

Post-induction hypotension and early intraoperative hypotension associated with general anaesthesia

S. Südfeld^{1,†}, S. Brechnitz^{1,†}, J. Y. Wagner¹, P. C. Reese¹, H. O. Pinnschmidt², D. A. Reuter¹ and B. Saugel^{1,*}

¹Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany and ²Department of Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

*Corresponding author. E-mail: bernd.saugel@gmx.de; b.saugel@uke.de

[†]These authors contributed equally to this work.

Abstract

Background. We hypothesized that different phases of intraoperative hypotension should be differentiated because of different underlying causative mechanisms. We defined post-induction hypotension (PIH; i.e. arterial hypotension occurring during the first 20 min after anaesthesia induction) and early intraoperative hypotension (eIOH; i.e. arterial hypotension during the first 30 min of surgery).

Methods. In this retrospective study, we included 2037 adult patients who underwent general anaesthesia. Arterial hypotension was defined as a systolic arterial blood pressure (SAP) <90 mm Hg or a need for norepinephrine infusion at > 6 µg min⁻¹ at least once during the phases of PIH and eIOH. Multivariate logistic regression analysis was used to test for association of clinical factors with PIH and eIOH.

Results. Independent variables significantly related to PIH were pre-induction SAP [odds ratio (OR) 0.97 (95% confidence interval 0.97–0.98)], age [OR 1.03 (1.02–1.04)], and emergency surgery [OR 1.75 (1.20–2.56); *P*<0.01 each]. Pre-induction SAP [OR 0.99 (0.98–0.99), *P*<0.01], age [OR 1.02 (1.02–1.03), *P*<0.01], emergency surgery [OR 1.83 (1.28–2.62), *P*<0.01], supplementary administration of spinal or epidural anaesthetic techniques [OR 3.57 (2.41–5.29), *P*<0.01], male sex [OR 1.41 (1.12–1.79), *P*<0.01], and ASA physical status IV [OR 2.18 (1.19–3.99), *P*=0.01] were significantly related to eIOH.

Conclusions. We identified clinical factors associated with PIH and eIOH. The use of these factors to estimate the risk of PIH and eIOH might allow the avoidance or timely treatment of hypotensive episodes during general anaesthesia.

Key words: arterial pressure; general surgery; logistic models

Arterial hypotension in patients undergoing surgery under general anaesthesia, usually described by the very general term 'intraoperative hypotension' (IOH), is highly prevalent and associated with unfavourable patient outcome.¹ An arterial blood pressure (ABP) decline below the lower limit of the vascular autoregulation curve might lead to ischaemia of vital organs

(i.e. heart, brain, and kidney).^{2–4} Moreover, a number of clinical studies have demonstrated an association between IOH and unfavourable effects on organ function and integrity (i.e. myocardial injury, stroke, and acute kidney injury) in patients undergoing general,^{5,6} neurological,⁷ or cardiovascular surgery.⁸ Also, IOH is associated with longer hospital length of

Editorial decision: March 16, 2017; Accepted: April 12, 2017

© The Author 2017. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved.

For Permissions, please email: journals.permissions@oup.com

Editor's key points

- Hypotension during anaesthesia and surgery has several possible causes, and these can differ at different time points.
- This study separated hypotension at two phases: early after induction of anaesthesia and during the first 30 min of surgery.
- Pre-induction blood pressure, age, and emergency surgery were associated with both post-induction hypotension and early intraoperative hypotension.
- However, early intraoperative hypotension was also associated with other factors, including neuraxial anaesthesia, ASA status, and male sex.
- These findings have implications for the study, prevention, treatment, and significance of hypotension during the perioperative period.

stay, postoperative surgery-related morbidity,⁹ and even mortality.^{10 11}

Prediction of IOH based on the variables available to the clinician before induction of anaesthesia remains a difficult task.

From a pathophysiological perspective, the concept of IOH might be misleading because it suggests that IOH is a uniform and distinct disease entity. The incidence and causes of IOH, however, might be affected by factors that are different depending on the phase of anaesthesia and surgery in which it occurs. We therefore hypothesize that different phases of IOH should be defined because of different underlying causative mechanisms. In addition, differential (i.e. adjusted to the procedural phase) management of IOH risk factors seems warranted. Thus, we defined the entities of 'post-induction hypotension' (PIH; i.e. arterial hypotension occurring during the first 20 min after anaesthesia induction, or from anaesthesia induction until the beginning of surgery) and 'early intraoperative hypotension'

(eIOH; i.e. arterial hypotension during the first 30 min of surgery; Fig. 1).

We aimed to evaluate the influence of the biometric, physiological, and procedural variables available before surgery on PIH and eIOH in a general patient population of surgical patients in a university hospital.

Methods

Study design

The study protocol of this retrospective observational study (ethics committee number PV4778) was reviewed and approved by the appropriate ethics committee (Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany). Owing to the retrospective nature of this study and the anonymization of data, the need for informed consent was waived.

We retrospectively extracted and analysed data from our digitized anaesthesia records, which included biometric, medical, procedural, and physiological variables of patients treated in our anaesthesia department (Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf) in November 2013.

Patients; inclusion and exclusion criteria

An unselected sample of 2037 patients who underwent general anaesthesia to facilitate surgical and diagnostic procedures was analysed. Eligible patients underwent general anaesthesia in conjunction with or without additional regional anaesthesia during the study period and were >18 yr of age at that time. We subsequently excluded patients who were already being treated in an intensive care unit before surgery, who were under general anaesthesia by the time of the encounter with the treating anaesthetist, or who were equipped with an implantable or external circulatory assist device (e.g. ventricular assist device or

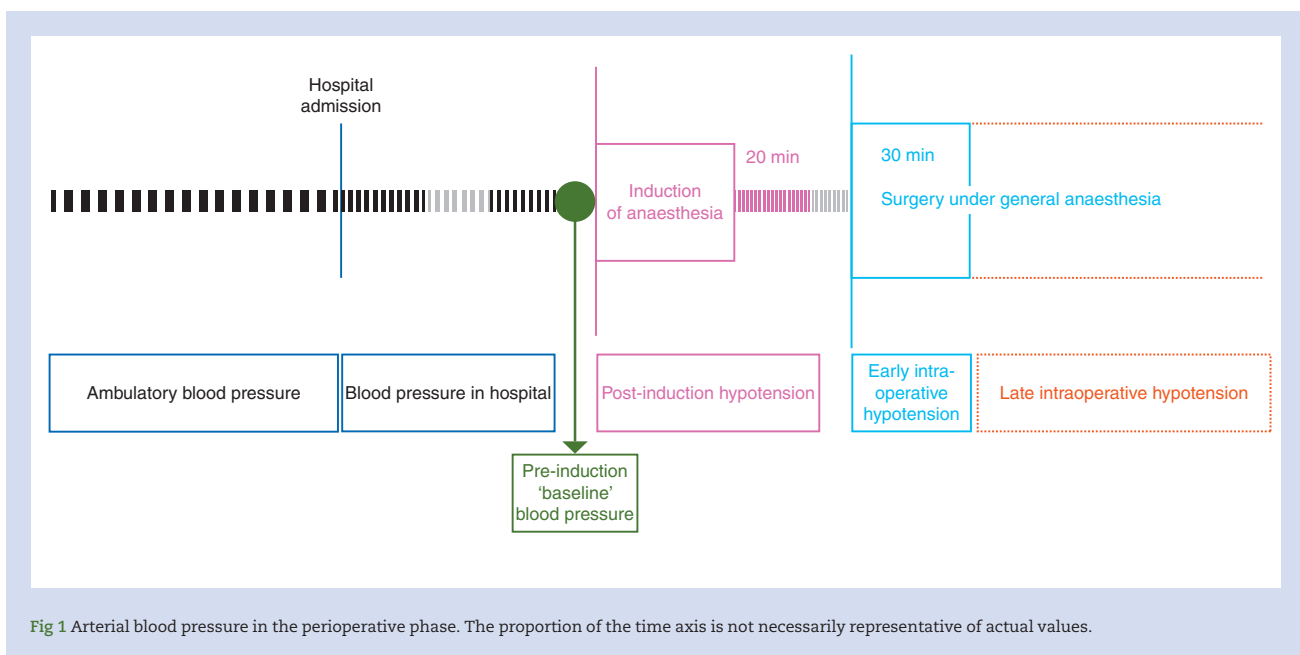


Fig 1 Arterial blood pressure in the perioperative phase. The proportion of the time axis is not necessarily representative of actual values.

extracorporeal membrane oxygenator), as its effects may interfere substantially with ABP physiology in these patients.

Definition of arterial hypotension

Arterial hypotension was defined as at least one measurement of systolic ABP (SAP) <90 mm Hg or at least one incident of norepinephrine infusion at a rate of $>6 \mu\text{g min}^{-1}$ during the respective period of interest.

We defined two distinct entities of arterial hypotension according to the time period during which it occurred: (i) from induction of general anaesthesia until 20 min post-induction, termed PIH; and (ii) during the period from the beginning of the operation until 30 min during surgery, termed eIOH.

Data acquisition

Available digitized anaesthesia records were automatically scrutinized for patients who met inclusion criteria and (after manual re-examination) only data of eligible patients were included in subsequent analyses. Biometrical, basic medical status, and procedural data including age, sex, weight, ASA physical status classification (ASA PS), patients' ability to achieve >4 metabolic equivalents of task (MET) (i.e. equivalent to 100 W, e.g. climbing one flight of stairs, according to results from pre-anaesthesia history taking or physical capacity testing), emergency status, type of anaesthesia, assigned surgical or medical service, intraoperative positioning, and duration of surgery were extracted. Further data on relevant pre-existing co-morbidities, long-term medication, perioperative anaesthetics doses, and haemodynamic measurements were manually transferred into evaluable data for the purpose of this study. The records were examined for the doses of administered anaesthetics, cardiovascular drugs (e.g. catecholamines), and ABP readings as intermittently documented by the treating anaesthetists, separately for the post-induction and early intraoperative periods. For non-invasive intermittent ABP measurements, we used an oscillometric device incorporated in the monitoring system Infinity Delta (Dräger Medical GmbH, Lübeck, Germany) set to a standardized 3 min measurement interval. Continuous invasive ABP measurements were conducted using arterial catheters and pressure transducers. For the early intraoperative period, catecholamine doses administered up to 15 min before the beginning of surgery were added to the amount of the catecholamine administered during the intraoperative period. In addition, baseline ABP, as documented at the time of the patients' arrival in the anaesthesia induction area that was not affected by the administration of induction drugs, was noted. Post-induction ABPs were expressed as minimal SAP values (in millimetres of mercury) for the post-induction and early intraoperative period, respectively. Doses of anaesthetics and cardiovascular drugs were expressed as the sum of administered boluses or the maximal infusion rate for continuous infusions during these respective time periods. The dose of anaesthetic drugs was normalized to body weight, if applicable.

Statistical analysis

We present descriptive statistical results as the median with 25th percentile to 75th percentile range for continuous data and as absolute frequencies with percentages for categorical data. Differences between PIH and eIOH groups were evaluated using Mann–Whitney *U*-tests for continuous variables and χ^2 tests or Fisher's exact tests (if 20% of expected frequencies were ≤ 5) for

categorical variables, as appropriate. To determine factors significantly associated with minimal ABP during the post-induction and the intraoperative period, multivariate logistic regression models were fitted, using a forward stepwise procedure involving clinically plausible independent variables (i.e. we started with no variables in the multivariate logistic regression models and added the variable, if any, whose inclusion gave the most statistically significant improvement of the model fit; we repeated this process until none of the variables remaining outside the model improved the model to a statistically significant extent). The stepwise forward approach was compared with stepwise backward selection that yielded the same final models. The clinically plausible independent variables tested in these multivariate logistic regression analyses were as follows: sex, BMI, baseline SAP, age, ASA PS, MET >4 , emergency surgery, anti-Trendelenburg patient positioning, history of chronic arterial hypertension, anti-hypertensive medication [i.e. angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor (AT1) blockers, calcium channel blockers or β -receptor blockers], and type of anaesthesia (spinal or epidural). Of note, ACE inhibitors and AT1 blockers were discontinued; calcium channel blockers and β -receptor blockers were not discontinued in the perioperative period. The models were adjusted for the dose of anaesthetics (normalized to body weight) and norepinephrine boluses around the respective time period by forcing these variables into the models. As effect measures, we present odds ratios (ORs) with their 95% confidence intervals (CIs). For continuous independent variables, ORs are considered as per unit increase of the respective independent variable.

For data management, we used Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA) and for statistical analyses we used IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA). Patients for whom respective data were missing were excluded in the respective analysis. Statistical significance was assumed for $P < 0.05$.

Results

Patient characteristics and procedural data

Patient selection is reported in the flow chart (Fig. 2). A total of 2037 patients were included in the final analysis. Of these, 368 (18.1%) met PIH and 503 (24.7%) met eIOH criteria, and 181 (8.9%) patients had both PIH and eIOH. The number of patients with an arterial catheter for invasive continuous ABP measurements was 570 (28.0%). As presented in Table 1, patients had a median age of 60 yr, with an almost even sex distribution [1136 (55.8%) male], and the majority of patients had ASA PS class II or III [793 (38.9%) and 851 (41.8%), respectively]. The leading co-morbidity was chronic arterial hypertension [773 (37.9%)]. Chronic arterial hypertension treated with anti-hypertensive medication (i.e. renin-angiotensin-aldosterone antagonists, β -receptor blockers, or calcium channel blockers) was present in 646 (31.7%) patients. A total of 835 (41.0%) patients were pretreated with these agents regardless of the indication. In accordance with the study protocol, all patients underwent general anaesthesia, including 168 (8.2%) administered supplementary regional techniques (i.e. neuraxial or peripheral blocks) for a variety of surgical interventions (Table 2). Additional procedural data are shown in the Supplementary Table S1. Neuraxial or peripheral nerve blocks were performed in the non-anaesthetized patient immediately before induction of general anaesthesia. In patients with an epidural catheter, the

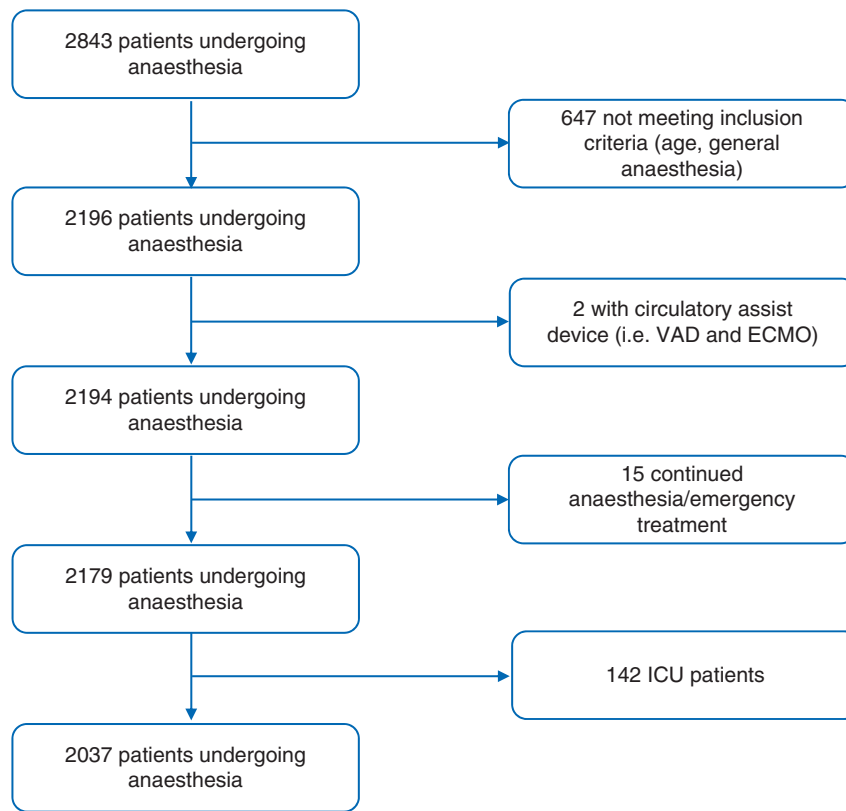


Fig 2 Flow chart of patient enrolment. ECMO, extracorporeal membrane oxygenator; ICU, intensive care unit; VAD, ventricular assist device.

effective dose of the long-acting local anaesthetic was injected in close temporal connection to the beginning of surgery.

The median pre-induction SAP was 135 mm Hg, ranging from 75 to 210 mm Hg.

Univariate analyses (Mann–Whitney U-test, χ^2 tests, and Fisher's exact test)

Patients found to have PIH were statistically significantly older compared with patients without PIH [65 (interquartile range 54–72) vs 59 (44–71) yr, $P < 0.01$], had lower BMI [24.65 (21.93–28.25) vs 25.51 (22.72–29.00) kg m⁻², $P < 0.01$], lower baseline (i.e. pre-induction) SAP [130 (115–145) vs 135 (120–150) mm Hg, $P < 0.01$], more frequently had ASA PS III or IV [172 (46.7%) vs 679 (40.7%), $P = 0.03$, and 48 (13.0%) vs 154 (9.2%), $P = 0.03$], more often underwent emergency operations [58 (15.8%) vs 196 (11.7%), $P = 0.04$], more often received long-term β -receptor blocker therapy [109 (29.9%) vs 410 (24.8%), $P = 0.04$], and had longer duration of surgery [80 (45–160) vs 70 (30–150) min, $P < 0.01$].

Patients in the group with eIOH, compared with those without eIOH, were statistically significantly more often male [314 (62.4%) vs 822 (53.6%), $P < 0.01$], had lower baseline (i.e. pre-induction) SAP [130 (120–145) vs 135 (120–150) mm Hg, $P = 0.02$], older age [65 (54–73) vs 59 (43–71) yr, $P < 0.01$], more frequently had ASA PS III or IV [254 (50.5%) vs 597 (38.9%) and 83 (16.5%) vs 119 (7.8%), $P < 0.01$ each], were less frequently able to achieve MET > 4 before

surgery [319 (63.4%) vs 1193 (77.8%), $P < 0.01$], were more likely to undergo emergency surgery [89 (17.7%) vs 165 (10.8%), $P < 0.01$], more often had known history of chronic arterial hypertension [213 (42.3%) vs 560 (36.5%), $P = 0.02$], were on long-term ACE inhibitors, β -receptor blockers, and calcium channel antagonists more often [122 (24.6%) vs 278 (18.3%), $P < 0.01$; 167 (33.6%) vs 352 (23.1%), $P < 0.01$; and 70 (14.1%) vs 160 (10.5%), $P = 0.03$], and had longer surgery [95 (50–180) vs 65 (30–136) min, $P < 0.01$; Tables 1 and 2; also see Supplementary Table S1].

Multivariate logistic regression analyses

As presented in Table 3, in our multivariate logistic regression model adjusted for anaesthetics and catecholamine use (other than continuous norepinephrine infusion), independent variables significantly associated with PIH were pre-induction SAP [OR 0.97 (95% CI 0.97–0.98)], age [OR 1.03 (1.02–1.04)], and emergency surgery [OR 1.75 (1.20–2.56); $P < 0.01$ each].

Significantly associated with eIOH were the variables and variable categories pre-induction SAP [OR 0.99 (0.98–0.99)], age [OR 1.02 (1.02–1.03)], emergency surgery [OR 1.83 (1.28–2.62)], supplementary administration of spinal or epidural anaesthetic techniques [OR 3.57 (2.41–5.29)], male sex [OR 1.41 (1.12–1.79); $P < 0.01$ each], and ASA PS IV [OR 2.18 (1.19–3.99), $P = 0.01$].

Table 1 Patient baseline characteristics. Data are presented as the median (25th–75th percentile) or number of patients (%). For categorical data, the χ^2 test or Fisher's exact test (*) was used, as appropriate; for continuous data, the Mann–Whitney U-test. Statistically significant differences (univariate analysis) are shown in bold. ACE, angiotensin-converting enzyme; AT₁, angiotensin II type 1 receptor; MET, (achievable) metabolic equivalents of task; n.s., non-significant; SAP, systolic arterial pressure

Variable	All	Post-induction hypotension		P-value	Early intraoperative hypotension		P-value
		Present n=368 (18.1)	Absent n=1669 (81.9)		Present n=503 (24.7)	Absent n=1534 (75.3)	
Age (yr)	60 (46–71)	65 (54–72)	59 (44–71)	<0.01	65 (54–73)	59 (43–71)	<0.01
Male sex (n)	1136 (55.8)	196 (53.3)	940 (56.3)	n.s.	314 (62.4)	822 (53.6)	<0.01
Height (cm)	173 (166–180)	172 (167–179)	173 (166–180)	n.s.	174 (168–180)	172 (165–180)	<0.01
Weight (kg)	77 (66–88)	74 (63–87)	78 (67–89)	<0.01	75 (65–89)	77 (66–88)	n.s.
BMI (kg m ⁻²)	25.4 (22.6–28.9)	24.7 (21.9–28.3)	25.5 (22.7–29.0)	<0.01	25.1 (22.0–28.7)	25.5 (22.7–29.0)	n.s.
Chronic arterial hypertension	773 (37.9)	151 (41.0)	622 (37.3)	n.s.	213 (42.3)	560 (36.5)	0.02
Pre-induction SAP (mm Hg)	135 (120–150)	130 (115–145)	135 (120–150)	<0.01	130 (120–145)	135 (120–150)	0.02
Long-term medication							
ACE inhibitor	400 (19.6)	70 (19.3)	330 (20.0)	n.s.	122 (24.6)	278 (18.3)	<0.01
AT ₁ blocker	203 (10.0)	44 (12.1)	159 (9.6)	n.s.	53 (10.7)	150 (9.9)	n.s.
β -Blocker	519 (25.5)	109 (29.9)	410 (24.8)	0.04	167 (33.6)	352 (23.1)	<0.01
Calcium antagonist	230 (11.3)	46 (12.5)	184 (11.0)	n.s.	70 (14.1)	160 (10.5)	0.03
ASA physical status classification							
I	188 (9.2)	15 (4.1)	173 (10.4)	<0.01	26 (5.2)	162 (10.6)	<0.01
II	793 (38.9)	132 (35.9)	661 (39.6)	n.s.	137 (27.2)	656 (42.8)	<0.01
III	851 (41.8)	172 (46.7)	679 (40.7)	0.03	254 (50.5)	597 (38.9)	<0.01
IV	202 (9.9)	48 (13.0)	154 (9.2)	0.03	83 (16.5)	119 (7.8)	<0.01
V	3 (0.1)	1 (0.3)	2 (0.1)	n.s.*	3 (0.6)	0 (0.0)	0.02*
MET >4 (n)	1512 (74.2)	267 (72.6)	1245 (74.6)	n.s.	319 (63.4)	1193 (77.8)	<0.01

Table 2 Univariate analysis of procedural variables for regression analysis. For continuous data, only applicable patients were considered. Data are presented as the median (25th–75th percentile) or number of patients (%). For categorical data, the χ^2 test or Fisher's exact test (*) was used, as appropriate; for continuous data, the Mann–Whitney U-test. Statistically significant differences (univariate analysis) are shown in bold. For further variables, please see the Supplemental material. n.s., non-significant

Variable	All	Post-induction hypotension		P-value	Early intraoperative hypotension		P-value
		Present n=368 (18.1)	Absent n=1669 (81.9)		Present n=503 (24.7)	Absent n=1534 (75.3)	
Emergency	254 (12.5)	58 (15.8)	196 (11.7)	0.04	89 (17.7)	165 (10.8)	<0.01
Anti-Trendelenburg positioning	7 (0.3)	2 (0.5)	5 (0.3)	n.s.*	1 (0.2)	6 (0.4)	n.s.*
Duration of surgery (min)	70 (35–150)	80 (45–160)	70 (30–150)	<0.01	95 (50–180)	65 (30–136)	<0.01
Epidural anaesthesia	76 (3.7)	19 (5.2)	57 (3.4)	n.s.	48 (9.5)	28 (1.8)	<0.01
Spinal anaesthesia	68 (3.3)	12 (3.3)	56 (3.4)	n.s.	12 (2.4)	56 (3.7)	n.s.
Post-induction cardiovascular medication							
Norepinephrine bolus (μ g; cumulative)	20 (10–30)	20 (10–30)	20 (10–30)	n.s.	20 (10–40)	15 (10–25)	<0.01
Norepinephrine infusion (μ g min ⁻¹)	4.0 (3.0–6.0)	3.0 (3.0–5.0)	8.0 (5.0–10.0)	<0.01	5 (3–10)	3 (3–5)	<0.01
Intraoperative cardiovascular medication							
Norepinephrine bolus (μ g; cumulative)	20 (10–30)	20 (10–40)	15 (10–30)	n.s.	20 (10–39)	15 (10–30)	n.s.
Norepinephrine infusion (μ g min ⁻¹)	5 (3–8)	7 (4–10)	5 (3–7)	<0.01	9 (7–12)	4 (3–5)	<0.01

Discussion

We hypothesized that different factors induce arterial hypotension during different phases of surgery under general anaesthesia; therefore, we defined different phases of IOH and identified factors associated with general anaesthesia-related hypotension in the post-induction (PIH) and early intraoperative (eIOH) phases.

The main findings of this retrospective analysis can be summarized as follows. In general surgical patients, lower pre-induction SAP, older age, and emergency surgery are independently associated with PIH. Factors independently associated with eIOH were lower pre-induction SAP, older age, emergency surgery, supplementary administration of spinal or epidural anaesthetic techniques, male sex, and ASA PS IV.

Table 3 Independent variables and variable categories significantly associated with post-induction and early intraoperative hypotension. CI, confidence interval; OR, odds ratio; SAP, systolic arterial pressure

Variable	OR (95% CI)	P-value
Post-induction hypotension		
Emergency surgery	1.75 (1.20–2.56)	<0.01
Age (yr)	1.03 (1.02–1.04)	<0.01
Pre-induction SAP (mm Hg)	0.97 (0.97–0.98)	<0.01
Early intraoperative hypotension		
Emergency surgery	1.83 (1.28–2.62)	<0.01
Spinal or epidural anaesthesia (additional)	3.57 (2.41–5.29)	<0.01
Male sex	1.41 (1.12–1.79)	<0.01
Age (yr)	1.02 (1.02–1.03)	<0.01
Pre-induction SAP (mm Hg)	0.99 (0.98–0.99)	<0.01
ASA class IV	2.18 (1.19–3.99)	0.01

We defined the post-induction period for the definition of PIH as the time span from induction of anaesthesia until 20 min after induction to ensure detection of arterial hypotension associated with anaesthesia induction without concomitant surgical stimulus and including the early post-induction phase, during which hypotension is most prevalent.¹² Additional factors, such as administration of regional anaesthetic techniques, intraoperative patient positioning, surgical interventions, or bleeding may become relevant with the beginning of the operation. Thus, we additionally investigated arterial hypotension in the early intraoperative period and defined eIOH; this we restricted to the first 30 min of surgery, because we aimed to account for anaesthesia-related and surgical influences that can potentially be modified *a priori*, but not complex surgery-related factors (e.g. major haemorrhage, haemodynamically relevant surgical manoeuvres, or secondary systemic inflammatory response). These factors may conceivably become relevant during the more advanced intraoperative period in terms of late IOH (Fig. 1). Distinguishing between PIH and eIOH might allow preventive and therapeutic measures customized to the individual patient and procedural phase.

In comparison with previous studies on factors associated with IOH, some of our findings warrant further discussion. In our study, lower baseline SAP as measured directly before anaesthesia induction was independently associated with PIH and eIOH in our general patient population.

The association of pre-induction ABP values and IOH has been investigated and discussed before.¹³ Our findings regarding this issue are in line with recent data from Cheung and colleagues¹³ showing that preoperative hypotension (i.e. SAP <110 mm Hg) was predictive for IOH in their statistical model. The means by which this finding might be used in the prevention of IOH remains to be determined. Discontinuation of renin-angiotensin-aldosterone system antagonists in patients with chronic arterial hypertension has been shown to decrease the risk of IOH. This might, in theory, be attributable in part to an increase in pre-induction ABP values, which in turn might decrease the risk of IOH. Whether treatment of preoperative hypotension may be beneficial is unclear and awaits further investigation. Of note, especially in asymptomatic patients, low baseline ABP values may be chronic and have therefore led to adjustment of the vascular autoregulation curve. Therefore,

somewhat lower intraoperative ABP values may be tolerable in this individual patient subgroup. Others have elaborated on the role of preoperative hypertension and the indication of pretreatment even at the expense of timely surgery and came to the conclusion that, if not extreme, hypertensive ABP values are tolerable if haemodynamics are handled cautiously in the perioperative period.¹⁴ Moreover, it remains to be determined whether lowering of baseline ABP values, which has been shown to normalize vascular autoregulation ranges,¹⁵ would be feasible given the urgency of many surgical interventions in our patient population. However, pre-emptive elevation of preoperative baseline values, such as by volume loading or the use of catecholamines pre-induction, might alleviate some of the adverse haemodynamic effects of anaesthetics.^{16–17} The results from our study may be used as a basis for the indication of such proactive measures.

Besides lower pre-induction SAP, older age was an independent risk factor for PIH and eIOH in our study. Recent studies by Cheung and colleagues¹³ and Reich and colleagues¹² also revealed an association in their respective multivariate regression analyses for an age of ≥ 66 and ≥ 50 yr, respectively.

Emergency surgery in our study was associated with PIH and eIOH. This finding might reflect the fact that patients undergoing emergency surgery in contrast to elective surgery are more likely to suffer from cardiocirculatory dysfunction because of their underlying disease. The same might hold true for patients categorized as ASA PS IV, which was predictive for eIOH but not PIH. The finding that supplementary neuraxial block is associated with eIOH but not PIH is self-explanatory, bearing in mind the delayed onset of local anaesthetic effects commonly used in spinal and epidural anaesthesia (i.e. mepivacaine, bupivacaine), with well-established effects on the incidence rate of acute arterial hypotension mediated by a depression of the sympathetic trunk.¹⁸ In addition, the injection of an effective bupivacaine bolus in patients with an epidural catheter immediately before the beginning of surgery explains the delayed haemodynamic side-effect from neuraxial block in these patients.

Definite conclusions about the pathophysiological mechanism by which male sex is independently associated with eIOH cannot be drawn from our data. This factor may need further investigation in the context of personalized medicine and pharmacogenetics.

We defined general anaesthesia-related hypotension, namely PIH or eIOH, using an absolute threshold value of SAP <90 mm Hg. A recent study supports this approach, showing that definitions of IOH using absolute ABP thresholds might lead to similar conclusions when assessing a patient's risk of postoperative IOH-related end-organ damage compared with a relative decline from an averaged preoperative ABP baseline value.¹⁹ In addition, we considered high norepinephrine doses to be an appropriate surrogate parameter for anaesthesia-related hypotension, because it is the routinely used vasopressor in patients undergoing general anaesthesia in our institution and is commonly indicated in the prevention and treatment of IOH, thus masking decreased SAP. It has to be mentioned as a limitation, however, that the decision to administer norepinephrine was at the discretion of the treating anaesthetist. One might argue that this definition of arterial hypotension was arbitrarily chosen; nevertheless, considering the variety of different definitions used in previous studies,¹ this definition seemed to be pathophysiologically sound and pragmatic with respect to our study design.

Moreover, our study does not take into consideration information on the duration of hypotensive episodes. A previous study showed that longer durations of hypotensive episodes

are associated with further increased perioperative morbidity rates.⁶ Even though it has been shown in the same study that intraoperative hypotensive episodes of as little as 1–5 min can be associated with an unfavourable outcome,⁶ the duration of hypotension should be considered in future studies using prospective designs.

In addition to the definition of arterial hypotension, our study has several limitations. Although our data were collected in a large number of unselected patients undergoing general anaesthesia, our findings might not be applicable to other settings because all patients underwent surgery under general anaesthesia in a single university medical centre, treating the patients according to local clinical standards. As examples, norepinephrine is the vasopressor of choice for stabilization of anaesthesia-related blood pressure instability in our department, whereas different agents might be used to this end in other institutions. In addition, other unique local practices concerning the approach to the individual patient may be implicit in nature, and thus not measurable, while very well having an impact both on some of the independent variables and on the occurrence of PIH and eIOH. Norepinephrine doses were recorded as standardized units and might instead be weight related in future data sets. Moreover, owing to the study design, our study does not allow us to make a statement on the effect of PIH and eIOH on clinical outcome variables (e.g. myocardial injury, renal failure, or stroke), because it was designed to find differentiated prediction models that enable the clinician to estimate the patients' risk for the highly incidental phenomenon of acute anaesthesia-associated arterial hypotension. If, in future studies, the predictive values of PIH or eIOH could be demonstrated in terms of the development of IOH, as defined by previous studies that showed its association with increased perioperative morbidity and mortality rates,^{9–11} this would be an important extension of our findings. To enable this, investigation of high-risk patients might be the preferred approach. We cannot make a statement on the predictive value of factors other than the independent variables in our models. Finally, we concentrated on PIH and eIOH; therefore, factors associated with late IOH in different patient collectives undergoing prolonged surgical procedures need to be elucidated in future studies.

Conclusions

There are distinct phases of IOH that differ in the underlying causative mechanism leading to arterial hypotension. We investigated PIH and eIOH in this retrospective study, which demonstrates that lower pre-induction SAP, older age, and emergency surgery are factors independently associated with both PIH and eIOH. In addition, we found that supplementary administration of spinal or epidural anaesthetic techniques, male sex, and ASA PS IV are independently associated with eIOH. Although further research is required to characterize the prevalence and causes of different phases of IOH, these findings may enable pre-emptive risk optimization through early implementation of continuous haemodynamic monitoring and intervention with regard to PIH and eIOH.

Authors' contributions

Study conception and design: S.S., B.S.
Supervision of the study: B.S.
Acquisition of data: S.S., S.B., P.C.R.
Statistical analyses: S.S., S.B., H.O.P., B.S.

Data analysis and interpretation: S.S., S.B., J.Y.W., P.C.R., H.O.P., D.A.R., B.S.

Drafted the manuscript: S.S., B.S.

Critical revision of the manuscript for important intellectual content: S.B., J.Y.W., P.C.R., H.O.P., D.A.R.

All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Declaration of interest

None declared.

References

1. 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
2. Bayliss WM. On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* 1902; **28**: 220–31
3. Harper AM. Autoregulation of cerebral blood flow: influence of the arterial blood pressure on the blood flow through the cerebral cortex. *J Neurol Neurosurg Psychiatry* 1966; **29**: 398–403
4. Mosher P, Ross J Jr, McFate PA, Shaw RF. Control of coronary blood flow by an autoregulatory mechanism. *Circ Res* 1964; **14**: 250–9
5. Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery. *Anesthesiology* 2012; **116**: 658–64
6. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**: 507–15
7. Chang HS, Hongo K, Nakagawa H. Adverse effects of limited hypotensive anesthesia on the outcome of patients with subarachnoid hemorrhage. *J Neurosurg* 2000; **92**: 971–5
8. Aronson S, Phillips-Bute B, Stafford-Smith M, et al. The association of postcardiac surgery acute kidney injury with intraoperative systolic blood pressure hypotension. *Anesthesiol Res Pract* 2013; **2013**: 174091
9. Tassoudis V, Vretzakis G, Petsiti A, et al. Impact of intraoperative hypotension on hospital stay in major abdominal surgery. *J Anesth* 2011; **25**: 492–9
10. Mascha EJ, Yang D, Weiss S, Sessler DI. Intraoperative mean arterial pressure variability and 30-day mortality in patients having noncardiac surgery. *Anesthesiology* 2015; **123**: 79–91
11. Monk TG, Bronsert MR, Henderson WG, et al. Association between intraoperative hypotension and hypertension and 30-day postoperative mortality in noncardiac surgery. *Anesthesiology* 2015; **123**: 307–19
12. Reich DL, Hossain S, Krol M, et al. Predictors of hypotension after induction of general anesthesia. *Anesth Analg* 2005; **101**: 622–8
13. Cheung CC, Martyn A, Campbell N, et al. Predictors of intraoperative hypotension and bradycardia. *Am J Med* 2015; **128**: 532–8

14. Howell SJ, Sear JW, Foëx P. Hypertension, hypertensive heart disease and perioperative cardiac risk. *Br J Anaesth* 2004; **92**: 570–83
15. Fu CH, Yang CC, Kuo TB. Effects of different classes of antihypertensive drugs on cerebral hemodynamics in elderly hypertensive patients. *Am J Hypertens* 2005; **18**: 1621–5
16. Ngan Kee WD, Khaw KS, Ng FF, Lee BB. Prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. *Anesth Analg* 2004; **98**: 815–21
17. Ripollés Melchor J, Espinosa Á, Martínez Hurtado E, et al. Colloids versus crystalloids in the prevention of hypotension induced by spinal anesthesia in elective cesarean section. A systematic review and meta-analysis. *Minerva Anesthesiol* 2015; **81**: 1019–30
18. Kasaba T, Kondou O, Yoshimura Y, Watanabe Y, Takasaki M. Haemodynamic effects of induction of general anaesthesia with propofol during epidural anaesthesia. *Can J Anaesth* 1998; **45**: 1061–5
19. Salmasi V, Maheshwari K, Yang D, et al. 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

Handling editor: J.P. Thompson