertheless, it is a powerful way to simply identify descriptive predictors (where confounding is not an issue) for 1-yr mortality.

Second, the problem of multiple testing should be considered. The hazard ratio was estimated using a large number of blood pressure threshold values and episode durations. For single testing, the chance that the null hypothesis is falsely rejected is widely accepted to be 5%. Hence, in our situation, for every 20 tests performed on average, one of those will falsely yield a statistically significant association of IOH with mortality. However, because for none of the 48 definitions of IOH was a significant association with 1-yr mortality found, correction for multiple testing was not meaningful. The hazard ratios for the confounding variables also differ with the use of different definitions. This means that the hazard ratios, CIs, and *P* values should be carefully interpreted. Even though the confidence intervals are already too wide to reach statistical significance, because of the aforementioned limitations they may still even be too narrow.

Third, cumulative deep hypnotic time was previously reported to be associated with 1-yr mortality by Monk *et al.*,[6] which was recently confirmed by Lindholm *et al.*,[16] and should therefore be considered as a potential confounding factor. However, our patient population was not routinely monitored with an electroencephalography monitor designed to provide information on the intensity of hypnotic effect such as the BIS® monitor (Aspect Medical Systems, Natick, MA) or entropy module (GE Healthcare, Chalfont St. Giles, United Kingdom). Instead, cumulative exposure to propofol or volatile agent was calculated and the area under the effect site concentration curve for propofol based anesthesia or the area under the inspired concentration curve for volatile based anesthesia was used in the analysis. Although ideally end-tidal concentrations should have been used to calculate cumulative exposure to volatile anesthetics, only the inspired concentrations were available from the anesthesia record-keeping system. We do not expect that this has caused significant bias, because inspiratory and expiratory concentrations of modern volatile anesthetics such as isoflurane and sevoflurane rapidly equilibrate. Furthermore, the group of patients with hypotension had a statistically significantly higher cumulative exposure to volatile anesthetics than did nonhypotensive patients (table 1), a difference that was not observed for cumulative exposure to propofol. This might reflect unintended overdose of volatile anesthetics. Because of the observational design of the study, there could be a difference in potential confounders across the studied exposure groups, which is often simply by chance. We adjusted for this difference in potential risk factors in the multivariable analysis.

Another issue is that a healthy patient might be more likely to have received noninvasive blood pressure measurement, whereas in sicker patients invasive blood pressure monitoring was used. Therefore, more IOH might have been detected in sicker patients, introducing bias. We tried to minimize this effect by defining IOH as the number of minutes spent under the IOH threshold value instead of the more usual approach of dichotomizing the entire procedure as hypotension/no hypotension.

Because preoperative administration of sedation to reduce anxiety might have influenced the baseline blood pressure, the blood pressure measurement from the preoperative evaluation clinic was incorporated in the base-

Table 4. Crude and Adjusted Hazard Ratios for All Definition Thresholds and Episode Durations of IOH

	Minimal Episode Duration of 1 Minute		Minimal Episode Duration of 5 Minutes		Minimal Episode Duration of 10 Minutes	
Threshold for IOH	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*	Crude HR (95% CI)	Adjusted HR (95% CI)*
Absolute systolic blood pressure thresholds						
SBP < 100 mmHg	1.006 (1.004–1.008)	1.000 (0.996–1.003)	1.005 (1.003–1.008)	0.999 (0.996–1.003)	1.005 (1.003–1.008)	0.999 (0.995–1.003)
SBP < 90 mmHg	1.007 (1.004–1.011)	0.988 (0.993–1.004)	1.007 (1.003–1.011)	0.998 (0.992–1.003)	1.006 (1.001–1.011)	0.997 (0.990–1.003)
SBP < 80 mmHg	1.013 (1.007–1.019)	1.000 (0.989–1.011)	1.011 (1.004–1.019)	0.999 (0.986–1.012)	1.010 (1.000–1.019)	1.000 (0.985–1.015)
SBP < 70 mmHg	1.014 (1.005–1.023)	1.006 (0.990–1.021)	1.010 (0.997–1.023)	1.002 (0.982–1.023)	1.005 (0.983–1.027)	0.996 (0.963–1.031)
Systolic blood pressure thresholds relative to a baseline						
Decrease SBP > 10%	1.006 (1.004–1.007)	1.000 (0.996–1.004)	1.006 (1.004–1.007)	1.000 (0.996–1.004)	1.006 (1.004–1.007)	1.000 (0.996–1.003)
Decrease SBP > 20%	1.006 (1.004–1.007)	1.000 (0.996–1.003)	1.006 (1.004–1.007)	1.000 (0.996–1.004)	1.005 (1.004–1.007)	1.000 (0.996–1.003)
Decrease SBP > 30%	1.006 (1.004–1.008)	0.999 (0.995–1.002)	1.006 (1.004–1.008)	0.999 (0.995–1.002)	1.006 (1.003–1.008)	0.999 (0.995–1.002)
Decrease SBP > 40%	1.009 (1.005–1.013)	0.999 (0.993–1.004)	1.008 (1.004–1.013)	0.998 (0.992–1.004)	1.008 (1.003–1.013)	0.998 (0.992–1.005)
Absolute mean blood pressure thresholds						
MBP < 70 mmHg	1.006 (1.005–1.008)	1.002 (0.999–1.006)	1.006 (1.005–1.008)	1.002 (0.999–1.006)	1.006 (1.005–1.008)	1.002 (0.999–1.006)
MBP < 60 mmHg	1.009 (1.007–1.012)	1.003 (0.998–1.008)	1.010 (1.007–1.013)	1.003 (0.998–1.009)	1.009 (1.006–1.013)	1.002 (0.996–1.008)
MBP < 50 mmHg	1.015 (1.008–1.023)	1.007 (0.995–1.019)	1.013 (1.003–1.022)	1.005 (0.990–1.020)	1.010 (0.998–1.022)	1.004 (0.987–1.021)
MBP < 40 mmHg	1.006 (0.985–1.028)	0.999 (0.965–1.035)	0.997 (0.947–1.050)	0.994 (0.939–1.053)	0.967 (0.697–1.342)	†
Mean blood pressure thresholds relative to a baseline						
Decrease MBP > 10%	1.006 (1.005–1.007)	1.001 (0.996–1.006)	1.006 (1.005–1.007)	1.001 (0.996–1.006)	1.006 (1.005–1.007)	1.001 (0.996–1.005)
Decrease MBP > 20%	1.006 (1.004–1.007)	1.001 (0.997–1.004)	1.006 (1.004–1.007)	1.001 (0.997–1.004)	1.006 (1.004–1.007)	1.000 (0.997–1.004)
Decrease MBP > 30%	1.006 (1.005–1.008)	1.001 (0.998–1.005)	1.006 (1.005–1.008)	1.002 (0.998–1.005)	1.006 (1.004–1.008)	1.002 (0.999–1.005)
Decrease MBP > 40%	1.007 (1.005–1.009)	1.002 (0.998–1.006)	1.007 (1.005–1.010)	1.002 (0.998–1.006)	1.007 (1.005–1.010)	1.002 (0.998–1.006)

* Adjusted for age, sex, American Society of Anesthesiologists physical status, type of surgery, duration of surgery, type of anesthesia, and cumulative exposure to anesthetics (table 3). † Unreliably low hazard ratio (HR) with immeasurably large confidence interval (CI).

IOH = intraoperative hypotension; MBP = mean blood pressure; SBP = systolic blood pressure.

line reference blood pressure. This reduced the blood pressure–decreasing effect of sedation on the baseline blood pressure. Furthermore, in the analyses using a definition of IOH with an absolute threshold value, where baseline blood pressures and the effect of sedation play no role, comparable results were found.

Finally, the causes of death could not be obtained for all patients (n = 26). When a patient had died outside the hospital, the date of death could be obtained from the civil registration system. However, the cause of death could not always be retrieved from the family physician. In theory, the cause of death for the 26 patients could be unrelated to the occurrence of IOH (*e.g.*, a traffic accident). Excluding these cases could change the effect of IOH on 1-yr mortality in either direction and would introduce selection bias. Therefore, these cases were not excluded. Furthermore, because the causes of death do not change the actual number of deaths, the association between IOH and all-cause 1-yr mortality is not affected.

The most frequently reported definitions of IOH in the anesthesia literature are a systolic blood pressure below 80 mmHg, a mean blood pressure below 55–60 mmHg, and a decrease in systolic or mean blood pressure of 20–25% from baseline.[7] In the current study, a trend of increasing hazard ratios—not statistically significant—around these blood pressures values was indeed found (fig. 2). The hazard ratio for mortality seemed to increase with a 40% relative decrease from baseline in systolic or mean blood pressure, which is a much larger relative blood pressure decrease than the textbook definition of 20–25% decrease in systolic or mean blood pressure. To date, only one study has described an association between IOH and 1-yr mortality.[6] In that study, the relative risk of dying within 1 yr after major noncardiac surgery was found to increase with 3.6% (95% CI, 0.6–6.6%) for every minute that the systolic blood pressure was below 80 mmHg (measured at 5-min intervals). Surprisingly, IOH defined as a mean blood pressure below 55 mmHg was also mentioned in that study without being associated with increased 1-yr mortality. This might be explained by a difference in patient population between the study by Monk *et al.* and the current study (major noncardiac surgery *vs.* major and minor general and vascular surgery). The mortality rate after 1 yr was comparable between the study by Monk *et al.* and the current study (5.5% *vs.* 5.2%), but the 30-day mortality rate of the current study seems higher (1.3% *vs.* 0.7%). However, this difference in 30-day mortality is not statistically significant if tested using a contingency table and chi-square test (current study: 23 deaths, 1,682 alive; Monk *et al.*: 7 deaths, 1,057 alive; $P = 0.09$). Still, the sample size of a study that might report statistically significant and clinically relevant differences in the risk of dying

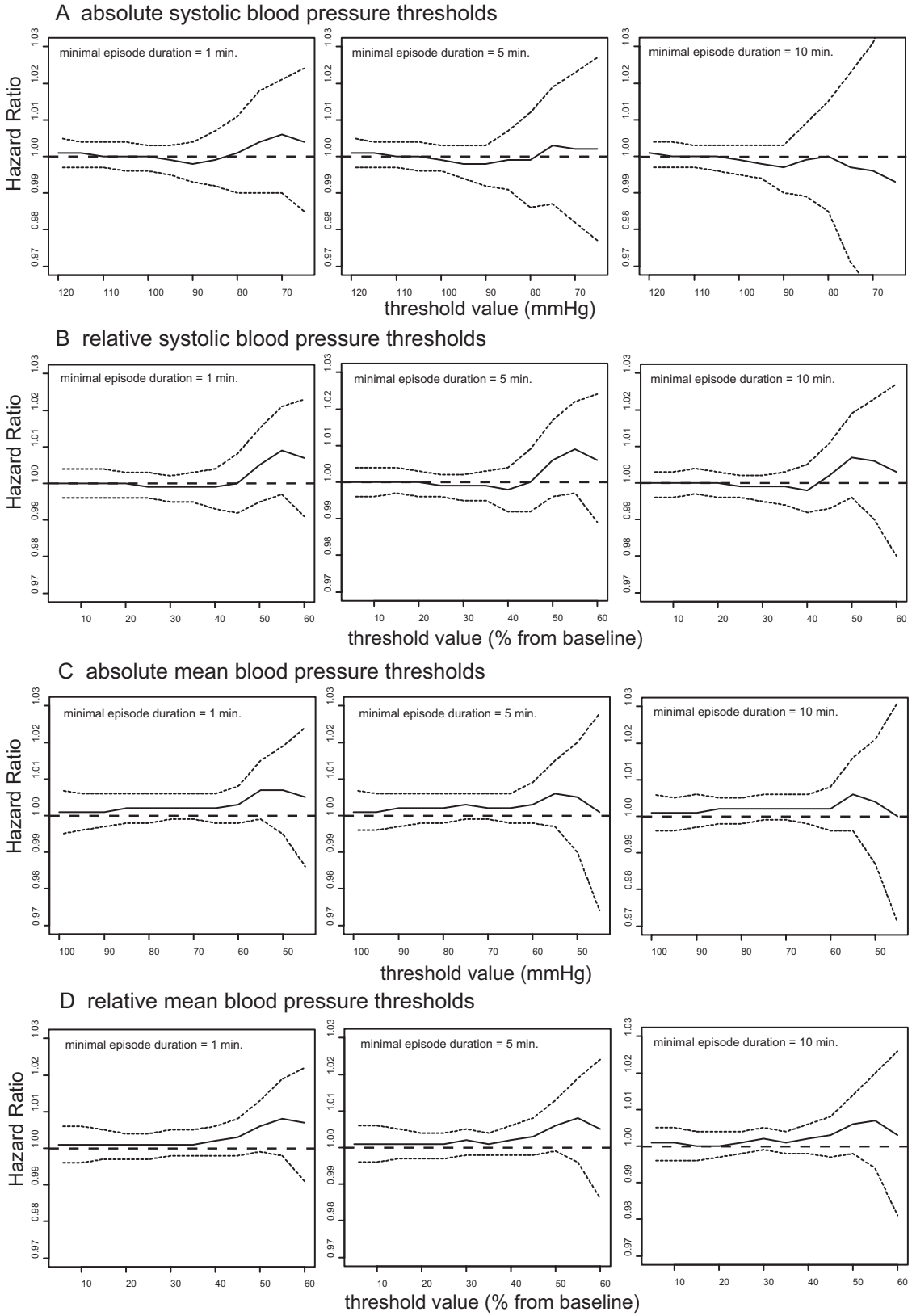

Fig. 2. Adjusted hazard ratios for the association between duration of intraoperative hypotension and all-cause 1-yr mortality plotted against absolute (*A* and *C*), relative (*B* and *D*), systolic (*A* and *B*), and mean (*C* and *D*) blood pressure threshold values for intraoperative hypotension. The *dotted lines* represent the 95% confidence interval. The *horizontal dotted line* represents the level of no effect (hazard ratio = 1).

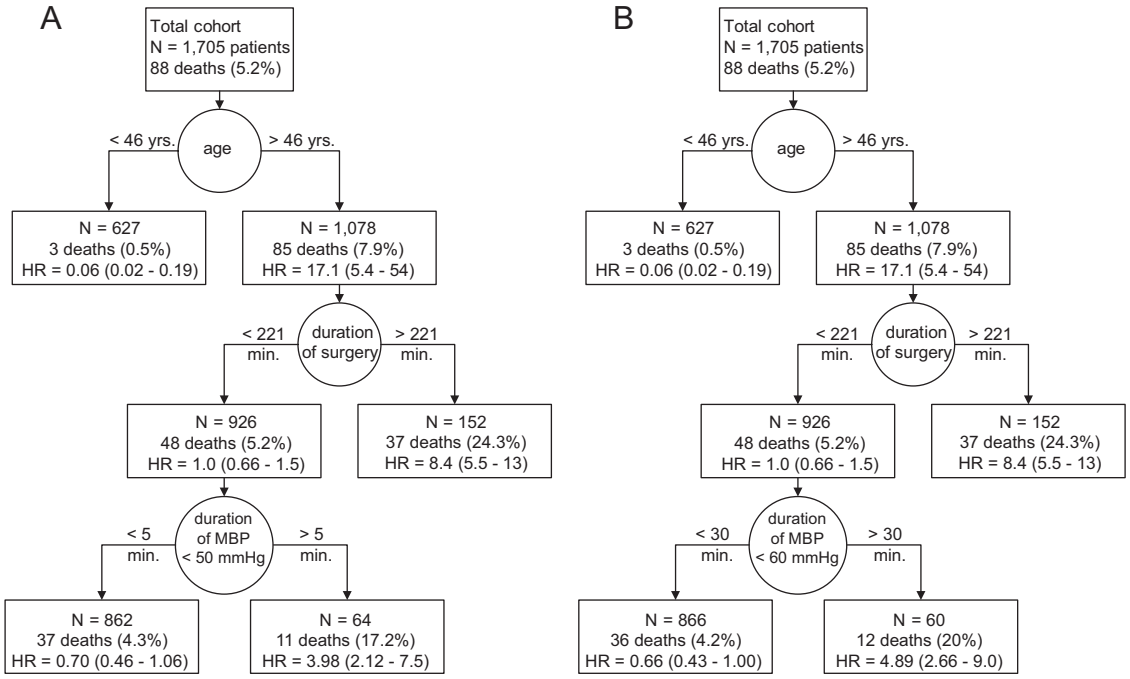

Fig. 3. Results of the classification and regression tree analysis using two different definitions of intraoperative hypotension: a mean blood pressure (MBP) below 50 mmHg for at least 1 min (*A*) or a MBP below 60 mmHg for at least 1 min (*B*). HR = hazard ratio.

within 1 yr after surgery due to IOH should be considerably larger than the sample sizes of both the current study and the study by Monk *et al.* If, for example, an increase in relative risk of dying of 1% per minute hypotension is considered clinically relevant, a sample size of approximately 83,000 patients would be required (calculated using a mortality rate of 5%, a power of 0.80, and an α of 0.05). If an increase in 1-yr mortality risk of 2% per minute hypotension would be considered relevant, the sample size is reduced to 21,000 patients. Even in a multicenter setting, such studies are challenging if not impossible to perform, and a case–control study seems to be the more promising initial design.

Table 5. CART Cutoff Values for the Duration of IOH According to Different Blood Pressure Threshold Values in Patients Older than 46 Years and with a Surgery Duration Less than 221 Minutes

BP Threshold Value, mmHg	CART Cutoff Value, min	Hazard Ratio* (95% CI) for IOH Duration < CART Cutoff	Hazard Ratio* (95% CI) for IOH Duration > CART Cutoff
MBP < 50	5	0.70 (0.46–1.06)	3.98 (2.12–7.5)
MBP < 55	21	0.74 (0.49–1.13)	6.42 (3.11–13.3)
MBP < 60	30	0.66 (0.43–1.00)	4.89 (2.66–9.0)
MBP < 65	34	0.58 (0.372–0.90)	3.29 (1.96–5.52)
MBP < 70	46	0.63 (0.41–0.98)	2.46 (1.46–4.12)
MBP < 75	55	0.62 (0.39–0.97)	2.28 (1.39–3.75)

* Hazard ratios (relative to the total cohort) were estimated by grouping the total cohort by terminal classification and regression tree (CART) nodes and entering this variable into a Cox proportional hazards model.

BP = blood pressure; CI = confidence interval; IOH = intraoperative hypotension; MBP = mean blood pressure.

In conclusion, an overall causal relation between IOH and 1-yr mortality could not be demonstrated in the current study. However, CART analysis revealed that in elderly patients, IOH is associated with 1-yr mortality according to a range of blood pressure thresholds and corresponding durations of the hypotensive episode, *i.e.*, lower blood pressures were tolerated for shorter durations. This confirms the clinical experience that besides the absolute or relative blood pressure thresholds, the duration of low blood pressure is equally important in the possible association of IOH with adverse outcome. Furthermore, patient and surgical characteristics, notably age and duration of surgery, do influence the relation between IOH and adverse outcome. Therefore, no conclusion on a single lowest acceptable intraoperative blood pressure could be drawn and the effects of IOH on adverse perioperative outcome remain debatable. However, the current study provides a different approach to study such relations, which better seems to fit daily clinical practice and reflect our clinical reasoning.

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ANESTHESIOLOGY REFLECTIONS

Fourneau Synthesizes Stovaine

A French pharmacist and chemotherapeutic researcher, Ernest A. Fourneau (1872–1949) synthesized a nonaddicting and less toxic alternative to cocaine for use as a local anesthetic. His Poulenc Frères Company of Paris filed for a trademark and at least three U.S. Patents to safeguard mass production of this agent synthesized by Fourneau, whose surname in French means "stove." When distributed from New York by Parmele Pharmacal Company (*see the example above from the Wood Library-Museum*), the synthetic local anesthetic was prudently released to the English-speaking world as "Stovaine," rather than the socially awkward "Fourneau-caine." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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