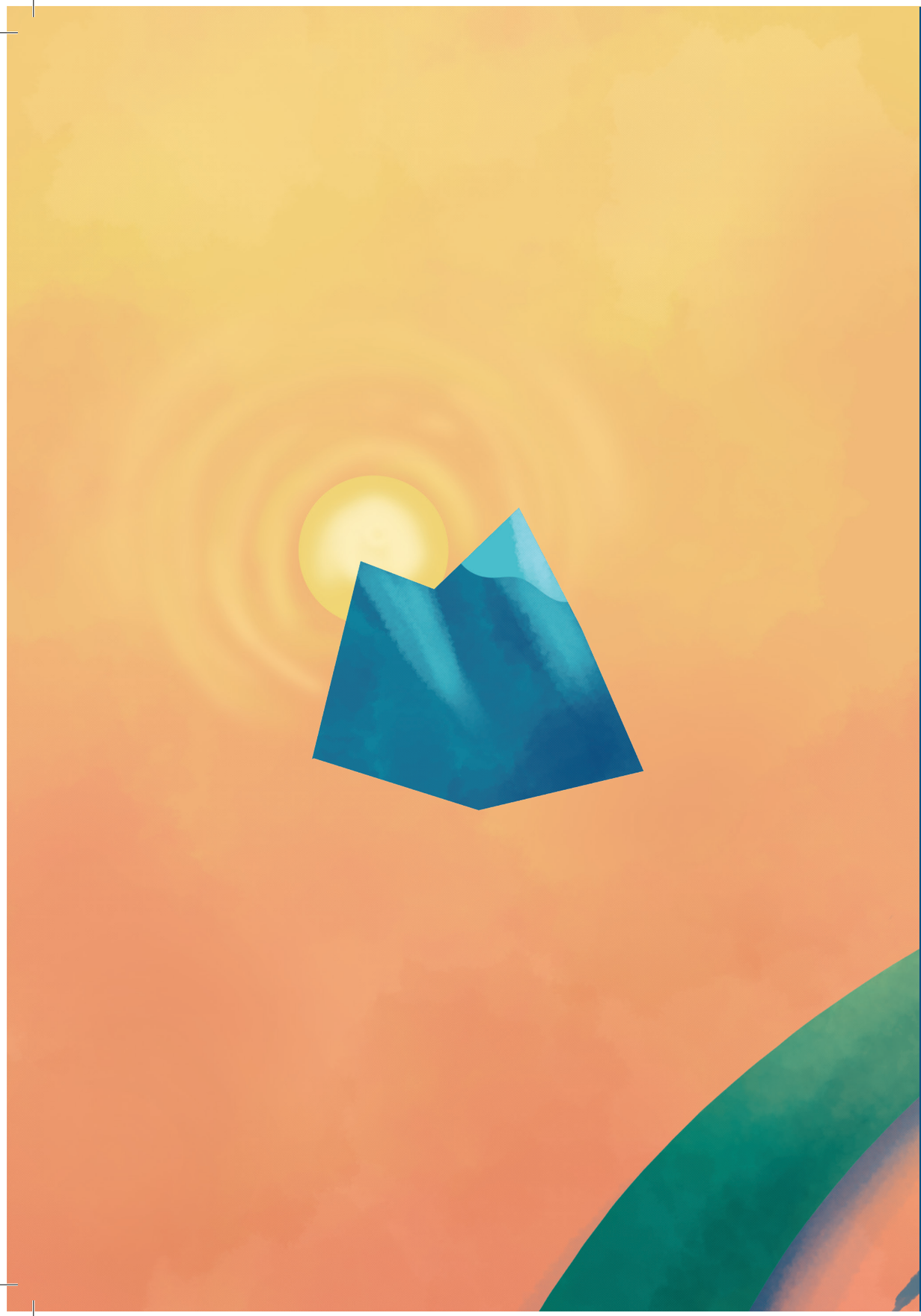
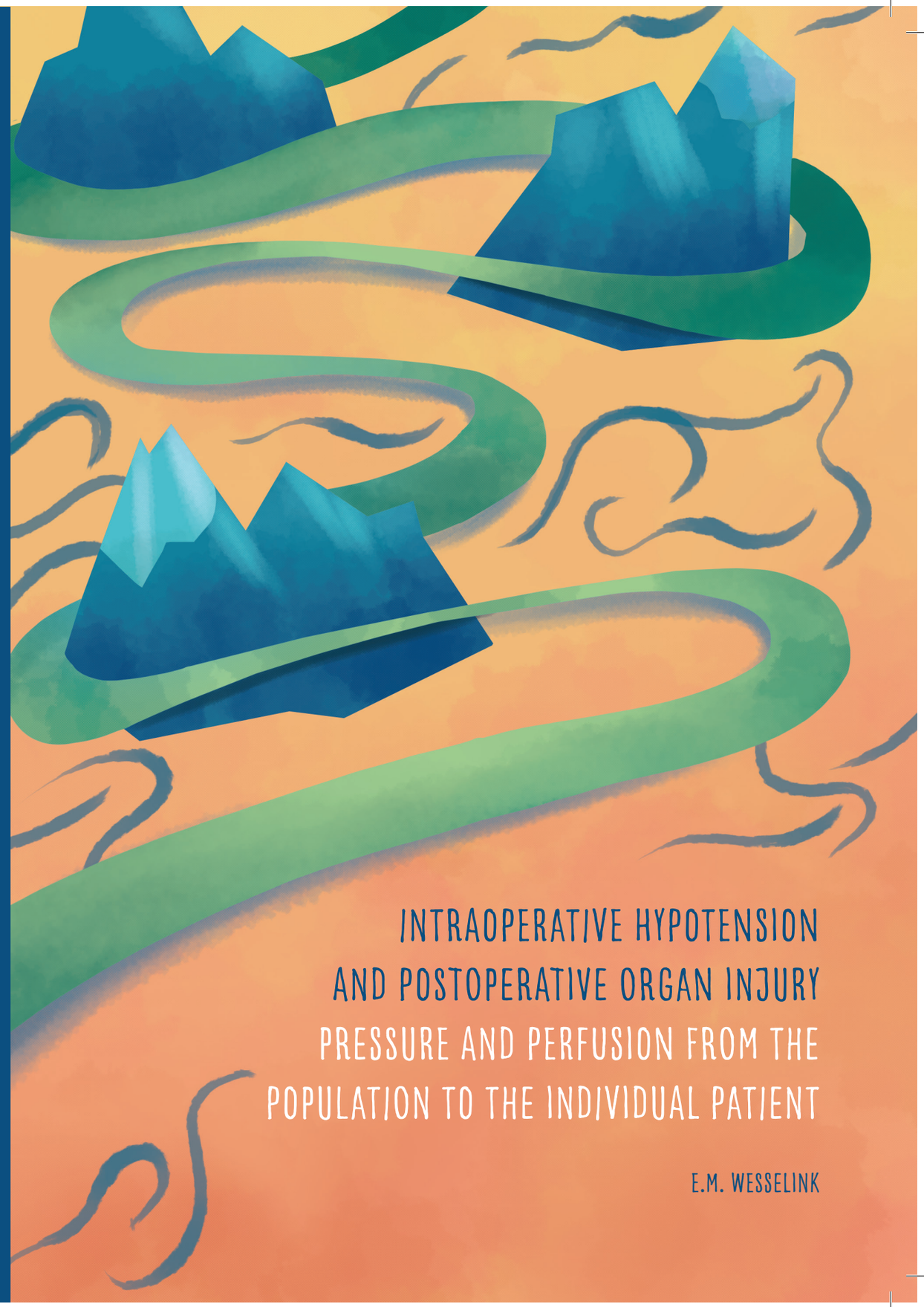


INTRAOPERATIVE HYPOTENSION AND POSTOPERATIVE ORGAN INJURY

E.M. WESSELINK



INTRAOPERATIVE HYPOTENSION AND POSTOPERATIVE ORGAN INJURY

PRESSURE AND PERFUSION FROM THE POPULATION TO THE INDIVIDUAL PATIENT

E.M. WESSELINK

INTRAOPERATIVE HYPOTENSION AND POSTOPERATIVE ORGAN INJURY

PRESSURE AND PERFUSION FROM THE POPULATION TO THE INDIVIDUAL PATIENT

E.M. WESSELINK

Intraoperative hypotension and postoperative organ injury
Pressure and perfusion from the population to the individual patient

Dutch title:
Intraoperatieve hypotensie en postoperatieve orgaanschade
Druk en perfusie van de populatie naar de individuele patiënt

University Medical Center Utrecht, Utrecht University, the Netherlands
Thesis, with a summary in Dutch

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(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus,
prof. dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op dinsdag 1 juni 2021 des middags te 2.15 uur

door

Esther Maria Wesselink
geboren op 21 september 1987
te Oldenzaal

Promotoren: Prof. dr. W.A. van Klei
Prof. dr. A.J.C. Slooter

Co-promotor: Dr. T.H. Kappen

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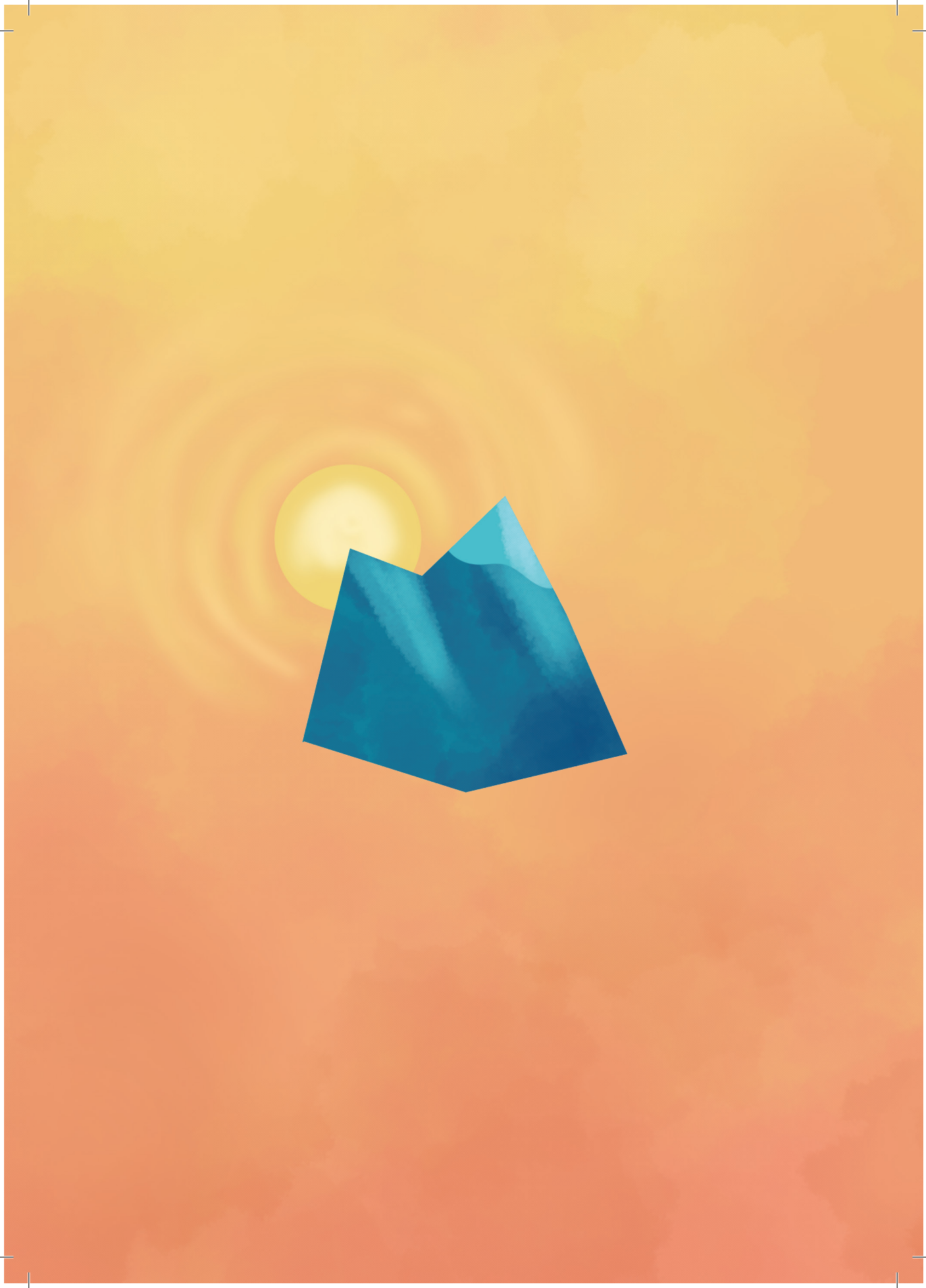
PART 1

INTRAOPERATIVE HYPOTENSION AND ORGAN PERFUSION AT POPULATION LEVEL



CHAPTER 1

INTRODUCTION

INTRODUCTION

Homeostatic disturbances are common during anaesthesia and surgery. The clinical condition, administration of anaesthesia-related medication and surgical stress undermine homeostasis and the intrinsic physiological regulatory mechanisms of the surgical patient [1–4]. In the perioperative period, the anaesthetist try to strive for maintaining or restoring the normal physiological situation. To that aim, monitoring of various vital parameters, for example with regard to respiration and blood flow in the perioperative period is essential.

The circulatory system is important for the maintenance of oxygen- and nutrients supply and removal of carbon dioxide and other waste products created by cell metabolism. Cardiac output is a measure for the amount of blood the heart pumps through the circulatory system in one minute and is determined by the heart rate and stroke volume. However, it is difficult to obtain accurate, non-invasive cardiac output measurements [5–9]. Blood pumped from the heart travels along the arteries, arterioles, capillary beds and veins return back to the heart. Along this circulatory system, the systemic vascular resistance varies to a great extent, thereby influencing the blood pressure. So, similar to the law of Ohm: blood pressure is a product of the flow (i.e. cardiac output) and vascular resistance [10]. According to the law of Hagen-Poiseuille, a difference in blood pressure is essential for blood flow [11–14]. Blood pressure is often used as a surrogate parameter to get an impression of the circulatory system function. Blood pressure measurements are routinely performed to detect intraoperative haemodynamic derangements. Anaesthetists are often faced with low intraoperative blood pressure, often with a multifactorial aetiology. Common causes of intraoperative hypotension are:

- Hypovolaemia (fasting, dehydration) and bleeding [15, 16]
- Unequal blood distribution or vasodilation (administration of anaesthetic medication, neuraxial anaesthesia, allergic reactions, sepsis, spinal cord injury) [17–19]
- Cardiac dysfunction (perioperative cardiac condition, use of cardiodepressant medication, arrhythmias) [17, 18, 20]
- Obstruction of blood flow (pneumothorax, cardiac tamponade) [16]

Blood pressure and cardiac output are both essential for blood flow and organ perfusion (so no organ perfusion without blood pressure). However, although they are related, they are not the same. Simply treating blood pressure values does not automatically lead to improvement of organ perfusion. A normal or high blood pressure does not guarantee adequate organ perfusion. Treatment, for example with vasopressors, might raise blood

pressure values, but it not necessarily improves organ perfusion. One explanation is that an increase of the vascular resistance might improve macrocirculation and the values on the monitor, but that it might impair microcirculation and subsequent organ perfusion [21–23].

Insight in physiological and pharmacological mechanisms is essential for the understanding and intervention of intraoperative hypotension in its clinical context. It remains important to be aware of the clinical context, i.e. the likelihood of certain hypotension mechanisms and adjustments based on (the lack of) blood pressure response after treatment in daily practice. The concept of 'one blood pressure threshold for all' is probably too simple when solely intraoperative blood pressure values without any context are studied and their association with postoperative organ injury. This can be explained based on a comparison of the two hypothetical patients below.

- Patient 1: 80-year old male with hypertension, peripheral artery disease, diabetes mellitus and chronic kidney injury who is scheduled for coronary artery bypass grafting. This patient has a high risk of occurrence of intraoperative hypotension due to for example preoperative antihypertensive drugs, anticoagulants, vascular dysfunction and probability of blood loss. The type of surgery, diabetes mellitus and preoperative kidney disease increase the risk of postoperative myocardial injury and acute kidney injury. In addition, major surgery and his age makes him more prone to develop a postoperative delirium.
- Patient 2: 39-year old female without a medical history or medication scheduled for strabismus surgery. During this short procedure, the risk of prolonged hypotension is negligible and the probable hypotension mechanisms are limited (cardiac dysfunction and blood loss are not expected). Absence of cardiovascular comorbidities or perioperative medication and different type of surgery result in a lower organ injury risk.

When comparing these patients, it is likely that there is both variation in intraoperative blood pressure course and the risk of postoperative organ injury between patients, even if they would undergo similar surgical procedures. This raises the question: which blood pressure is too low for an individual patient?

Objectives of this thesis

The main objective of the thesis was to study when intraoperative blood pressures are too low. This main objective was studied at different levels:

- Influence of intraoperative hypotension on different organs: assessment of various cerebral and myocardial outcomes.
- Influence of depth and duration of intraoperative blood pressures: is the commonly used threshold-based intraoperative hypotension analysis suitable? Or do we need to develop alternative hypotension analysis methods to deal with depth and duration of hypotension?
- Influence of different intraoperative hypotension mechanisms

Outline of this thesis

Before we studied the effect of intraoperative hypotension to more detail, first a systematic review was performed. In this review, an overview of the current knowledge about the relation between intraoperative hypotension and postoperative organ injury and mortality after noncardiac surgery is provided (**Chapter 2**). The results of this review show limited knowledge of the relation between intraoperative hypotension and cerebral outcomes. Therefore, we performed two studies in which occurrence of postoperative delirium was studied. In a substudy of the Dexamethasone for Cardiac Surgery trial, the association between area under two absolute and two relative mean blood pressure thresholds was related to occurrence of postoperative delirium after cardiac surgery (**Chapter 3**). The second study on postoperative delirium was performed in a cohort of patients who underwent transcatheter aortic valve replacement (**Chapter 4**). In the next study on cerebral outcomes, there was a focus on a particular hypotension mechanism. The effects of perioperative β-blockers and β-blocker selectivity on occurrence of intraoperative hypotension and the need for a temporary shunt during carotid endarterectomy were studied (**Chapter 5**). In the last two chapters, the focus shifted from cerebral outcomes to individual intraoperative blood pressure dynamics in the complex intraoperative context. Two new intraoperative hypotension analysis methods were developed which consider the depth and duration without a low cut-off threshold. In this study, these analysis methods were applied to intraoperative blood pressure data of a large cohort of patients who underwent noncardiac surgery (**Chapter 6**). Additionally, the effects of blood pressure components in relation to hypotension mechanisms was studied. Intraoperative arterial waveform parts were decomposed and analysed in relation to mean blood pressure change after a bolus of phenylephrine or ephedrine (**Chapter 7**). The final chapter provides a **General discussion** of this thesis and considers the impact of intraoperative blood pressures on postoperative organ dysfunction.

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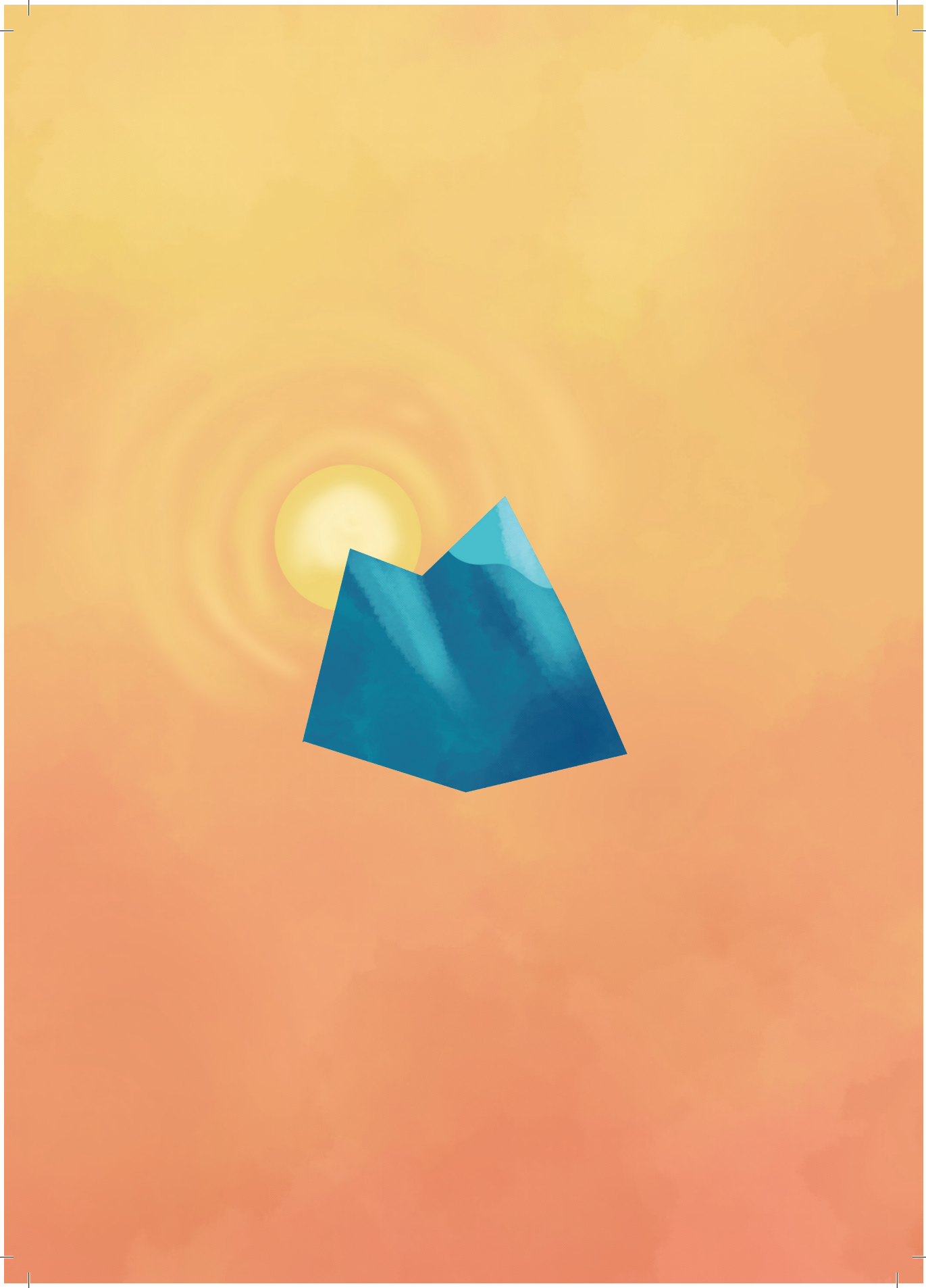

CHAPTER 2

INTRAOPERATIVE HYPOTENSION AND THE RISK OF POSTOPERATIVE ADVERSE OUTCOMES: A SYSTEMATIC REVIEW

E.M. Wesselink, T.H. Kappen, H.M. Torn, A.J.C. Slooter, W.A. van Klei

British Journal of Anaesthesia 2018; 121(4): 706-721.

ABSTRACT

Background: Intraoperative hypotension is a common side effect of general anaesthesia and might lead to inadequate organ perfusion. It is unclear to what extent hypotension during noncardiac surgery is associated with unfavourable outcomes.

Methods: We conducted a systematic search in PubMed, Embase, Web of Science, and CINAHL, and classified the quality of retrieved articles according to predefined adapted STROBE and CONSORT criteria. Reported strengths of associations from high-quality studies were classified into end-organ specific injury risks, such as acute kidney injury, myocardial injury, and stroke, and overall organ injury risks for various arterial blood pressure thresholds.

Results: We present an overview of 42 articles on reported associations between various absolute and relative intraoperative hypotension definitions and their associations with postoperative adverse outcomes after noncardiac surgery. Elevated risks of end-organ injury were reported for prolonged exposure (≥ 10 min) to mean arterial pressures < 80 mmHg and for shorter durations < 70 mmHg. Reported risks increase with increased durations for mean arterial pressures < 65 – 60 mmHg or for any exposure < 55 – 50 mmHg.

Conclusions: The reported associations suggest that organ injury might occur when mean arterial pressure decreases < 80 mmHg for ≥ 10 min, and that this risk increases with blood pressures becoming progressively lower. Given the retrospective observational design of the studies reviewed, reflected by large variability in patient characteristics, hypotension definitions and outcomes, solid conclusions on which blood pressures under which circumstances are truly too low cannot be drawn. We provide recommendations for the design of future studies.

INTRODUCTION

Intraoperative hypotension is a common side-effect of general anaesthesia and has received much attention in recent years due to its frequent occurrence and presumed adverse consequences. However, no widely accepted definition of intraoperative hypotension is available [1]. Despite this lack of a uniform definition, researchers have addressed the association between intraoperative hypotension and postoperative mortality and organ dysfunction after general anaesthesia. Monk et al. were one of the first researchers who showed a significant association between duration of intraoperative hypotension and mortality [2]. More recent landmark studies showed associations between hypotension and other adverse outcomes such as acute kidney injury (AKI) and myocardial injury (MI) [3,4].

It remains however a topic of debate if, and to what extent, hypotension disrupts organ perfusion resulting in organ damage. Furthermore, such organ damage may depend on the depth and duration of the hypotensive episodes. A summary of what is known about the effects of intraoperative hypotension on postoperative organ dysfunction and mortality is essential for anaesthetists to determine which range of blood pressures is acceptable during surgery. So far, no systematic search of the literature has been conducted to summarise the available evidence regarding the association between intraoperative hypotension and adverse postoperative outcomes. As hypotension has not clearly been defined yet, such a summary needs to include an analysis at which blood pressure threshold the association with adverse outcomes starts to become clinically relevant.

We studied the relationship between intraoperative hypotension and postoperative adverse outcomes after noncardiac surgery by performing a systematic search of the literature. We classified studies according to quality criteria, and report strengths of associations for various blood pressure thresholds and postoperative adverse outcomes.

METHODS

Search strategy and selection of articles

We conducted a systematic search of literature in Pubmed, Embase, Web of Science and CINAHL on 8 March 2017. Synonyms and medical subject headings for intraoperative hypotension were combined with synonyms and medical subject headings for complication, mortality, AKI, MI, ischaemic stroke, delirium and length of stay (LOS) as described in *Box 1*. The search filters were restricted to presence of the synonyms in titles and abstracts. No

other limits were used. The articles obtained by this search were independently screened by two reviewers (EW and HMT). In case of inconsistency, consensus was achieved by a third independent reviewer (THK). The reference lists of all selected and included articles were checked to retrieve relevant publications that were not found by the above-described search strategy. The in- and exclusion criteria for publication type, study design, hypotension and studied outcome definitions are described in *Box 2*.

Box 1 Search string

Determinant

((((hypotension[title and abstract] OR hypotensive[title and abstract]) AND (intraoperative[title and abstract] OR perioperative[title and abstract] OR intraoperatively[title and abstract] OR perioperatively[title and abstract] OR peroperative[title and abstract] OR peroperatively[title and abstract]))))).

Outcome

(mortal*[title and abstract] OR death[title and abstract] OR 'moribund'[title and abstract] OR die*[title and abstract] OR fatal[title and abstract]) OR ((kidney[title and abstract] OR renal[title and abstract]) AND (insuff*[title and abstract] OR failure[title and abstract] OR injury[title and abstract] OR 'ATN'[title and abstract]) OR (((heart[title and abstract] OR myocard*[title and abstract] OR cardial[title and abstract] OR coronary[title and abstract]) AND (ischem*[title and abstract] OR ischaem*[title and abstract] OR infarct*[title and abstract]) OR (acute AND coronary AND syndrome[title and abstract] OR ACS[title and abstract])) OR (((Brain[title and abstract] OR cerebr*[title and abstract]) AND (Vascular[title and abstract] OR cerebrovascular[title and abstract]) AND (embol*[title and abstract] OR accident*[title and abstract] OR complication*[title and abstract] OR ischaem*[title and abstract] OR ischem*[title and abstract] OR infarct*[title and abstract] OR incident*[title and abstract] OR stroke[title and abstract] OR stroke*[title and abstract] OR apoplexy[title and abstract]) OR (((Delirium[title and abstract] OR Deliriou*[title and abstract])) OR ((admission[title and abstract] OR stay[title and abstract]) AND (day*[title and abstract] OR duration[title and abstract] OR LOS[title and abstract] OR length[title and abstract]) OR (morbidity[title and abstract] OR complication[title and abstract] OR 'adverse event'[title and abstract] OR 'adverse events'[title and abstract]))

Data extraction and quality assessment

Data on study design, hypotension definitions, studied outcomes and (adjusted) strengths of association were extracted from all included studies (*Table 1 and Table 2*). Commonly reported baseline characteristics were summarised by calculating weighted means of medians across study groups for each variable (*Table 2*). Two reviewers (EMW and HMT) independently assessed the methodological quality of the included articles. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria

and Consolidated Standards of Reporting Trials (CONSORT) criteria were adapted and used for the composition of a checklist with predefined quality criteria [5 6] These criteria focused on the internal validity, external validity, bias and precision (*Supplementary table 1 in Appendix 1*). In short, all criteria on study design were scored as positive (+), negative (-), unclear (?) or not applicable (NA). The latter option was used when the criterion was not appropriate for the specific study design, such as loss-to-follow-up for a case-control study. Depending on the type of study design, a maximum of 13 'positive' items (case-control studies), 14 items (randomised clinical trials; RCTs) or 15 items (cohort studies) could be assigned (*Table 1 and Supplementary table 1 in Appendix 1*). Disagreements between both reviewers were discussed. In case of persistent disagreement, the third reviewer made the final decision. Whereas the maximum score depended on study type, normalisation was achieved by calculating the quality score, defined as the number of positive items divided by the maximum number of items for that study type and expressed as a percentage.

Box 2 Selection criteria

Publication type

- The articles are full reports and published before 8 March 2017.
- The article was written in English or Dutch.

Study design

- Studies in which the majority (≥ 50%) of the adult patients underwent general anaesthesia or general anaesthesia combined with local or regional anaesthesia for noncardiac surgery were included. Studies in animals or children and emergency procedures for ruptured vessels were excluded.
- Studies were excluded when they selected a subgroup of patients with a specific comorbidity that was not part of the reason to perform the surgical procedure.
- The study design had to be a randomised controlled clinical trial, a cohort study or a case-control study with more than 10 patients. Case series, case reports, meta-analyses and (systematic) reviews were excluded.
- The association between intraoperative hypotension and at least one outcome (mortality, acute kidney injury, myocardial injury, stroke, delirium, length of stay) had to be reported. The definition of determinant or outcome did not belong to the in- or exclusion criteria. Studies focusing on intentional or induced IOH or on the effects of antihypertensive medication were excluded.

Definition of intraoperative hypotension

- Intraoperative hypotension had to be defined in the article as an absolute or relative blood pressure threshold. Blood pressure thresholds had to be clinically relevant (i.e. not a mean blood pressure < 100 mmHg or more than 5% decrease compared to baseline blood pressure).

RESULTS

Included studies

In total, our search strategy yielded 5,224 articles. After removal of duplicates (n = 1,955) and removing articles based on screening of title and abstract (n = 3,128), 131 abstracts adhered to the inclusion and exclusion criteria and the corresponding articles were retrieved (*Figure 1*). After assessment of the full publications, 89 articles were excluded with the third reviewer adjudicating 10 of them. Eventually, 42 papers published between 2002 and 2017 were included for data extraction and quality assessment (*Table 1 and Supplementary table 2 in Appendix 1*). Eighteen studies (43%) had a quality score ≥ 80%, whereas the median quality score of the articles was 73% (interquartile range 49 – 80%) (*Table 1 and Supplementary table 2 in Appendix 1*).

Two observational substudies of RCTs were included in which postoperative effects of intraoperative hypotension were analysed. One RCT focused on goal-directed therapy during major abdominal surgery [7]. The other RCT investigated the efficacy of N-acetylcysteine in the prevention of acute kidney injury during elective abdominal aorta repair [8]. In these two trials, both intervention arms were analysed for the association between intraoperative hypotension and AKI.

Patient characteristics

The number of included patients in the 42 included studies varied from 40 to 152,445 (*Table 2: panel 'Studies'*),[9 10] with a median of 1,523 patients (IQR 261 – 17,739). In four studies (10%), the reported mean or median age was below 50 years and in seven studies the reported mean or median age was above 70 years. (*Table 2: panel 'Demographics'*). Information about sex was reported in 40 studies. In 26 studies, the number of included females and males was comparable (40-60%), while in the remainder either males or females were overrepresented. Twenty-three studies (55%) provided information about the American Society of Anesthesiologists (ASA) classification of the included patients (*Table 2: panel 'Comorbidity'*). In 36 studies (86%) any baseline information was reported on the occurrence of stroke, hypertension, diabetes, coronary artery disease or renal disease. In 15 (42%) of these 36 studies, information on at least four of these five conditions was reported. Twenty-six studies (72%) provided information on preoperative hypertension. In 22 of these 26 studies (85%), hypertension was found in ≥ 40% of the included patients. In 22 studies (52%) all patients underwent general anaesthesia, in one study less than 50% of the patients underwent general anaesthesia and twelve studies (24%) did not report any information on type of anaesthesia nor was it obvious from the included surgical procedures that it always had to be general anaesthesia. In several studies (n = 12; 29%), large groups of patients underwent

abdominal surgery, among which liver transplantation (n = 3 studies; 7%). Other frequent types of surgery were orthopaedic (n = 7 studies; 17%) and vascular surgery (n = 7 studies; 17%). In 11 studies (26%), no information was reported on type of surgery (*Table 2: panel 'Procedure characteristics'*).

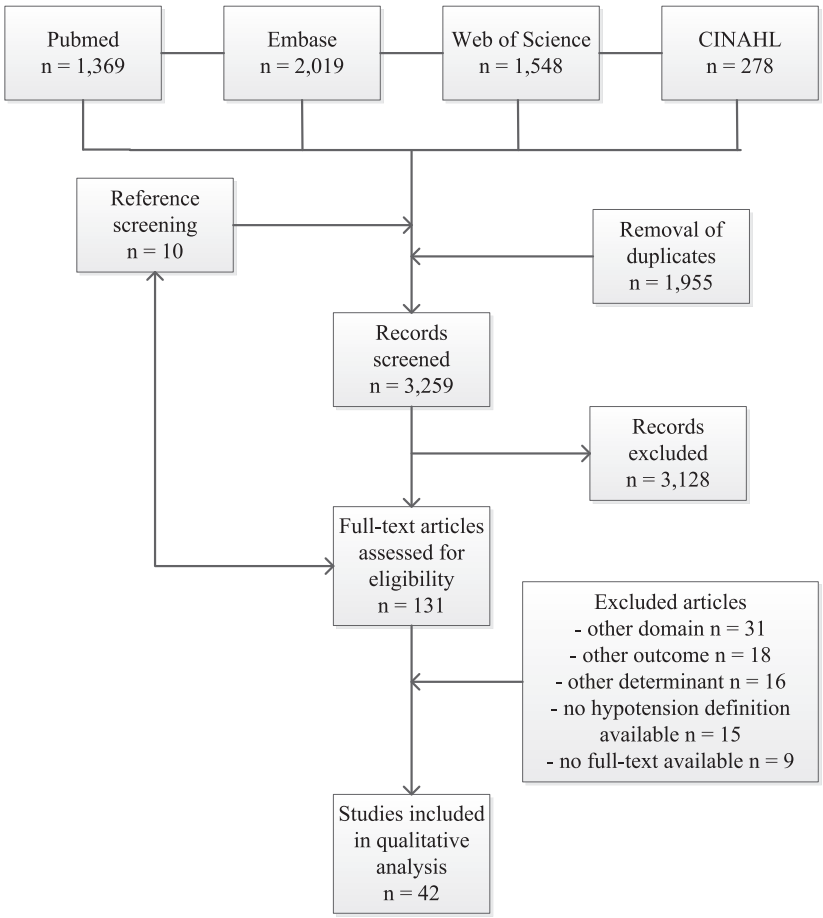

Figure 1 Flow chart of search strategy and article selection of studies on intraoperative hypotension and postoperative adverse outcomes

Intraoperative hypotension definitions

Types of blood pressure thresholds

In most studies, one or more hypotension definitions included a threshold based on absolute blood pressures (*Table 2: panel 'Intraoperative hypotension'*). Of the 42 studies, 29 (69%) used an intraoperative hypotension definition based on an absolute mean blood pressure

threshold and 17 studies (40%) used hypotension definition based on an absolute systolic blood pressure threshold. Seventeen (40%) studies used a hypotension definition based on a relative blood pressure threshold (a percentagewise or absolute decrease from baseline blood pressure). In nine studies, relative mean blood pressure thresholds were used and in seven studies relative systolic blood pressure thresholds were used. One study did not report whether their relative threshold was based on a mean or systolic blood pressure [11].

Intraoperative hypotension duration

In 20 studies (48%) dichotomous analyses were performed, of which seven (17%) included minimum time duration in their hypotension definition (*Table 2: panel 'Intraoperative hypotension'*). Fifteen studies (36%) performed a comparative analysis on whether the duration of hypotension was associated with any of the studied outcomes. Two studies (5%) analysed time as the duration in minutes below a blood pressure threshold. Two studies (5%) included an area under the threshold, and three studies (7%) used a different type of time-dependent analysis such as time-weighted average or percentage of the total procedure time. Four studies (10%) applied a different type of hypotension definition, e.g. lowest blood pressure, triple low conditions or blood pressure as part of the Surgical Apgar Score. Fourteen studies reported associations for a minimum hypotension duration ≥ 1 minute, eight studies ≥ 5 minutes, twelve studies ≥ 10 minutes and seven studies ≥ 20 minutes.

Reporting and aggregation of results

For the reported strengths of association for absolute blood pressure thresholds and hypotension durations, multivariable associations from etiological studies were presented when available; otherwise univariable strengths of associations were shown (*Table 3*). Strengths of associations were grouped according to (cumulative) durations of ³ 1 minute, ³ 5 minutes, ³ 10 minutes and ³ 20 minutes exposure to intraoperative hypotension below particular absolute thresholds. Studies that used a threshold that was relative to a baseline blood pressure, were grouped with the absolute threshold that corresponded with the relative departure from the reported mean baseline blood pressure or a baseline of 140/90 mmHg when no mean baseline was reported. For example, Hallqvist et al. used a relative threshold of 50% decrease in systolic blood pressure (SBP). As no mean baseline blood pressure was reported, the study was grouped with absolute thresholds SBP < 70 mmHg (50% of 140 mmHg). For studies that reported their strength of association per time-unit increase, the strengths of associations for other durations were estimated from the reported strengths of associations using the lower bound of the duration category. For example, Monk et al. 2005 reported a relative risk (RR) of 1.036 per minute that the SBP was below 80 mmHg. For the category SBP ³ 5 minutes below 80 mmHg the RR was then estimated by 1.036^5 = 1.193.

The reported strengths of associations were aggregated into single risk categories per blood pressure threshold and per hypotension duration for the five organ injury outcomes – i.e. mortality, AKI, MI, stroke and delirium – and combined into an overall organ injury risk per threshold and duration (*Table 4*). For each category, the highest association (odds ratio (OR), RR, or hazard ratio (HR)) among the available evidence of sufficient quality was classified into a risk of mild, moderate or high as defined below. Studies were considered qualitatively sufficient, when they received a quality score ≥ 80%, and defined an intraoperative hypotension analysis in their primary of secondary objectives. The highest organ injury risk for a specific blood pressure threshold and duration category was then considered to be the overall organ injury risk.

Several additional assumptions and conversions were made to compare studies and their strengths of associations. First, strengths of associations that could not be converted in to an OR, RR or HR per blood pressure threshold and duration category, were not considered in the risk categorisation summary. Second, ORs, RRs and HRs were deemed interchangeable in their magnitude, as the outcome incidences were relatively low (the rare disease assumption). Third, the cut-off to classify a strength of association as high risk was chosen at a 'doubled risk' or more ($OR/RR/HR_{high}$ ³ 2.0). The cut-off for moderate risk was chosen at half the high-risk cut-off on an exponential scale (square root (2) = 1.4 ≤ $OR/RR/HR_{moderate}$ < 2.0), with the mild-risk category starting at a minimal increased risk (1.0 < $OR/RR/HR_{mild}$ < 1.4). Fourth, all blood pressure thresholds were converted to mean blood pressure (MAP) equivalents based on a pulse pressure of 40 mmHg (i.e. a systolic blood pressure (SBP) threshold < 90 mmHg represents a blood pressure of 90/50 mmHg which is comparable to a MAP threshold of < 65 mmHg). The 40 mmHg pulse pressure was chosen, because it was considered the most plausible pulse pressure across all reported systolic blood pressure thresholds. MAP was calculated by adding systolic blood pressure to two times diastolic blood pressure divided by three. Fifth, once a specific MAP threshold and hypotension duration reached a certain risk classification, that classification carried over to all subsequent lower MAP thresholds or longer hypotension durations at the same MAP threshold. This means that a moderate risk at MAP < 60 mmHg for acute kidney injury, could not become a mild risk at MAP < 55 mmHg, nor could it become 'no risk' because no appropriate study reporting an association for that threshold was available. This reflects the assumption that lower blood pressures or longer intraoperative hypotension episodes always aggravate the risk of organ injury.

Table 1 Results of the methodological assessment of studies on intraoperative hypotension and postoperative adverse outcomes

First author (year)	Design	A	B	C	D	E	F
Hirsch 2015 [25]	cohort	+	+	+	+	+	+
Monk 2015 [31]	cohort	+	+	+	+	+	+
Willingham 2015 [32]	cohort	+	+	+	+	+	+
Bijker 2012 [23]	case-control	-	+	+	+	+	NA
Mizota 2017 [33]	cohort	-	+	+	+	+	+
Sun 2015 [3]	cohort	+	+	+	+	+	+
Schmid 2016 [7]	RCT	+	-	+	+	+	+
Roshanov 2017 [20]	cohort	+	+	+	+	+	+
Salmasi. 2017 [26]	cohort	-	+	+	+	+	+
Babazade 2016 [34]	cohort	-	+	+	+	+	+
Hallqvist 2016 [18]	cohort	-	+	+	+	+	+
Van Waes 2016 [27]	cohort	-	+	+	+	+	+
Mascha 2015 [35]	cohort	+	+	+	+	+	+
Pipanmekaporn 2014 [19]	cohort	+	-	+	+	+	?
Walsh 2013 [4]	cohort	-	+	+	+	+	+
Bijker 2009 [13]	cohort	-	+	+	-	+	+
Kheterpal 2009 [36]	cohort	+	+	+	+	+	+
Monk 2005 [2]	cohort	+	-	+	+	+	+
White 2016 [37]	cohort	-	-	+	+	+	+
Brinkman 2015 [9]	cohort	+	+	+	+	-	+
Petsiti 2015 [38]	cohort	+	+	+	+	+	+
Marcantonio 1998 [24]	cohort	+	+	+	+	+	+
Tallgren 2007 [8]	RCT	+	-	+	+	-	+
House 2016 [39]	cohort	-	-	+	+	+	+
Sessler 2012 [40]	cohort	-	+	+	+	+	?
Sabaté 2011 [22]	cohort	+	-	+	+	+	?
Taffé 2009 [12]	cohort	+	+	+	+	+	?
Sirivatanauksorn 2014 [17]	cohort	+	-	+	+	+	+
Tassoudis 2011 [41]	cohort	+	+	+	+	-	+
Stapelfeldt 2017 [10]	cohort	-	+	+	-	+	-
Jiang 2016 [42]	cohort	-	-	+	+	+	+
Yang 2016 [11]	cohort	-	+	-	+	+	+
Yue 2013 [43]	cohort	-	+	+	-	+	?
Franck 2011 [44]	cohort	-	+	+	-	+	?
Patti 2011 [45]	cohort	+	-	+	+	-	?
Vasivej 2016 [46]	case-control	-	-	+	+	+	NA

G	H	I	J	K	L	M	N	O	Quality score (%)
+	+	+	+	+	+	+	+	+	15 (100)
+	+	+	+	?	+	+	+	+	14 (93)
+	+	+	+	+	?	+	+	+	14 (93)
NA	+	+	+	+	+	+	+	+	12 (92)
+	+	+	+	+	-	+	+	+	13 (87)
+	-	+	+	+	?	+	+	+	13 (87)
+	+	+	**NA**	+	-	+	+	+	12 (86)
+	-	+	+	+	-	+	+	+	12 (80)
+	-	+	+	+	-	+	+	+	12 (80)
+	-	+	+	+	?	+	+	+	12 (80)
+	-	+	-	+	+	+	+	+	12 (80)
+	-	+	+	+	?	+	+	+	12 (80)
?	-	+	+	+	?	+	+	+	12 (80)
+	+	+	+	+	?	+	+	+	12 (80)
+	-	+	+	+	?	+	+	+	12 (80)
+	+	+	+	+	?	+	+	+	12 (80)
+	-	+	-	+	?	+	+	+	12 (80)
?	-	+	+	+	+	+	+	+	12 (80)
+	+	+	+	+	?	+	-	+	11 (73)
?	+	+	+	+	+	+	-	-	11 (73)
-	+	+	?	-	+	-	+	+	11 (73)
?	+	+	o	-	?	+	-	+	11 (73)
?	+	+	NA	+	+	+	+	-	10 (71)
+	-	+	-	+	?	+	+	+	10 (67)
?	+	+	+	+	?	+	-	+	10 (67)
?	+	+	-	+	?	+	+	+	10 (67)
?	-	+	-	+	?	+	+	+	10 (67)
?	-	+	-	+	?	+	-	+	9 (60)
?	+	+	-	-	?	+	+	-	9 (60)
?	-	+	+	+	-	+	-	+	8 (53)
?	+	-	-	-	-	+	+	+	8 (53)
-	+	-	-	-	-	+	+	-	7 (47)
?	-	-	-	+	?	+	+	+	7 (47)
?	+	+	-	-	?	-	+	+	7 (47)
?	-	-	-	+	?	+	+	+	7 (47)
NA	-	-	-	+	?	+	+	-	6 (46)

Table 1 Continued

First author (year)	Design	A	B	C	D	E	F
Thakar 2007 [47]	cohort	-	-	+	-	-	?
Barone 2002 [21]	case-control	-	+	-	-	-	NA
Lima 2003 [15]	cohort	-	-	+	-	-	+
Nakamura 2009 [14]	case-control	-	-	+	-	-	NA
Davidovic 2017 [48]	cohort	+	-	+	-	-	-
Sharma 2006 [16]	case-control	-	-	-	-	-	?

+ if sufficient information is available and positive assessment. - if insufficient information and/or negative assessment. ? : unknown. NA: not applicable.

Table 2 Summary of the patient-, surgery and hypotension characteristics of each study

Studies		Demographics						Comorbidity			
First author	Total	Age	sex	ASA				Stroke	HT	DM	CAD
year	n	years	F	1	2	3	4				
Hirsch 2015	594	74 (6)	51%	48%		–	–	4%	–	–	–
Monk 2015	18,756	60 (13)	7%	3%	26%	58%	13%	–	–	–	–
Willingham 2015	13,198	56 [44-66]	47%	9%	39%	35%	16%	any: 3%	48%	17%	20%
Bijker 2012*	48,241 (42/252)	66 [57-76]	40%	68%		32%		38%	69%	–	–
Mizota 2017 *	231	54 [44-60]	51%	-	-	-	-	-	-	19%	-
Sun 2015*	5,127	61 (14)	53%	–	–	–	–	any: 2%	48%	15%	11%
Schmid 2016*	180	66 (12)	23%	-	-	-	-	-	-	56%	20%
Roshanov 2017	14,687	65 (12)	52%	-	-	-	-	7%	47%	19%	12%
Salmasi 2017 *	57,315	56 (15)	56%	2%	38%	54%	7%	3%	49%	17%	-
Babazade 2016	2,521	56 (15)	45%	45%		50%	5%	-	42%	14%	-
Hallqvist 2016	300	67 [57 – 74]	53%	10%	46%	43%	0.3%	-	43%	8%	-
van Waes 2016 *	890	74 (8)	31%	1%	14%	36%	49%	21%	-	10%	-
Mascha 2015*	104,401	57 (18)	53%	5%	40%	47%	8%	1%	48%	17%	14%
Pipanmekaporn 2014*	719	49 (16)	29%	14%	58%	28%	–	–	18%	10%	2%
Walsh 2013*	33,330	56 (16)	50%	2%	40%	50%	8%	5%	–	13%	–

G	H	I	J	K	L	M	N	O	Quality score (%)
?	-	+	-	+	?	+	+	+	6 (40)
NA	-	+	-	+	?	+	+	-	5 (38)
?	-	-	+	+	?	+	-	-	5 (33)
NA	-	-	-	+	?	+	+	-	4 (31)
?	-	-	-	+	-	+	-	-	4 (27)
?	-	-	-	+	?	+	+	-	3 (23)

Scoring system to obtain a quality score for every included article based on 15 categories as described in *Supplementary table 1* (*Appendix 1*). Depending on the type of study design, a maximum of 13 points (case-control studies), 14 points (randomised controlled trials) or 15 points (cohort studies) were assigned.

Comorbidity		Procedure characteristics			Intraoperative hypotension		
Renal disease	Gen. anaesth	Length of surgery	Emergency surgery	Type of surgery	BP threshold type	Threshold	Analysis
any		min		most frequent			
–	71%	300 (144)	0%	orthopaedic 53%	rSBP, rMAP, aMAP	↓ > 10 - 40%, < 50 mmHg	Du, Var
19%	–	120 (72-186)	8%	general 32%	aSBP	< 80 mmHg	Du
–	100%	178 (115-259)	–	–	aMAP, TL	< 75mmHg	Du
–	–	163 (130-232)	–	vascular 48%	aSBP, aMAP, rSBP, rMAP	< 100 - 70 mmHg, < 70 - 40 mmHg, ↓ > 10 - 40%	Du
22%	100%	838 (752-960)	-	liverTX 100%	aMAP	< 40, < 50 mmHg	Du, Di
16%	–	>120: 79%	0%	general 26%	aMAP	< 65, < 60, < 55 mmHg	Du
6%	100%	-	100%	abdominal 100%	aMAP	> 70 mmHg	AR
eGFR: 79 (23)	-	-	14%	orthopaedic 20%	aSBP	< 90 mmHg	Di
1%	-	225(121)	4%	abdominal 23%	aMAP, rMAP	< 80 - 40 mmHg, ↓> 10 - 60%	Du, TWA
4%	100%	199 (142 - 265)	1%	colorectal 100%	aSBP, aMAP	< 80mmHg, < 55mmHg	Du
-	39%	-	0%	abdominal 40%	rSBP	↓ > 50%, > 5min	Di
8%	100%	191 (108)	30%	(T)EVAR 24%	aMAP	< 50, < 60 mmHg, ↓> 30%, ↓ > 40%	Du, (AUT)
6%	–	174 (114-252)	5%	–	aMAP	< 80 - 50 mmHg	Du, TWA, Var
10%	100%	142 (65)	46%	thoracic 100%	aSBP, aMAP	< 80 or < 60 mmHg, >15 min	Di
eGFR: 93 (27)	–	–	7%	–	aMAP	< 75 - 55 mmHg	Du

Table 2 Continued

Studies		**Demographics**						**Comorbidity**			
First author	**Total**	**Age**	**sex**			**ASA**		**Stroke**	**HT**	**DM**	**CAD**
year	**n**	**years**	**F**	**1**	**2**	**3**	**4**				
Bijker 2009	1,705	52 (16)	48%	38%	51%	11%		7%	22%	8%	any: 15%
Kheterpal 2009*	7,740	≥ 68: 23%	49%	–	–	–	–	any: 5%	40%	13%	–
Monk 2005	1,064	51 [37-65]	64%	13%	52%	35%		4%	33%	4%	6%
White 2016	11,085	83 [24 – 104]	72%	3%	30%	55%	12%	11%	55%	7%	-
Brinkman 2015 *	40	69 (9)	35%	-	-	-	-	-	68%	13%	-
Petsiti 2015	248	64 (11)	48%	–	–	32%		1%	47%	13%	8%
Marcantonio 1998	1,341	67 (9)	55%	–	–	–	–	–	–	–	–
Tallgren 2007*	69	67 [60-74]	22%	–	–	–	–	–	66%	7%	43%
House 2016 *	46,799	54 (13)	47%			41%		3%	43%	16%	-
Sessler 2012	24,120	–	–	–	–	–	–	–	–	–	–
Sabaté 2011	3,387	67 [47-81]▲	52%	8%	55%	33%	4%	–	–	–	RCRI ≥ 3: 7%
Taffé 2009*	147,573	55 (18)	56%	27%	48%	22%	3%	–	–	–	–
Sirivatanauksorn 2014*	81	53 (23~70)	31%	–	–	–	–	–	–	–	–
Tassoudis 2011	100	62 (14)	47%	–	32%	–	–	1%	46%	12%	8%
Stapelfeldt 2017	152,445	-	-	-	-	-	-	-	-	-	-
Jiang 2016 *	451	65 (18)	50%	-	-	-	-	-	14%	6%	-
Yang 2016 *	480	81 (6)	51%	-	71%	29%	-	-	43%	30%	43%
Yue 2013*	71	> 70: 37%	21%	–	–	–	–	–	–	11%	–
Franck 2011*	2,350	53 [41-65]	50%	50%		50%		–	–	–	–
Patti 2011*	100	70 (3)	60%	9%	41%	29%	21%	–	–	–	–
Vasivej 2016 *	55,648 (42/168)	58 (14)	52%	-	-	-	-	6%	43%	27%	23%
Thakar 2007*	504	43 (10)	83%	–	–	–	–	–	57%	26%	–
Barone 2002*	25,501	74 (11)	45%		Mean ASA: 2.9			–	40%	19%	any: 30%

Comorbidity		Procedure characteristics			Intraoperative hypotension		
Renal disease	Gen. anaesth	Length of surgery	Emergency surgery	Type of surgery	BP threshold type	Threshold	Analysis
any		min		most frequent			
–	88%	112 (73-163)	0%	general 88%	aSBP, rSBP, aMAP, rMAP	< 100 - 70 mmHg, ↓ > 10 - 40%, < 70-40 mmHg, ↓ > 10 - 40%	Du
3%	88%	–	12%	–	aSBP, aMAP, rSBP, rMAP	< 80 - 70 mmHg, < 60 - 50 mmHg, ↓ > 30 - 40%	Di?
–	100%	186 (138-258)	–	orthopaedic 26%	aSBP	< 80 mmHg	Du
14%	54%	-	-	hip surgery 100%	aSBP, aMAP	Lowest BP	Low
-	100%	228 (84)	0%	aorta 100%	aMAP	< 65 mmHg	AUT
3%	100%	232 (55)	0%	abdominal 100%	aMAP, rMAP	< 60 or < 70 mmHg + ↓ > 30%	Di
–	–	–	–	orthopaedic 43%	aSBP or rSBP	< 90 mmHg or ↓ > 33%	Di
–	100%	–	0%	aorta 100%	aMAP	< 65 mmHg, > 15 min	Di
4%	-	162 (108)	4%	-	aMAP	< 40 mmHg	Di/SAS
–	100%	–	–	–	aMAP, TL	< 70 mmHg	Du
–	61%	120 (60-248)†	7%	orthopaedic 34%	aSBP or aMAP/rMAP	< 100 mmHg or ↓ > 20 mmHg/20%, > 60 min	Di
–	67%	104 (?-?)	20%	–	rMAP	↓ > 30%, > 10 min	Di
Cr: 90 (38-168)	100%	276 (168-438)	–	liverTX 100%	aMAP	< 70 mmHg, > 30 min	Di
3%	100%	195 (71)	0%	abdominal 100%	aMAP, rMAP	< 60 or < 70mmHg + ↓ > 30%	Di
-	-	179 (118–259)	90%	-	aMAP	< 75 - 45 mmHg	Du
1%	100%	164 (62)	-	spine 100%	aSBP	< 80 mmHg	Di
-	100%	188 (32)	0%	-	r?BP	↓ > 30%	Di
23%	100%	–	38%	aorta 100%	aSBP/aMAP	< ↓ 30/ < 65 mmHg	Di
–	100%	98 (63-148)	–	–	aSBP, rSBP	< 100 or ↓> 30%, < 92 mmHg, < 80 mmHg, ↓ > 20%	Di
–	100%	121 (24)	0%	abdominal 100%	aMAP	≤ 60mmHg	Di
39%	59%	153 (78-244)	7%	-	aMAP	< 65 mmHg	Di
4%	100%	–	0%	abdominal 100%	aMAP	< 60 mmHg	Di
–	–	124 (55)	27%	–	aSBP	<100 mmHg, >10 min	Di

Table 2 Continued

Studies		Demographics						Comorbidity			
First author	**Total**	**Age**	**sex**			**ASA**		**Stroke**	**HT**	**DM**	**CAD**
year	**n**	**years**	**F**	**1**	**2**	**3**	**4**				
Lima 2003*	92	44 (14)	48%	–	–	–	–	–	–	–	–
Nakamura 2009*	72	71 (10)	29%	–	–	–	–	any: 15%	88%	7%	any: 19%
Davidovic 2017	450	66 (7)	12%	-	-	-	-	-	70%	-	26%
Sharma 2006*	1,800	43 (9)	80%	–	–	–	–	–	57%	22%	–

Continuous variables are expressed as x (x) = mean (standard deviation) or x (x–x) = mean (range) or x [x-x] = median [interquartile range]. Categorical variables are expressed as xx% BMI or weight (W) is expressed as $kg \cdot m^{-2}$ or kg. Any definition of history of arrhythmia or renal dysfunction was included. If available, renal dysfunction was expressed as serum creatinine in $\mu mol \cdot l^{-1}$.
Other symbols: - (not available), * (values are the weighted mean values of the study groups), ▲ (median (10th – 90th percentile))

Blood pressure threshold values

After ranking the included studies according to blood pressure threshold, quality score and studied outcome, strengths of associations per threshold were compared (*Table 3: panel 'Intraoperative hypotension thresholds'*). In addition, results based on a blood pressure threshold including duration were extrapolated to longer durations of hypotension. For each reported MAP threshold between ≤ 50 mmHg and ≤ 75 mmHg (5 mmHg increments), seven to twelve studies with MAP based thresholds were available. Six studies reported on MAP thresholds ≤ 40 mmHg, ≤ 45 mmHg and ≤ 80 mmHg. There was no apparent relation between blood pressure threshold values and either quality score, intraoperative hypotension duration or studied outcome.

Studied outcomes

Fourteen studies investigated mortality, with a follow-up duration between 1 day and 1 year [2 12 13] and an outcome incidence between 0.03% (follow-up: < 1 day) and 5.6% (during hospital admission) [12 14] (*Table 3: panel 'Outcomes under study'*). Twelve studies reported on associations between intraoperative hypotension and AKI. Follow-up duration varied between 1 day and 30 days [9 15] and incidence of AKI between 2.8% (7 days) and 72% (7 days) [16 17]. Nine studies investigated myocardial injury or –infarction, with a follow-up duration between 1 day and 30 days [18–20]. The incidence of myocardial injury varied between 0.09% (in-hospital) and 30% (1 day) [20 21]. Stroke was reported in four studies, with incidences varying from 0.004% (in-hospital) and 0.09% (10 days) [22 23]. Five studies reported on delirium with incidences between 9% (2 days) and 33% (5 days) [24 25]. Another five studies reported on length of hospital stay, either prolonged LOS (three studies, incidences between 29.7% and 37%) or duration of LOS (two studies, median LOS between 4 and 7 days).

Comorbidity		Procedure characteristics			Intraoperative hypotension		
Renal disease	Gen. anaesth	Length of surgery	Emergency surgery	Type of surgery	BP threshold type	Threshold	Analysis
any		min		most frequent			
Cr: 88 (35)	100%	–	–	liverTX 100%	aMAP	< 60 mmHg	Di
11%	–	–	15%	aorta 100%	aSBP	< 70 mmHg	Di
11%	100%	-	0%	aorta 100%	aSBP	< 100 mmHg	Di
2%	100%	223 (63)	0%	abdominal 100%	aSBP	< 100 mmHg, > 5 min	Di

Abbreviations: a-: absolute threshold expressed as mmHg; AR: achievement rate; AUT: area under the threshold; BMI: body mass index; BP: blood pressure; CAD: coronary artery disease; CVD: cerebrovascular disease; Cr: creatinine; DBP: diastolic blood pressure; Di: dichotomous; DM: diabetes mellitus; Du: duration under a blood pressure threshold; eGFR: estimated glomerular filtration rate; GI: gastro-intestinal; TIA: transient ischaemic attack; Gen. anaesth: general anaesthesia; HT: hypertension; LiverTX: liver transplantation; Low: lowest blood pressure; MAP: mean blood pressure; MI: myocardial injury; r-: relative threshold expressed as a percentage decrease from baseline blood pressure; RCRI: revised cardiac risk index; SAS: blood pressure as part of Surgical Apgar Score; SBP: systolic blood pressure; TL: triple low; TWA: time-weighted average; V: blood pressure variance; Var: variability or variance

Summary of evidence for the most reported outcomes

Based on the methods described above, two studies with a high-quality score were not used for the determination of organ injury risks. The study of Roshanov was excluded because studying hypotension was not part of the primary or secondary research objectives [20]. The strengths of associations reported by Schmid could not be converted into a comparable OR, RR of HR as they reported a regression coefficient for the decrease of creatinine clearance (- 0.28 $ml{\cdot}min^{-1}$) per percent of total surgery time with MAP ≥ 70 mmHg [7].

The reported risks of any end-organ injury after noncardiac surgery started to increase with prolonged exposure (≥ 10 minutes) to MAPs below 80 mmHg, resulting in a mildly elevated risk, with OR/RR/HRs between 1.0 and 1.4 (*Table 4*). For shorter durations (< 10 minutes), mildly elevated risks have been reported for thresholds of 70 mmHg and lower. The reported risks increased to moderate (OR/RR/HRs between 1.4 and 2.0) with exposures to MAPs below 65 - 60 mmHg for more five minutes or more, or any exposure below 55 - 50 mmHg. High risks (OR/RR/HRs ≥ 2.0) are reported for MAPs below 65 mmHg for 20 minutes or more, MAPs below 50 mmHg for five minutes or more, or any exposure below 40 mmHg.

There were small differences between individual outcomes. For AKI and MI, the risks started at thresholds below 65 mmHg and increased gradually with depth and duration in a pattern that is largely similar between the two outcomes. For mortality, associations were reported for higher thresholds than AKI and MI, starting when there was prolonged exposure to MAP < 80 mmHg. The reported risks were mild for thresholds down to 55 mmHg, at which the reported risks increased with prolonged exposures to MAP < 55 mmHg or lower. For ischaemic stroke, only non-significant, small strengths of associations were reported. For delirium, non-significant associations were found for a duration of MAP < 50 mmHg. For LOS, insufficient data were available.

Table 3 Summary of reported and extrapolated strength of associations of mortality and organ injury in noncardiac patients

Intraoperative hypotension thresholds *Studies with reported thresholds*				**Outcome under study** ***studied outcome, follow-up and outcome incidence***					
Threshold		**First author (year)**	**QS (%)**	**Mortality**	**AKI**	**MI**	**Stroke**	**Delirium**	**LOS**
MAP (mmHg)	< 80	Mascha (2015)	80	X					
MAP (mmHg)	< 75	Willingham (2015)	93	X					
	< 75	Willingham (2015)	93	X					
	< 75 ■	White (2016)	73	X					
	< 75 ■	White (2016)	73	X					
	< 75 ■	Sessler (2012)	67	X					
	< 75 ●	Taffé (2009)	67	X					
	< 75 ▲ ■	Sabaté (2011)	67	X		Tn, CK-MB, + ECG or Clin	Clin		
	< 75 ■	Stapelfeldt (2017)	53	X					
	< 75 ■	Sessler (2012)	67						X
MAP (mmHg)	< 70	Mascha (2015)	80	X					
	< 70 ▼ ◊	Bijker (2009)	80	X					
	< 70	Stapelfeldt (2017)	53	X					
	< 70 ■	Schmid (2016)	86		KD, RF				
	< 70	Sirivatanauksorn (2014)	60		Cr				
	< 70 ▼	Bijker (2012)	92				Clin + CT		
	< 70 ▲	Petsiti (2015)	73						X
	< 70 ▲	Tassoudis (2011)	60						X

			Strength of association per intraoperative hypotension duration *OR/RR/HR (95% CI) per duration of blood pressure below threshold*			
	Duration of follow-up	**Incidence outcome (%)**	**≥ 1 min**	**≥ 5 min**	**≥ 10 min**	**≥ 20 min**
	30 days	1.3%			1.02 per 10 min (1.01 – 1.03)	*1.04*
	30 days	0.8%			HR 1.09 per 15 min (1.07 – 1.11)	
	90 days	1.9%			HR 1.09 per 15 min (1.08 – 1.11)	
	5 days	1.5%	1.020 (1.007 – 1.034)			
	30 days	5.1%	1.024 (1.012 – 1.037)			
	30 days	0.8%	0.729 (0.342 – 1.558)	*0.209*	*0.042*	*0.002*
	< 1 day	0.03%			5.80 (2.98 – 11.30)* ↓ ≥ 30%, ≥ 10 min	
	In hospital	4.3%				2.3 (1.5 – 3.7)* > 1 hour
	30 days	1.8%	1.002 (1.000 – 1.004)	*1.01*	*1.02*	*1.04*
	Excessive LOS	29.7%	0.969 (0.850 – 1.104)	*0.854*	*0.730*	*0.533*
	30 days	1.3%			1.04 per 10 min (1.03 – 1.05)	*1.08*
	1 year	5.2%	HR 1.002 (0.999 – 1.006)	*HR 1.01*	*HR 1.02*	*HR 1.04*
	30 days	1.8%	1.004 (1.001 – 1.006)	*1.02*	*1.04*	*1.08*
	7 days	KD: 55% RF: 55%	-0.28			
	7 days	71.6%				3.84 (1.11 – 13.30)* > 30 min
	10 days	0.09%	1.003 (99% CI 0.993 – 1.014)	*1.02*	*1.03*	*1.06*
	≤ or > 9 days	Not reported	4.269 (1.743 – 10.455)*			
	≤ or > 9 days	37%	4.56 (1.85 – 10.96)*			

Table 3 Summary of reported and extrapolated strength of associations of mortality and organ injury in noncardiac patients

Intraoperative hypotension thresholds *Studies with reported thresholds*				**Outcome under study** ***studied outcome, follow-up and outcome incidence***					
Threshold		**First author (year)**	**QS (%)**	**Mortality**	**AKI**	**MI**	**Stroke**	**Delirium**	**LOS**
MAP (mmHg)	< 65	Stapelfeldt (2017)	53	X					
	< 65	Sun (2015)	87		AK				
	< 65 ▼	Salmasi (2017)	80		AK				
	≤ 65	Brinkman (2015)	73		AK				
	< 65	Yue (2013)	47		RF				
	< 65 ▼	Salmasi (2017)	80			TnT, CK-MB			
	< 65	Vasivej (2016)	46				TOAST		
	< 65 ●	Yang (2016)	47					DSM-IV	
MAP (mmHg)	< 60	Mascha (2015)	80	X					
	< 60 ▼	Bijker (2009)	80	X					
	< 60	Stapelfeldt (2017)	53	X					
	< 60	Sun (2015)	87		AK				
	< 60	Tallgren (2007)	71		RF				
	< 60	Thakar (2007)	40		Cr				
	< 60	Lima (2003)	33		Cr				
	< 60 ▼	Van Waes (2016)	80			TnI			
	< 60 ▼	Kheterpal (2009)	80			TnI, ECG			
	< 60	Pipanmekaporn (2014)	80			Tn, CK-MB,+ ECG			
	< 60 ▼	Bijker (2012)	92				Clin+CT		
	≤ 60	Patti (2011)	47					CAM	

			Strength of association per intraoperative hypotension duration *OR/RR/HR (95% CI) per duration of blood pressure below threshold*			
	Duration of follow-up	**Incidence outcome (%)**	**≥ 1 min**	**≥ 5 min**	**≥ 10 min**	**≥ 20 min**
	30 days	1.8%	1.007 (1.004 – 1.009)	*1.04*	*1.07*	*1.15*
	2 days	6.3%	1.28 (0.57 – 2.87) 1 – 5 min	1.56 (0.69 – 3.50) 6 – 10 min	1.57 (0.70 – 3.53) 11 – 20 min	2.25 (0.99 – 5.07) > 20 min
	7 days	5.6%	1.04 (98.8%CI 0.89 – 1.22) 1 – 5 min	1.15 (98.8%CI 0.98 – 1.35) 6 – 12 min	1.20 (98.8%CI 1.02 – 1.40) 13 – 28 min	1.35 (98.8%CI 1.14 – 1.58) > 28 min
	1 day	20%	Not reported; p = 0.04			
	In hospital	45.1%	6.008 (1.176 – 30.68)*			
	7 days	3.1%	1.01 (98.8%CI 0.80 – 1.27) 1 – 5 min	1.15 (98.8%CI 0.90 – 1.45) 6 – 12 min	1.34 (98.8%CI 1.06 – 1.68) 13 – 28 min	1.60 (98.8%CI 1.28 – 2.01) > 28 min
	30 days	0.075%	Not reported; NS*			
	3 days	28.5%	1.47 (0.583 – 2.354)* ↓ > 30%			
	30 days	1.3%			1.09 per 10 min (1.07 – 1.11)	*1.2*
	1 year	5.2%	HR 1.003 (0.998 – 1.008)	*HR 1.015*	*HR 1.030*	*HR 1.062*
	30 days	1.8%	1.012 (1.008 – 1.015)	*1.06*	*1.13*	*1.27*
	2 days	6.3%	1.10 (0.70 – 1.74) 1 – 5 min	1.08 (0.65 – 1.78) 6 – 10 min	1.84 (1.11 – 3.06) 11 – 20 min	1.70 (0.93 – 3.10) > 20 min
	3 days	22%				8.5 (1.8 – 39.4)* > 1 hour
	3 days	8.5%	Not reported, p = 0.01*			
	30 days	61%	3.85 (1.05 – 13.7)*			
	3 days	Injury: 24%	RR 1.1 (98.8% CI 0.7 – 1.7) 2 - 5 min	RR 0.9 (98.8% CI 0.5 – 1.6) 6 – 10 min	RR 1.5 (98.8% CI 1.0 – 2.3) 11 – 20 min	RR 1.5 (98.8% CI 1.0 – 2.5) > 30 min
	2 days	0.3%			Not reported* 10 min episodes	
	30 days	0.83%			RR 2.6 (1.6 – 4.3)* > 15 min	
	10 days	0.09%	1.003 (99% CI 0.988 – 1.019)	*1.015*	*1.030*	*1.062*
	In hospital	18%	9.74 (2.5 – 37.9)*			

Table 3 Summary of reported and extrapolated strength of associations of mortality and organ injury in noncardiac patients

Intraoperative hypotension thresholds *Studies with reported thresholds*				**Outcome under study** ***studied outcome, follow-up and outcome incidence***					
Threshold		**First author (year)**	**QS (%)**	**Mortality**	**AKI**	**MI**	**Stroke**	**Delirium**	**LOS**
MAP (mmHg)	< 55	Mascha (2015)	80	X					
	< 55	Walsh (2013)	80	X					
	< 55	Stapelfeldt (2017)	53	X					
	< 55	Sun (2015)	87		AK				
	< 55	Walsh (2013)	80		AK				
	< 55	Walsh (2013)	80			TnT + CK-MB			
	< 55	Babazade (2016)	80						X
MAP (mmHg)	< 50	Mascha (2015)	80	X					
	< 50 ▼	Bijker (2009)	80	X					
	< 50	Stapelfeldt (2017)	53	X					
	< 50	Mizota (2017)	87		KD				
	< 50 ▼	Van Waes (2016)	80			TnI			
	< 50 ▼	Kheterpal (2009)	80			TnI, ECG			
	< 50 ▼	Bijker (2012)	92				Clin + CT		
	< 50 ▼	Hirsch (2015)	100					CAM	
MAP (mmHg)	< 45	Stapelfeldt (2017)	53	X					
MAP (mmHg)	< 40 ▼	Bijker (2009)	80	X					
	< 40	Mizota (2017)	87		KD				
	< 40	House (2016)	67			TnI, TnT			
	< 40 ▼	Bijker (2012)	92				Clin + CT		

			Strength of association per intraoperative hypotension duration *OR/RR/HR (95% CI) per duration of blood pressure below threshold*			
	Duration of follow-up	**Incidence outcome (%)**	**≥ 1 min**	**≥ 5 min**	**≥ 10 min**	**≥ 20 min**
	30 days	1.3%			1.13 per 10 min (1.09 – 1.17)	*1.28*
	30 days	1.5%	1.16 (0.91 – 1.46) 1 – 5 min	1.16 (0.84 – 1.60) 6 – 10 min	1.26 (0.89 – 1.80) 11 – 20 min	1.79 (1.21 – 1.65) > 20 min
	30 days	1.8%	1.024 (1.018 – 1.030)	*1.13*	*1.27*	*1.61*
	2 days	6.3%	1.35 (0.98 – 1.86) 1 – 5 min	1.45 (0.94 – 2.22) 6 – 10 min	2.34 (1.35 – 4.05) 11 - 20 min	3.53 (1.51 – 2.85) > 20 min
	7 days	7.4%	1.18 (1.06 – 1.31) 1 – 5 min	1.19 (1.03 – 1.39) 6 – 10 min	1.32 (1.11 – 1.56) 11 – 20 min	1.51 (1.24 – 1.84) > 20 min
	7 days	2.3%	1.3 (1.06 – 1.58) 1 – 5 min	1.47 (1.13 – 1.93) 6 – 10 min	1.79 (1.33 – 2.39) 11 – 20 min	1.82 (1.31 – 2.55) > 20 min
	Time to discharge alive	Not reported		0.97 (0.91 – 1.04) ≥ 2.73 min		
	30 days	1.3%			1.23 (1.15 – 1.30)	*1.52*
	1 year	5.2%	HR 1.007 (0.995 – 1.019)	*HR 1.035*	*HR 1.072*	*HR 1.15*
	30 days	1.8%	1.054 (1.041 – 1.067)	*1.30*	*1.69*	*2.86*
	7 days	30.7%	1.64 (0.49 – 5.43) 1 – 9 min		2.11 (0.61 – 7.22) ≥ 10 min	
	3 days	Injury: 24%	RR 1.3 (98.8% CI 0.8 – 2.2) 2 - 5 min	RR 2.0 (98.8% CI 1.1 – 3.6 6 – 10 min	RR 1.0 (98.8% CI 0.4 – 2.2) 11 – 20 min	RR 2.0 (98.8% CI 0.8 – 5.1) >30 min
	30 days	0.3%			Not reported* 10 min episodes	
	10 days	0.09%	1.004 (99% CI 0.962 – 1.046)	*1.015*	*1.030*	*1.062*
	2 days	31-33%	Not reported, p = 0.409			
	30 days	1.8%	1.11 (1.08 – 1.14)	*1.69*	*2.84*	*8.06*
	1 year	5.2%	HR 0.999 (0.965 – 1.035)	*HR 0.995*	*HR 0.990*	*HR 0.980*
	7 days	30.7%	3.80 (1.17 – 12.30) 1 – 9 min		5.06 (1.26 – 20.40) ≥ 10 min	
	7 days	0.9%	1.35 (1.12 – 1.63)* > 2 min			
	10 days	0.09%	1.013 (99% CI 0.939 – 1.088)	*1.067*	*1.138*	*1.295*

Table 3 Summary of reported and extrapolated strength of associations of mortality and organ injury in noncardiac patients

Intraoperative hypotension thresholds *Studies with reported thresholds*				**Outcome under study** ***studied outcome, follow-up and outcome incidence***					
Threshold		**First author (year)**	**QS (%)**	**Mortality**	**AKI**	**MI**	**Stroke**	**Delirium**	**LOS**
SBP (mmHg)	< 100 ▼	Bijker (2009)	80	X					
	< 100 ■	White (2016)	73	X					
	< 100 ■	White (2016)	73	X					
	< 100	Davidovic (2017)	27	X					
	< 100	Sharma (2006)	23		Cr				
	< 100	Barone (2002)	38			CK-MB, ECG			
	< 100 ▼	Bijker (2012)	92				Clin+CT		
	< 100 ▼	Franck (2011)	47						X
SBP (mmHg)	< 90 ■	Monk (2015)	93	X					
	< 90	Roshanov (2017)	80	X					
	< 90 ▼	Bijker (2009)	80	X					
	< 90	Roshanov (2017)	80			TnT			
	< 90 ▼	Bijker (2012)	92				Clin+CT		
	< 90	Roshanov (2017)	80				Clin		
	< 90 ▲	Marcantonio (1998)	73					CAM	
SBP (mmHg)	< 80 ■	Monk (2015)	93	X					
	< 80	Monk (2005)	80	X					
	< 80 ▼	Bijker (2009)	80	X					
	< 80 ▼	Kheterpal (2009)	80			TnI, ECG			
	< 80 ▼	Bijker (2012)	92				Clin+CT		
	< 80	Jiang (2016)	53					Clin	
	< 80	Babazade (2016)	80						X

			Strength of association per intraoperative hypotension duration *OR/RR/HR (95% CI) per duration of blood pressure below threshold*			
	Duration of follow-up	**Incidence outcome (%)**	**≥ 1 min**	**≥ 5 min**	**≥ 10 min**	**≥ 20 min**
	1 year	5.2%	HR 1.000 (0.996 – 1.003) ≥ 1 min episode duration	HR 0.999 (0.996 – 1.003) ≥ 1 min episode duration	HR 0.999 (0.995 – 1.003) ≥ 1 min episode duration	*HR 0.998*
	5 days	1.5%	1.017 (1.006 – 1.028)			
	30 days	5.1%	1.033 (1.015 – 1.052)			
	30 days	1.55%	6.61 (0.71 – 61.07)*			
	7 days	2.8%		5.6 (CI not reported)* > 5 min		
	In hospital	0.09%			6.15 (1.89 – 20.05)* ≥ 10 min	
	10 days	0.09%	1.005 (99% CI 0.993 – 1.016)	*1.025*	*1.051*	*1.105*
	Mean LOS	Not reported	Not reported*			
	30 days	1.8%	1.1 (0.6 – 1.9) 2 – 4.9 min	1.1 (0.6 – 1.8) > 5 min		
	30 days	2.1%	RR 1.41 (1.07 – 1.86)*			
	1 year	5.2%	HR 0.988 (0.993 – 1.004) ≥ 1 min episode duration	HR 0.998 (0.992 – 1.003) ≥ 1 min episode duration	HR 0.997 (0.990 – 1.003) ≥ 1 min episode duration	*HR 0.994*
	30 days	7.9%	RR 1.04 (0.90 – 1.20)*			
	10 days	0.09%	1.006 (99% CI 0.991 – 1.022)	*1.030*	*1.062*	*1.127*
	30 days	0.6%	RR 1.14 (0.85 – 1.54)*			
	5 days	9%	0.8 (0.5 – 1.3)*			
	30 days	1.8%	0.9 (0.5 – 1.5) 2 – 4.9 min	1.0 (0.5 – 1.7) > 5 min		
	1 year	5.5%	1.036 (1.006 – 1.066)	*1.193*	*1.424*	*2.029*
	1 year	5.2%	HR 1.000 (0.989 – 1.011) ≥ 1 min episode duration	HR 0.999 (0.986 – 1.012) ≥ 1 min episode duration	HR 1.000 (0.985 – 1.015) ≥ 1 min episode duration	*HR 1.000*
	30 days	0.3%			Not reported* 10 min episodes	
	10 days	0.09%	1.007 (99% CI 0.981 – 1.034)	*1.035*	*1.072*	*1.150*
	3 days	9.3%	7.52 (0.181 – 17.938)*			
	Time to discharge alive	Not reported		0.97 (0.93 – 1.01) ≥ 3.69 min		

Table 3 Summary of reported and extrapolated strength of associations of mortality and organ injury in noncardiac patients

Intraoperative hypotension thresholds *Studies with reported thresholds*				**Outcome under study** ***studied outcome, follow-up and outcome incidence***					
Threshold		**First author (year)**	**QS (%)**	**Mortality**	**AKI**	**MI**	**Stroke**	**Delirium**	**LOS**
SBP (mmHg)	< 70 ■	Monk (2015)	93	X					
	< 70 ▼	Bijker (2009)	80	X					
	< 70	Nakamura (2009)	31	X					
	< 70 ●	Hallqvist (2016)	80			TnT			
	< 70 ▼	Kheterpal (2009)	80			TnI, ECG			
	< 70 ▼	Bijker (2012)	92				Clin+CT		

Grey cells represent statistically not significant results. Bold cells represent statistically significant results. Italic cells represent extrapolated results. * : adherence to dichotomous definition instead of an analysis of depth and/or duration of a certain threshold or continuous variable. ● : relative threshold, ▲ : based on combination relative and absolute threshold, ▼ : based on both relative and absolute threshold(s) analysed, ◊ : exception of duration or time definition: Bijker (2009) = hazard risk 1 years mortality translated to 30 day mortality, ■ : exception of hypotension definition or analysis: White (2016) = odds ratio per mmHg mean blood pressure decrease or per 5 mmHg systolic blood pressure increase. Sessler (2012) = single low (low MAP / high bispectral index/ high mean alveolar concentration). Sabaté (2011) = composite endpoint. Stapelfeldt (2017) = odds ratio for percentage increase in the odds of the outcome per limit exceeded, Schmid (2016) = regression coefficient for the achievement rate time spend with mean blood pressure > 70 mmHg compared to total surgery time, Monk (2015) = odds ratio for systolic blood pressures 89 – 80 mmHg, 79 – 70 mmHg or 69 – 60 mmHg for 2 - 4.9 min or > 5 min respectively.

		Strength of association per intraoperative hypotension duration *OR/RR/HR (95% CI) per duration of blood pressure below threshold*			
Duration of follow-up	**Incidence outcome (%)**	**≥ 1 min**	**≥ 5 min**	**≥ 10 min**	**≥ 20 min**
30 days	1.8%	1.4 (0.8 – 2.4) 2 – 4.9 min	2.9 (1.7 – 4.9) > 5 min		
1 year	5.2%	HR 1.006 (0.990 – 1.021) ≥ 1 min episode duration	HR 1.002 (0.982 – 1.023) ≥ 1 min episode duration	HR 0.996 (0.963 – 1.031) ≥ 1 min episode duration	*HR 0.992*
In hospital	5.6%	5.80 (2.98 – 11.30)*			
1 day	Injury: 30%		4.4 (1.8 – 11.1)* ↓ ≥ 50%, > 5 min		
30 days	0.3%			Not reported* 10 min episodes	
10 days	0.09%	1.002 (99% CI 0.952 – 1.051)	*1.010*	*1.020*	*1.041*

Abbreviations: AK: Acute Kidney Injury Network definition (AKIN); Clin: diagnosis based on clinical signs and symptoms; CK-MB: creatinine-kinase MB concentration; Cr: creatinine concentration; CT: computed tomography scan; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV); HR: hazard ratio; KD: Kidney Disease Improving Global Outcomes (KDIGO); NS: not significant; OR: odds ratio; RR: relative risk; TnT: troponin T concentration; TOAST: Trial of ORG 10172 in Acute Stroke Treatment

Table 4 Summary of highest strength of associations of association of mortality and organ injury in noncardiac patients translated to risk categories

Depth	Duration	Mortality		Acute kidney injury	
MAP	Minutes	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result
< 80 mmHg	≥ 1				
	≥ 5				
	≥ 10	1.02	1.02		
	≥ 20	1.04	1.04		
< 75 mmHg	≥ 1				
	≥ 5				
	≥ 10	1.02	1.02		
	≥ 20	1.09	1.09		
< 70 mmHg	≥ 1	1.002 *			
	≥ 5	1.01 *			
	≥ 10	1.04	1.04		
	≥ 20	1.09	1.09		
< 65 mmHg	≥ 1	1.002 *		1.3 *	
	≥ 5	1.01 *		1.6 *	
	≥ 10	1.04	1.04	1.6 *	
	≥ 20	1.09	1.09	2.3 *	
< 60 mmHg	≥ 1	1.1 *		1.3 *	
	≥ 5	1.1 *		1.6 *	
	≥ 10	1.1 *	1.09	1.8	1.8
	≥ 20	1.2	1.2	2.3	2.3
< 55 mmHg	≥ 1	1.2 *	1.04	1.4*	1.2
	≥ 5	1.2	1.2	1.6 *	1.2
	≥ 10	1.4	1.4	2.3	2.3
	≥ 20	2.0	2.0	3.5	3.5
< 50 mmHg	≥ 1	1.2 *	1.04	1.6 *	1.2
	≥ 5	2.4	2.4	1.6 *	1.2
	≥ 10	2.4	2.4	2.3	2.3
	≥ 20	2.4	2.4	3.5	3.5
< 45 mmHg	≥ 1	1.2 *	1.04	1.6 *	1.2

2

	Myocardial injury		Stroke		Delirium		Overall organ injury	
	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result
							Low	Low
							Low	Low
							Low	Low
							Low	Low
			1.003*				Low	
			1.015*				Low	
			1.030*				Low	Low
			1.062*				Low	Low
	1.01 *		1.003*				Low	
	1.2 *		1.015*				Moderate	
	1.3	1.3	1.030*				Moderate	Low
	1.8	1.8	1.062*				High	Moderate
	1.1 *		1.003*				Low	
	1.2 *		1.015*				Moderate	
	1.5	1.5	1.030*				Moderate	Moderate
	2.5	1.8	1.062*				High	High
	1.3	1.3	1.003*				Moderate	Low
	1.5	1.5	1.015*				Moderate	Moderate
	1.8	1.8	1.030*				High	High
	2.5	2.5	1.062*				High	High
	1.3	1.3	1.004*		• p = 0.409 *		Moderate	Low
	4.4	4.4	1.020*		• p = 0.409 *		High	High
	4.4	4.4	1.041*		• p = 0.409 *		High	High
	4.4	4.4	1.083*		• p = 0.409 *		High	High
	1.3	1.3	1.013*		• p = 0.409 *		Moderate	Low

Table 4 Continued

Depth	Duration	Mortality		Acute kidney injury	
MAP	Minutes	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result
	≥ 5	2.4	2.4	1.6 *	1.2
	≥ 10	2.4	2.4	2.3	2.3
	≥ 20	2.4	2.4	3.5	3.5
< 40 mmHg	≥ 1	1.2 *	1.04	3.8	3.8
	≥ 5	2.4	2.4	3.8	3.8
	≥ 10	2.4	2.4	5.1	5.1
	≥ 20	2.4	2.4	5.1	5.1

Low	1.0 < OR, RR or HR < 1.4
Moderate	1.4 ≤ OR, RR or HR < 2.0
High	OR, RR or HR ≥ 2.0
	Evidence with quality score < 80%
	No evidence available

	Myocardial injury		Stroke		Delirium		Overall organ injury	
	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result	Based on quality score ≥ 80%	Based on quality score ≥ 80% and significant result
	4.4	4.4	1.067*		● p = 0.409 *		High	High
	4.4	4.4	1.138*		● p = 0.409 *		High	High
	4.4	4.4	1.295*		● p = 0.409 *		High	High
	1.3	1.3	1.013*		● p = 0.409 *		High	High
	4.4	4.4	1.067*		● p = 0.409 *		High	High
	4.4	4.4	1.138*		● p = 0.409 *		High	High
	4.4	4.4	1.295*		● p = 0.409 *		High	High

* Not statistically significant. ● Hirsch (2015) performed a multivariable logistic regression model to analyse their data but did not report odds ratios but only p-values (p-value 0.409 for duration of mean blood pressure < 50 mmHg.

Abbreviations: HR: hazard ratio; MAP: mean blood pressure; OR: odds ratio; RR: relative risk

DISCUSSION

This systematic review summarised the current literature on the relation between intraoperative hypotension and postoperative outcomes. It provides an overview of blood pressures which were reported to be associated with inadequate organ perfusion. Prolonged exposure (≥ 10 minutes) to a MAP below 80 mmHg and for shorter durations below 70 mmHg was associated with mildly elevated risks of any end-organ injury. Increased durations for a MAP below 65 - 60 mmHg, or for any exposure below 55 - 50 mmHg was associated with moderately or highly elevated risks.

The interpretation and clinical applicability of the results of this review are hampered by the large differences between the studies and their observed associations. First, the included studies differed substantially in their selection of patient groups or procedures. *Table 2* demonstrates that few studies are comparable in terms of baseline characteristics of the patients included. Further, the selection of surgical procedures ranged from very wide (e.g. noncardiac surgery) to very narrow (e.g. thoracic aortic aneurysm repair, gastric bypass surgery). Finally, there was also large variability in what patient and procedure characteristics were – or were not – reported by the various studies.

Second, there was large variation in the way that intraoperative hypotension was defined and analysed. Definitions of hypotension across the studies included a wide range of depths and durations for various types of blood pressure. Different thresholds were used for systolic, mean or diastolic blood pressure, or even multiple thresholds were combined into a single definition. In addition to a threshold definition, the variable for hypotension can also be modelled in different ways. The thresholds often introduce a cut-off: anything above the threshold is considered to be the same, i.e. analysed as 'zero' or 'no intraoperative hypotension', even when the values are close to the threshold. However, everything below the threshold can be modelled in several ways: duration of blood pressure below the threshold, the area under the threshold (AUT), or simply a 'one' – i.e. 'yes' the patient's blood pressure was below the threshold.

Third, there was important variation in the way that postoperative adverse outcomes were defined, analysed and reported. Six different groups of postoperative adverse outcomes were reported as outcomes in this review: mortality, acute kidney injury, myocardial injury, ischaemic stroke, delirium and length of hospital stay. Within each group different adverse outcomes with different definitions were studied. For example, the definition of myocardial injury ranged from only elevated biomarkers with or without ECG changes to cardiovascular complications. Residual confounding might have been present in studies that analysed postoperative cardiac or renal biomarkers drawn by

clinical indication compared to routine postoperative biomarker measurements [4, 26, 27]. Furthermore, not all outcomes are interchangeable in their severity and incidence rates. Delirium may be an outcome more sensitive to find the low blood pressure threshold, but regarding severity and incidence rates it is not on par with mortality and acute kidney injury.

The fourth issue is a result of the three issues mentioned before. The large heterogeneity in baseline characteristics, hypotension definitions and studied outcomes made it challenging to come to a quantitative summary of the results. Hence, we made various conversions and assumptions on how to merge definitions of intraoperative hypotension and reported strengths of associations of these studies in a qualitative way. Additionally, we only used high quality studies (quality score ≥ 80%) with blood pressure thresholds converted to MAP thresholds for the organ-injury risk classification.

Based on several assumptions and variations in patients, intraoperative hypotension definitions, outcome definitions and analyses, it is still difficult to reliably define a common 'cut-off' for which blood pressure is too low. Although the risk of end-organ injury seems to increase rapidly with prolonged exposure to lower intraoperative blood pressures, based on current evidence, we cannot prove a causal relation between intraoperative blood pressures and outcomes. Current studies on intraoperative hypotension aim to answer: 'Which blood pressure is too low?', but their data can only be used to answer 'Which blood pressure is associated with adverse outcomes given current treatment standards?' In other words, this review does not address the question which blood pressure thresholds result in organ hypoperfusion, but whether there is remaining hypoperfusion despite present routines to manage our patients' blood pressures.

All contributing factors and interactions are difficult to unravel and discriminate and is seems unlikely that we will be able to explore the contribution of separate factors using only observational data. Therefore, intervention studies – such as pragmatic trials – are required to understand the causal chain of intraoperative low blood pressure and adverse outcomes. Recently, after completion of the systematic search described in this review, three trials concerning intraoperative blood pressure manipulation have been published. In the first trial, elderly patients with chronic hypertension who underwent major abdominal surgery were randomised to one of three target MAP groups. Vasopressor therapy and a fluid management protocol based on stroke volume variation were used to adjust MAP. This study showed that a target MAP of 80 – 95 mmHg, compared to lower (65 – 79 mmHg) and higher targets (96 – 110 mmHg) may decrease the incidence of AKI. Incidences of stroke and mortality did not significantly

differ among groups. The lower incidence of AKI in the midrange MAP group compared to the lower MAP group is in accordance with results from observational studies (*Table 4*). Strict in- and exclusion criteria regarding age, comorbidities and preoperative medication use limit generalizability of this trial [28]. In a second trial two blood pressure management strategies and their effects on postoperative organ dysfunction in patients undergoing major surgery were studied. This study showed that achieving a systolic blood pressure within 10% of the reference value by using continuous vasopressor infusion may prevent postoperative organ dysfunction compared to a strategy of only treating systolic blood pressures less than 80 mmHg or lower than 40% of the reference value (standard care). However, anticipation on an expected blood pressure decline was not allowed and the standard care group treatment thresholds may not really represent current clinical care [29]. In a third trial it was shown that avoidance of 'double low' events defined as mean arterial pressure < 75 mmHg and BIS < 45 by automated alerts, did not significantly decrease the ninety-day mortality incidence in adults who underwent noncardiac surgery. In this study, no standardised blood pressure treatment protocols were used [30]. Future studies on intraoperative hypotension should aim to explore blood pressure thresholds within specific patient groups and for specific outcomes. These should include other variables that are indicative of underlying causes and mechanisms of hypotension, such as heart rate, pulse pressure variation, cardiac output estimated by advanced techniques, and specific biomarkers. This will allow us to study mechanistic hypotheses that are outcome-specific and whether mechanism-specific interventions will improve outcomes.

In conclusion, the reported associations suggest that organ injury might occur when the mean blood pressure drops below 80 mmHg for at least 10 minutes, and that this risk increases with blood pressures becoming progressively lower. Given the retrospective observational design of most studies, reflected by large variability in patient characteristics, hypotension definitions and outcomes, solid conclusions on which blood pressures under which circumstances are truly too low cannot be drawn. We are in need of prospective interventional studies in specific patient groups and for specific outcomes to further unravel this topic.

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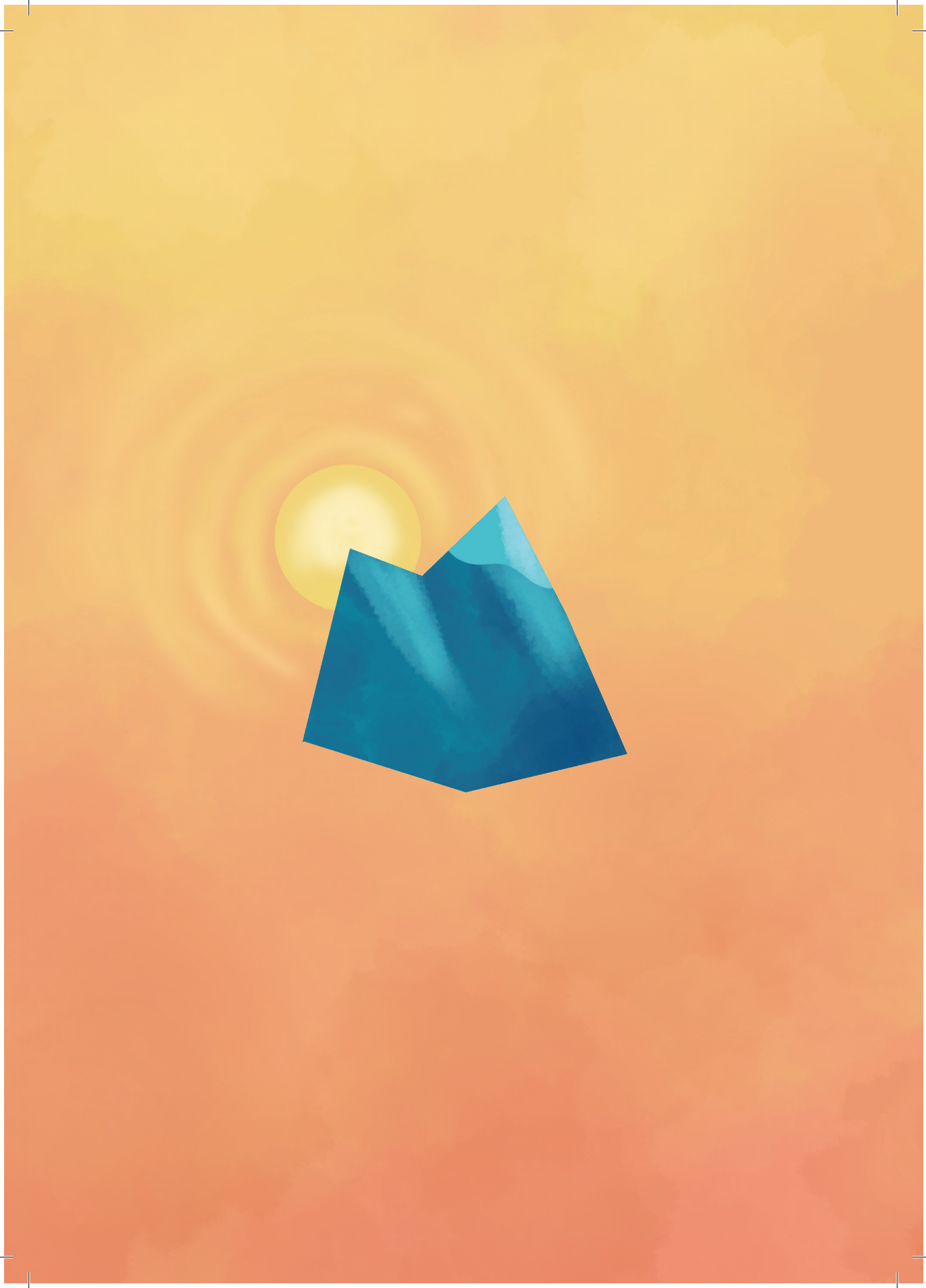
PART 2

INTRAOPERATIVE HYPOTENSION AND CEREBRAL OUTCOMES AFTER CARDIAC AND NONCARDIAC SURGERY



CHAPTER 3

INTRAOPERATIVE HYPOTENSION AND DELIRIUM AFTER ON-PUMP CARDIAC SURGERY

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ABSTRACT

Background: Delirium is a common complication after cardiac surgery and may be as a result of inadequate cerebral perfusion. We studied delirium after cardiac surgery in relation to intraoperative hypotension (IOH).

Methods: This observational single-centre, cohort study was nested in a randomised trial, on a single intraoperative dose of dexamethasone vs placebo during cardiac surgery. During the first four postoperative days, patients were screened for delirium based on the Confusion Assessment Method (CAM) for Intensive Care Unit on the intensive care unit, CAM on the ward and by inspection of medical records. To combine depth and duration of IOH, we computed the area under the curve for four blood pressure thresholds. Logistic regression analyses were performed to investigate the association between IOH and the occurrence of postoperative delirium, adjusting for confounding and using a 99% confidence interval to correct for multiple testing.

Results: Of the 734 included patients, 99 patients (13%) developed postoperative delirium. The adjusted odds ratio for the mean arterial pressure < 60 mmHg threshold was 1.04 (99% confidence interval: 0.99 – 1.10) for each 1000 $mmHg^2 \cdot min^2$ AUC^2 increase. IOH, as defined according to the other three definitions, was not associated with postoperative delirium either. Deep and prolonged IOH seemed to increase the risk of delirium, but this was not statistically significant.

Conclusions: Independent of the applied definition, IOH was not associated with the occurrence of delirium after cardiac surgery

INTRODUCTION

Delirium is characterised by an acute change in mental status and has been associated with adverse outcomes, such as prolonged hospital stay, long-term cognitive impairment and mortality [1–5]. With an incidence between 3% and 52% during hospital admission, delirium frequently complicates cardiac surgery [6-10]. Although the pathophysiology of postoperative delirium is incompletely understood, inadequate cerebral perfusion as a result of intraoperative hypotension (IOH) is one of the possible mechanisms [5,11,12].

IOH is a common side-effect of general anaesthesia, but a widely accepted definition of IOH is not available [13]. In previous studies, IOH has been associated with postoperative adverse events, such as mortality [14–16], acute kidney injury [17], and myocardial ischaemia [17, 18]. In studies on IOH and postoperative ischaemic stroke, no clear association was observed in different groups of patients [16, 18–21]. Nevertheless, it seems plausible that brain perfusion becomes compromised when a patient experiences a too low blood pressure for a too long period of time. Delirium may be a more sensitive manifestation of postoperative cerebral dysfunction as a result of temporarily insufficient cerebral perfusion than ischaemic stroke. However, the association of intraoperative blood pressure with delirium is currently unclear. We hypothesised that severe and prolonged low blood pressure during anaesthesia and cardiac surgery increases the risk of postoperative delirium. The aim of the study was to investigate whether IOH is related to the occurrence of delirium after cardiac surgery.

METHODS

Design and patients

This observational single-centre cohort study was nested within a large multicentre clinical trial, the Dexamethasone for Cardiac Surgery (DECS) trial. The design of the DECS trial has been published in detail elsewhere [22]. Briefly, adult patients scheduled for cardiac surgery requiring cardiopulmonary bypass (CPB) were randomised to an injection of either 1 $mg \cdot kg^{-1}$ dexamethasone or placebo at the induction of anaesthesia. Exclusion criteria were emergency procedures or a preoperative life expectancy less than six months. Patients from the DECS trial who participated in a sub-study on postoperative delirium within one of the participating centres, the University Medical Center Utrecht, were eligible for the current study on IOH and postoperative delirium. Patients who had a stroke during the study period were excluded from postoperative delirium monitoring. This study was carried out according to Good Clinical Practice standards and national regulations. The Medical Ethics Committee of the University

Medical Center Utrecht approved the DECS-trial (protocol number 05-301) and the sub-study on delirium (protocol number 12-423). All patients provided written informed consent before randomisation. For the current study on IOH and delirium, the Medical Ethics Committee waived the need to obtain separate informed consent.

Data collection and anaesthesia protocol

Demographic and postoperative data were obtained from the DECS trial database [22] and the hospital information system. Intraoperative data from the patient monitor and anaesthesia machine were stored as the median for each minute of collected data in the electronic anaesthesia information management system (AnStat®, CarePoint Nederland BV, Ede, the Netherlands). Intraoperative fluid management and anaesthesia were performed according to protocol. Anaesthesia was initiated using 0.1 $mg \cdot kg^{-1}$ midazolam, 1 $\mu g \cdot kg^{-1}$ sufentanil, and 0.1 $mg \cdot kg^{-1}$ pancuronium. For maintenance, inhalational anaesthesia with sevoflurane or isoflurane was applied together with 0.5 $\mu g^{-1} \cdot kg^{-1} \cdot h^{-1}$ sufentanil i.v. Patients received a restricted intravenous fluid regimen.

Intraoperative hypotension

IOH was defined as the cumulative exposure to mean arterial pressures (MAPs) below a predefined threshold during surgery. As inadequate brain perfusion was expected to depend on both the depth and the duration of hypotension, IOH was defined as the Area Under the Curve (AUC) for a certain MAP threshold [23, 24]. Therefore, the AUC was expressed in mmHg·min. Intra-arterial blood pressure (IABP) measurements were used or non-invasive blood pressure (NIBP) measurements when IABP was unavailable at any time point. Given the lack of a widely accepted definition for IOH [13], IOH was studied using four predefined, but exploratory thresholds: a MAP below 60 mmHg, a MAP below 50 mmHg, a MAP decrease > 30% relative to baseline blood pressure and a MAP decrease > 40% relative to baseline blood pressure. The baseline blood pressure was defined as the mean of all measured blood pressure measurements in the operating theatre before induction of anaesthesia. Time of induction was defined as the moment of the administration of induction medication or three minutes before the first registration of expired carbon dioxide, whichever came first [13].

Delirium assessment

The outcome of this study was the occurrence of delirium at any time point during the first four days after cardiac surgery. Trained research personnel assessed all patients for delirium daily, including weekend days.[25] The following assessment scales were used: the Richmond Agitation Sedation Scale (RASS) to assess the level of consciousness, the Confusion Assessment Method adapted for the Intensive Care Unit (CAM-ICU) to detect delirium during Intensive Care Unit (ICU) admission, and the Confusion Assessment

Method (CAM) to detect delirium during admission at the cardiothoracic surgery ward [26, 27]. In addition, medical records were screened for signs of delirium and treatment with haloperidol. Patients with uncertainty regarding the diagnosis of delirium were discussed with a neurologist-intensivist (AS), who made the final classification. Research personnel were unaware of the occurrence of IOH during their assessment of postoperative delirium.

Potential confounders

We selected a priori the following possible confounders, based on clinical experience and previously performed studies [28, 29]. These included the EuroSCORE [30], duration of surgery, duration of CPB, intraoperative use of vasopressors, intraoperative use of inotropes and administration of either dexamethasone or placebo. As the EuroSCORE includes age, sex, and various comorbidities and risk factors for surgical complexity, we did not adjust for these variables separately. Vasopressor use was expressed by the cumulative number of minutes in which a patient received phenylephrine, ephedrine, adrenaline or noradrenaline i.v. during surgery. Inotrope use was expressed by the cumulative number of minutes in which a patient received milrinone or dobutamine i.v. during surgery.

Statistical analysis

Continuous variables were visually assessed for a normal distribution using histograms and qq-plots. Normally distributed data were presented as means with standard deviations (SD) and studied using two-sample Student's t-tests. Skewed continuous data were presented as medians with interquartile ranges (IQR) and evaluated using Wilcoxon signed rank tests. Categorical variables were expressed as numbers (percentage) and tested using $\chi 2$ tests. The association between the AUC of each MAP threshold and occurrence of delirium was analysed using multivariable logistic regression analysis. Based on assessment for nonlinearity using restricted cubic splines, the AUCs for IOH were included into regression analysis after quadratic transformation. Odds ratios (ORs) were calculated per 1000 mm Hg^2 min^2 increase of intraoperative hypotension and presented as a scaled OR between the 75th and 25th percentile. The analyses included the above-described confounders. As four different MAP thresholds were analysed, Bonferroni correction was applied to adjust for multiple testing. The resulting two-sided α was rounded down to 0.01 and therefore 99% confidence intervals (99% CI) were used to present ORs. All analyses were performed using R (release 3.0.0; R foundation for Statistical Computing, Vienna, Austria)

RESULTS

In total, 768 patients were included in the DECS trial at the University Medical Center Utrecht, between June 2009 and November 2011. Thirty patients could not be evaluated for occurrence of delirium, because of logistic reasons (i.e. unexpected rescheduling of the surgery, no available study nurse). One patient withdrew informed consent and was not analysed. Intraoperative data of three other patients could not be merged, because of an inability to link the unique surgery number to the DECS study number. Therefore, this study cohort included 734 patients (96% of the eligible 768 subjects), and most of them underwent combined cardiac surgery (*Table 1*). There were no missing values in patient-, surgery-, or outcome-related variables. During the first four postoperative days, 99 patients (13%) were diagnosed with delirium. Patients who developed delirium were older, more often female, had a higher EuroSCORE, and more often had ischaemic stroke or peripheral artery disease in their medical history.

Table 2 provides an overview of the duration of surgery and use of vasopressors and inotropes. Overall, the mean duration of surgery was 284 min (SD 86) and the mean duration of CPB 91 min (SD 53). Delirious patients had longer cross-clamp durations and had more min of vasopressor infusion during surgery than non-delirious patients. On average, the baseline MAP of delirious patients and non-delirious patients were 90 mmHg (SD17) and 92 mmHg (SD 15) respectively.

Table 3 shows the median AUC of various thresholds for IOH. Delirious patients had higher median AUCs than non-delirious patients when MAP < 60 mmHg or MAP < 50 mmHg thresholds were applied. However, delirious patients had lower median AUCs based on both relative thresholds compared with non-delirious patients.

In the crude analysis, an increase of the AUC of IOH based on MAP < 60 mmHg, was significantly associated with the occurrence of delirium (OR 1.05 per 1000 $mmHg^2$ min^2 AUC increase, 99% CI 1.01–1.09) (*Table 4*). After adjusting for confounding and multiple testing, there were no significant associations between IOH based on any of the definitions, and delirium. Our findings did not change when we added age and aortic cross clamp time to the models. When comparing a patient with an AUC of the 75th percentile based on MAP < 60 mmHg threshold (1861 mmHg · min) to a patient with an AUC of 25th percentile based on MAP < 60 mmHg threshold (774 mmHg · min), the adjusted OR was 1.12 (99% CI 1.07–1.16). This can roughly be interpreted as a 12% increased risk for the occurrence of postoperative delirium. *Figure 1* is a graphical representation of the results of the logistic regression analyses. In this figure, the AUCs based on the four MAP thresholds are plotted against the ORs from the multivariable

regression analyses. In patients with a relatively low AUC, the OR remained close to 1, but the OR gradually increased with increasing AUCs for every definition. However, the risk of delirium associated with IOH did never reach statistical significance.

Table 1 Patient characteristics

	All patients (n = 734)	**Non-delirium (n = 635)**	**Delirium (n = 99)**	**p-values**
Female, n (%)	224 (31)	179 (28)	45 (45)	< 0.01
Age, years, mean (SD)	66 (12)	65.1 (12)	73.8 (9)	< 0.01
Essential hypertension, n (%)	413 (56)	350 (55)	63 (64)	0.11
Diabetes mellitus, n (%)	140 (19)	117 (18)	23 (23)	0.26
History of stroke, n (%)	41 (6)	35 (5)	6 (6)	0.02
Peripheral artery disease, n (%)	64 (9)	49 (8)	15 (15)	0.02
Preoperative creatinine concentration, $\mu mol \cdot l^{-1}$, median [IQR]	92 [81 - 108]	92 [81 - 107]	93 [80 - 117]	0.18
EuroSCORE, median [IQR]	5 [3 – 7]	4 [3 - 7]	7 [5 - 9]	< 0.01
Left ventricular function, n (%)				0.51
Good (> 50%)	528 (72)	460 (72)	68 (69)	
Moderate (30 - 50%)	176 (24)	151 (24)	25 (25)	
Poor (< 30%)	30 (4)	24 (4)	6 (6)	
Type of surgery, n (%)				< 0.01
Mitral valve surgery	73 (10)	69 (11)	4 (4)	
Aortic valve surgery	104 (14)	90 (14)	14 (14)	
CABG	266 (36)	238 (37)	28 (28)	
CABG with mitral valve surgery	27 (4)	26 (4)	1 (1)	
CABG with aortic valve surgery	83 (11)	57 (9)	26 (26)	
Other surgery	181 (25)	155 (25)	26 (26)	

†: EuroSCORE consists of the following weighted patient-, cardiac- and surgery-related variables: age, sex, chronic pulmonary disease, extracardiac arteriopathy, neurological dysfunction, previous cardiac surgery, serum creatinine, active endocarditis, critical preoperative state, presence of unstable angina, left ventricle dysfunction, recent myocardial infarction, pulmonary hypertension, emergency surgery, other than isolated coronary artery by-pass grafting, surgery on thoracic aorta, postinfarct septal rupture [30]. Higher EuroSCORE presents increased risk of perioperative mortality. ‡: Definition of left ventricular function (LVF) [31]: good, ejection fraction of more than 50%; moderate, ejection fraction of 30% to 50%; and poor, ejection fraction of less than 30%.

Abbreviations: CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LVF: left ventricular function; SD: standard deviation

Table 2 Duration of surgery and use of inotropes

	All patients (n = 734)	Non-delirium (n = 635)	Delirium (n = 99)	p-values
Duration of surgery, minutes, mean (SD)	284 (86)	282 (83)	299 (100)	0.16
Duration of cardiopulmonary bypass, minutes, mean (SD)	91 (53)	91 (53)	95 (51)	0.21
Duration of cross-clamp time, minutes, mean (SD)	31 (25)	29 (23)	38 (35)	< 0.01
Reoperation, yes, n (%)	45 (6)	35 (5)	10 (10)	0.08
Baseline blood pressure, mmHg, mean (SD)	92 (15)	92 (15)	90 (17)	0.07
Total minutes any vasopressor, minutes, median [IQR]	54 [0 – 165]	46 [0 – 154]	119 [0 – 226]	0.01
Total minutes any inotrope, minutes, median [IQR]	0 [0 – 0]	0 [0 – 0]	0 [0 – 52]	0.09

† Vasopressor use was expressed by the cumulative number of minutes in which a patient received phenylephrine, ephedrine epinephrine, norepinephrine or dopamine intravenously during surgery.
‡ Inotrope use was expressed by the cumulative number of minutes in which a patient received milrinone or dobutamine intravenously during surgery.
Abbreviations: AUC: area under the curve; MAP: mean arterial pressure; IQR: interquartile range; SD: standard deviation

Table 3 Intraoperative hypotension, expressed as the area under the curve based on four mean blood pressure thresholds, during cardiac surgery

	All patients (n = 734)	Non-delirium (n = 635)	Delirium (n = 99)	p-values
MAP < 60 mmHg	1,272 [774 – 1,861]	1,265 [768 – 1,852]	1,399 [846 – 2,088]	0.09
MAP < 50 mmHg	251 [114 – 448]	241 [110 – 444]	297 [150 – 520]	0.05
MAP decrease > 30% relative to baseline	1,901 [763 – 3,653]	1,929 [811 – 3,637]	1,796 [642 – 3,964]	0.41
MAP decrease > 40% relative to baseline	631 [183 – 1,570]	649 [186 – 1,542]	559 [150 – 1,795]	0.59

Expressed by the area under the curve of various thresholds for hypotension, mmHg·min, median [IQR].
Abbreviations: CPB: cardiopulmonary bypass; IQR: interquartile range; MAP: mean arterial pressure

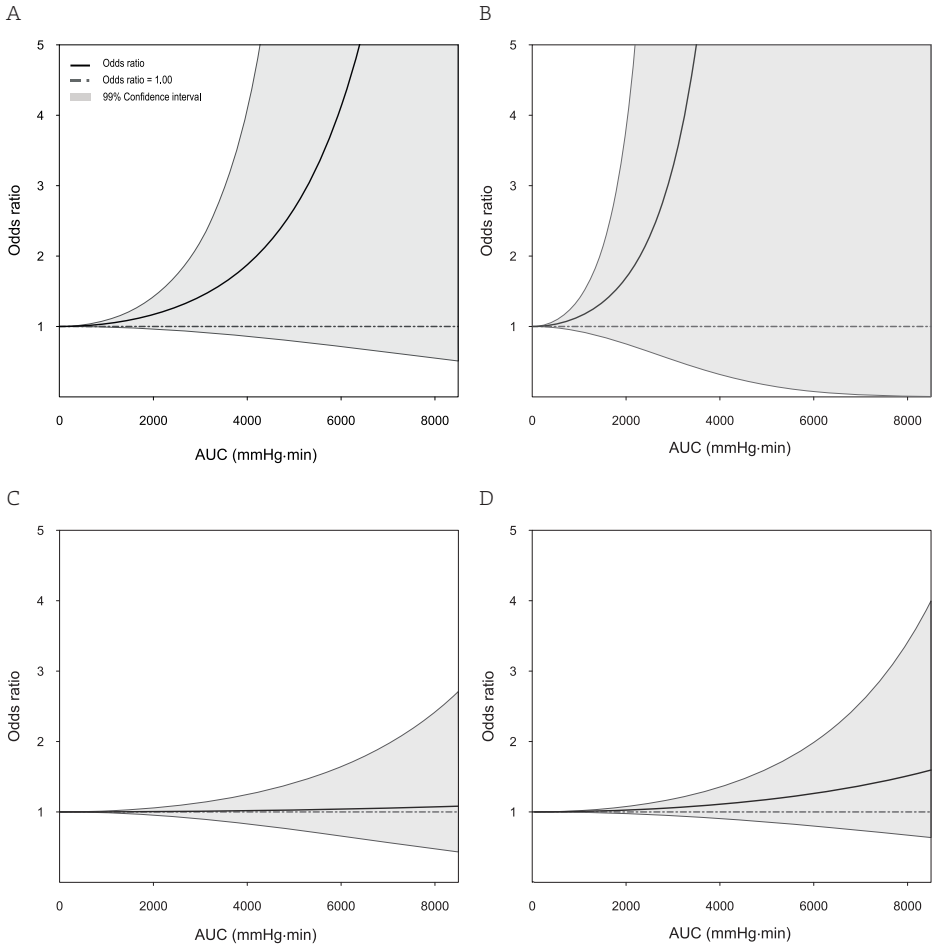

Figure 1 The odds ratio for delirium as a function of intraoperative hypotension

The areas under four mean blood pressure (MAP) thresholds were plotted against the adjusted odds ratios (*solid bold lines*) with their 99% confidence intervals (*solid thin lines*).

Panel a: MAP < 60 mmHg threshold. The median and interquartile range of the area under the curve (AUC) was 1,272 mmHg·min (774 – 1,861 mmHg·min).

Panel b: MAP < 50 mmHg threshold. The median and interquartile range of AUC was 251 mmHg·min (114 – 448 mmHg·min).

Panel c: MAP decrease > 30% relative to baseline. The median and interquartile range of AUC was 1,901 mmHg·min (763 – 3,653 mmHg·min).

Panel d: MAP decrease > 40% relative to baseline. The median and interquartile range of AUC was 631 mmHg·min (183 – 1,570 mmHg·min).

Table 4 Crude and adjusted odds ratios for the association between the area under the curve of intraoperative hypotension during cardiac surgery and occurrence of postoperative delirium

	Unadjusted analysis		
	OR #	**99% CI**	**p-value ‡**
MAP < 60 mmHg	1.05	1.01 - 1.09	< 0.01
MAP < 50 mmHg	1.22	1.02 - 1.66	0.04
MAP decrease > 30% relative to baseline	1.00	0.996 - 1.01	0.23
MAP decrease > 40% relative to baseline	1.00	0.990 - 1.02	0.32

* Results were adjusted for EuroSCORE, duration of surgery and cardiopulmonary bypass, intraoperative fluid, vasopressor and inotrope use. # Estimates per 1000 $mmHg^2 \cdot min^2$ AUC^2 increase of intraoperative hypotension depth and/or duration. ‡Considered statistically significant when $p < 0.01$ and multiple testing was taken into account.

DISCUSSION

Several possible pathophysiologic mechanisms have been proposed for postoperative delirium and cognitive dysfunction after cardiac surgery. The cause of delirium appears to be multifactorial, where patient-related factors interact with perioperative events [32–34]. Specifically, it has been suggested that alterations of neurotransmission, inflammation and an aberrant stress response play a role in the pathogenesis of delirium [34-36]. These include dopaminergic hyperactivity and cholinergic deficiency [36]. Levels of chemokines and cytokines have been associated with delirium as well. These inflammatory mediators may disrupt the blood-brain barrier and thereby induce neuro-inflammation influencing neurotransmission [37, 38]. Further, an aberrant stress response, as indicated by perioperative raised cortisol concentrations has been associated with postoperative delirium [39–41]. Another suggested mechanism is inadequate cerebral perfusion [42]. We therefore hypothesised that IOH is associated with the occurrence of postoperative delirium.

With this observational cohort study using clinical trial data, we investigated whether IOH was related to the occurrence of delirium after cardiac surgery. Our findings contrast with previous studies. Recently, a strategy was developed to prevent occurrence of postoperative delirium in patients undergoing cardiac surgery, by identifying patients with a high risk for poor cerebral haemodynamics. This strategy included preoperative transcranial doppler screening, perioperative cerebral oximetry monitoring, and intraoperative optimisation of cerebral haemodynamics. In this retrospective cohort study, optimisation of intraoperative haemodynamics was found to lower the incidence

Unadjusted analysis		Adjusted analysis*				
75th - 25th percentile					75th - 25th percentile	
OR†	99% CI	OR #	99% CI	p-value ‡	OR†	99% CI
1.14	1.10 - 1.18	1.04	0.99 - 1.10	0.04	1.12	1.07 - 1.16
1.04	0.81 - 1.33	1.14	0.98 - 1.53	0.09	1.03	0.80 - 1.31
1.03	1.03 - 1.04	1.00	0.99 - 1.01	0.45	1.02	1.02 - 1.03
1.01	1.00 - 1.02	1.00	0.99 - 1.02	0.55	1.01	1.0 - 1.02

† Interquartile ranges: MAP < 60 mmHg (774 – 1,861 mmHg·min); MAP < 50 mmHg (114 - 448 mmHg·min); MAP decrease > 30% relative to baseline (763 – 3,653 mmHg·min); MAP decrease > 40% relative to baseline (183 – 1,570 mmHg·min).

Abbreviations: CI: confidence interval; MAP: mean arterial pressure; OR: odds ratio

of postoperative delirium after cardiac surgery [43]. However, there were some limitations, for example the observational design of this study, the fact that delirium assessment has not been performed by trained research personnel and the fact that an important proportion of patients did not receive the complete work-up. These limitations could have resulted in confounding and selection bias. In a recent randomised clinical trial, patients undergoing CABG were randomised to low (60 – 70 mmHg) or high (80 – 90 mmHg) systemic perfusion pressure during CPB. The incidence of postoperative delirium and cognitive dysfunction was significantly higher in the low-pressure group (13%) compared with the high-pressure group (0%, p = 0.017) [5]. However, only the effects of low or high MAP during CPB were studied, and blood pressure before and after CPB were not taken into account. In addition, delirium was assessed with the Mini-Mental-State examination, which has not been designed as a delirium scale. Occurrence of delirium has also been studied in elderly undergoing noncardiac surgery. However, the results of these studies were ambiguous [44-46]. In one study [44], no significant association was found between IOH and the occurrence of delirium, but in two other studies, IOH [45] and the number of hypotensive episodes [46], were significantly associated with the occurrence of postoperative delirium.

The strengths of our study in comparison to the above studies on IOH and delirium, are the large sample size, and the active and continuous monitoring of delirium by trained research personnel during the first four postoperative days. Moreover, in the absence of a universally accepted definition for IOH, we studied four commonly used definitions [13]. We further analysed IOH exposure as a continuous variable instead of a dichotomous variable. We did not dichotomise hypotension as this results in lack of detail and loss of

information. Instead, we used the AUC of a certain blood pressure threshold, which is a function of both duration and severity of hypotension. As a result of the absent pulse pressure during CPB, we only chose definitions which included MAP thresholds and not systolic or diastolic thresholds.

Our study has some limitations. Firstly, although the results were adjusted for a priori defined confounders, residual confounding could still have influenced the results. Secondly, our predefined definitions were arbitrarily chosen non-individualised definitions. Thus, the blood pressure thresholds were not based on patient's individualised cerebral autoregulatory curves. However, there are studies in which patients managed at blood pressures during CPB below their cerebral autoregulatory range, may have an increased risk of postoperative major morbidity or operative mortality [47]. Thirdly, we studied patients who received treatment for hypotension. Although we adjusted for intraoperative vasopressor and inotrope use, it is unknown in which direction and to what extent these drugs influenced the association of IOH and the occurrence of delirium. Fourthly, we assumed that the effect of hypotension was constant over time and that effect modification did not play a role. Finally, we did not register which form of delirium was present when delirium assessment was performed with the CAM(-ICU). Therefore, we might have patients in the immediate postoperative period, particularly with a hypoactive presentation. This might have led to an underestimation of delirium incidence and thus to a bias towards the null hypothesis and subsequent lack of statistical significant findings in this study. For example, the effect of hypotension during induction of anaesthesia was presumed to be similar to the consequences of hypotension later on during surgery. However, in this study we could not discriminate between different parts of surgery (i.e. before, during and after CPB or postoperatively).

The results of the present study have potential clinical implications for intraoperative blood pressure management. Our results suggest that there is no absolute or relative cut-off point for low blood pressure during cardiac surgery, below which the blood pressure should definitely be treated to prevent postoperative delirium. Future studies should focus on autoregulation of cerebral perfusion during cardiac surgery to increase our understanding of IOH and cerebral perfusion. In these studies, a more heterogeneous study population could be analysed, for example patients undergoing noncardiac surgery. In conclusion, independent of the applied definition, IOH was not associated with the occurrence of delirium after cardiac surgery. A small number of patients with prolonged and/or deep hypotension had an increased risk to develop postoperative delirium, but this risk did not reach statistical significance.

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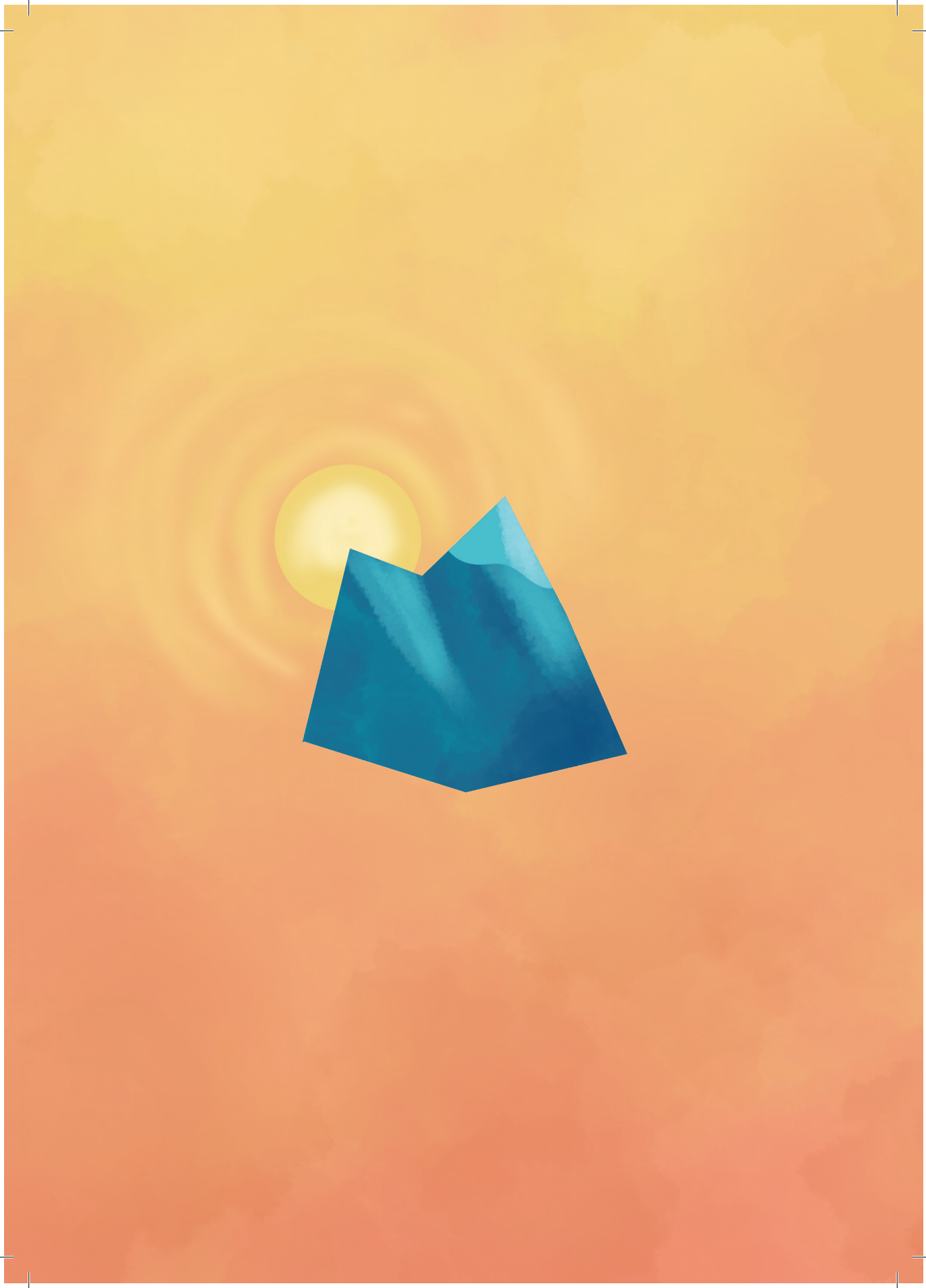

CHAPTER 4

INTRAOPERATIVE HYPOTENSION AND DELIRIUM AFTER TRANSCATHETER AORTIC VALVE REPLACEMENT

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ABSTRACT

Background: Postoperative delirium (POD) is a frequently observed complication after transcatheter aortic valve replacement (TAVR). The effects of intraoperative hypotension (IOH) on POD occurrence are currently unclear.

Methods: A retrospective observational cohort study of patients who underwent TAVR was conducted. We predefined IOH as area under the threshold (AUT) of five mean blood pressures (MAP), varying from < 100 mmHg to < 60mmHg. The AUT consisted of the combination of duration and depth under the MAP thresholds, expressed in mmHg·min. All MAP AUTs were computed based on the complete procedure, independent of procedural phase or duration.

Results: This cohort included 675 patients who underwent TAVR under general anaesthesia (n=128, 19%) or procedural sedation (n=547, 81%). Delirium occurred mostly during the first two days after TAVR, and was observed in n=93 (14%) cases. Furthermore, 674, 672, 663, 630, and 518 patients had at least one minute an intraoperative MAP < 100 mmHg, < 90 mmHg, < 80 mmHg, < 70 mmHg, and < 60 mmHg, respectively. Patients who developed POD had higher AUT based on all five MAP thresholds during TAVR. The penalised adjusted odds ratio varied between 1.08 (99% confidence interval (CI) 0.74 – 1.56) for the AUT based on MAP < 100 mmHg and OR 1.06 (99% CI 0.88 – 1.28) for the AUT based on MAP < 60 mmHg.

Conclusions: Intraoperative hypotension is frequently observed during TAVR, but not independently associated with POD after TAVR. Other potential factors than intraoperative hypotension may explain the occurrence of delirium after TAVR.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has emerged as a valuable option to treat symptomatic severe aortic valve stenosis in older adults considered to be inoperable or at increased risk for surgical aortic valve replacement [1,2]. Compared with surgical replacement, TAVR is a less invasive treatment strategy that is performed on a beating heart without involvement of cardiopulmonary bypass, or sternotomy [3]. Relief of aortic valve stenosis by TAVR is associated with short and mid-term favourable cardiac, haemodynamic and geometrical changes, including improvement of coronary microvascular function, increase in cardiac output and cerebral blood flow, and decrease in interventricular septum and posterior wall thickness [4-7]. Despite improvement in procedural techniques, minimalistic transfemoral approach, and reduced procedural complications rate, the occurrence of postoperative delirium (POD) remains an important complication after TAVR [8].

Delirium is a clinical expression of acute encephalopathy with a multifactorial aetiology and impaired outcome [9]. The reported frequency of POD following TAVR ranges from 10% to 44% depending on the access strategy [10-13]. Clinical adverse outcomes associated with POD after TAVR include prolonged hospital stay, increased readmission rate, and early and long-term post discharge mortality [8, 10-15].

Delirium is a multifactorial syndrome due to predisposing and precipitating factors. The pathophysiology of POD after TAVR is not well understood, and intraoperative hypotension (IOH) is presumed to play a role [16-18].

Patients during TAVR experience IOH and cerebral hypoperfusion due to temporary reduction in cardiac output, particularly during valve deployment. For instance, few studies have shown reduction in cerebral oxygenation during TAVR using Near-Infrared Spectroscopy [19-22]. However, literature on the association of IOH with delirium after TAVR is limited, and heterogeneous with regard to study populations and IOH definitions.

With the increasing number of TAVR procedures, and expanding indications towards patients with lower surgical risk, understanding the aetiologies of delirium is crucial to be able to apply preventive strategies. The aim of this study was to investigate the association between IOH and POD after TAVR.

METHODS

Design and study population

For this retrospective cohort study, consecutive patients were included who underwent TAVR between 26 August 2008 and 29 March 2018 at the University Medical Center Utrecht, Utrecht, the Netherlands. The need to obtain informed consent for the current study was waived by the Institutional Review Board (protocol number 18-287/C). Baseline, clinical, and procedural characteristics were derived from the dedicated local TAVR registry and the electronic medical records.

Preoperative data

Demographic, preoperative and surgical data were collected from the electronic hospital information system (HiX, ChipSoft, Amsterdam, the Netherlands). Frailty was assessed by an interventional cardiologist and/or cardiothoracic surgeon based on informal 'eyeballing' (including cognition function, physical weakness and walking speed). Atrial fibrillation at baseline was defined as a history of atrial fibrillation before TAVR or as the presence of atrial fibrillation on hospital admission. Peripheral artery disease was defined as claudication and/or a history of peripheral surgery and/or angioplasty, and/or stenosis of ≥ 50% of the iliofemoral axis which was assessed prior to TAVR by multislice computed tomography. Carotid artery disease was defined as prior or planned carotid artery intervention and/or ≥ 50% diameter stenosis of the common carotid artery evaluated by computed tomography angiography or Duplex investigation.

Transcatheter aortic valve replacement procedure

All patients had been judged inoperable or at high operative risk by at least one interventional cardiologist and one cardiac surgeon. Motivations to refuse surgical aortic valve replacement in patients were: 1. logistic EuroSCORE ≥15% [23], or 2. the presence of contra-indications to cardiac surgery.

All transfemoral procedures involved a fully percutaneous technique. Local anaesthesia of the access sites was performed by lidocaine infiltration. Procedural sedation was the default method in transfemoral procedures. In non-transfemoral TAVR procedures general anaesthesia was applied. For the transfemoral approach, procedural sedation was established by infusion of the sedative propofol (0,4 – 0,75 $mg \cdot kg^{-1} \cdot h^{-1}$) and the analgesic remifentanil (1,5 – 3 $\mu g \cdot kg^{-1} \cdot h^{-1}$). General anaesthesia was also initiated and maintained with propofol and remifentanil. The level of intraoperative procedural sedation was frequently assessed according to the Ramsay sedation scale and was maintained between 3 - 5 [24]. Intraoperative hypotension was typically treated with fluids, norepinephrine, phenylephrine or ephedrine at the discretion of the anaesthetist.

Intraoperative hypotension

Intraoperative data from the patient monitor and anaesthesia machine were stored as the median for each minute of collected data in the electronic anaesthesia information management system (AnStat®, CarePoint Nederland BV, Ede, the Netherlands). Mean arterial blood pressures (MAP) of both invasive and non-invasive measurements were extracted. If invasive intra-arterial blood pressures were not available at any time point, oscillometric non-invasive blood pressure measurements were used instead when available. Missing blood pressure data was imputed based on a weighted average of a linear slope component (slope from last available blood pressure measurement to the next available measurement) [27]. The following values were considered artefacts and were removed prior to the analyses: diastolic pressure < 20 mmHg or > 200 mmHg, MAP < 0 mmHg and systolic blood pressure < 30 mmHg and > 300 mmHg.

As there is no generally accepted definition of IOH, we predefined IOH as area under the threshold (AUT) of five MAP thresholds (100, 90, 80, 70 and 60 mmHg). The AUT consisted of the combination of duration and depth under these MAP thresholds, expressed in mmHg·min, e.g. a MAP of 50 mmHg during 5 minutes corresponds to an AUT of 10 * 5 = 50 mmHg·min when the threshold was set to a MAP < 60 mmHg. All MAP thresholds were applied during the complete procedure, independent of procedural phase.

Postoperative delirium

The main outcome of this study was the presence of POD during in hospital stay after TAVR. Description of signs of both hypoactive, hyperactive and mixed delirium in patients' records were reviewed using a protocol based on the diagnostic features of delirium in the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) [25]. A delirium observational score (DOS) was rated at the end of every shift by a trained nurse or attending physician according to the local protocol [26]. This way, further evolution (signs) of delirium could be monitored. POD was defined as DOS ≥ 3 and/or a combination of the clinical features. The timing of onset of the delirium was also reviewed.

Potential confounders and missing variables

Based on previously performed studies and clinical experience, the following possible confounders were selected a priori: age (years), sex, EuroSCORE [23,27], preoperative frailty (yes/no), preoperative atrial fibrillation (yes/no), approach (transapical/transfemoral), balloon expandable aortic valves (yes/no), type of anaesthesia (general anaesthesia/procedural sedation) and duration of the procedure (minutes). All potential confounders were used for both the primary analysis and sensitivity analyses. No potential effect modifiers were defined a priori, nor analysed.

Missing values (except blood pressure data and outcome) were imputed through multiple imputation (n = 20 datasets) using predictive mean matching 'rms ('aregImpute' function, 'rms'-package release 5.1-3.1 in R release 3.5.1; R foundation for Statistical Computing, Vienna, Austria). All variables listed in *Table 1* were used during the multiple imputation strategy. Missing blood pressure data was imputed based on a weighted average of a linear slope component (slope from last available blood pressure measurement to the next available measurement) [28]. Patients without any POD assessments during the hospital stay were used for the multiple imputation procedure, but were excluded after imputation and not included in the primary and sensitivity analyses.

Statistical analysis

All analyses were performed using R (release 3.5.1). Skewed continuous data were presented as medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies (percentage). Based on assessment for nonlinearity, age and areas under the MAP threshold were analysed in regression models after transformation with restricted cubic splines with three knots. The association between IOH based on five MAP thresholds and occurrence of POD was analysed with multivariable logistic regression models using penalised maximum likelihood estimation ('lrm' function, 'rms'-package, release 5.1-3.1). Bootstrapping (n = 500 repetitions) and penalisation were used to determine and optimise model performance. Penalisation is a shrinkage procedure to avoid overfitting of the model [29]. The 'rms' function 'pentrace' was used for the selection of penalty factors with a vector containing the following predefined penalties: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24. The results of the regression analyses were expressed as scaled adjusted odds ratios (OR) between the 75th and 25th percentile with 99% confidence intervals (CI). Statistical significance was defined as a two-sided α of 0.01.

During data analysis, a profound difference in delirium incidence and areas under various MAP thresholds was noted. Therefore, post hoc secondary analyses were performed to compare the association between profound IOH, indicated by MAP < 70 mmHg and < 60 mmHg, and occurrence of POD in patients who underwent procedural sedation or general anaesthesia. Due to the limited numbers of patients who underwent TAVR under general anaesthesia, the numbers of potential confounders included in the models were limited compared to the primary analyses. Age (included in EuroSCORE), sex (included in EuroSCORE and frailty (comparable incidence in both groups)) were not included in these models.

RESULTS

We included 753 patients, of whom 78 (10%) were excluded because the primary outcome was missing. Of the remaining 675 patients, 93 patients (14%) developed POD. Patients who developed POD after TAVR were more often male and had a higher EuroSCORE, a smaller aortic valve area, and more frequently carotid stenosis. General anaesthesia and a non-transfemoral approach were also more common among patients with POD compared to patients who did not develop POD (*Table 1*). Depending on the threshold, 674 (100% with MAP < 100 mmHg) and 518 patients (77% with MAP < 60 mmHg) had at least one minute of IOH. Patients with POD had higher AUTs based on all five thresholds compared to patients who did not develop delirium (*Table 1*).

We did not find a statistically significant association between IOH for any threshold and occurrence of POD after TAVR. The scaled penalised adjusted ORs between the 75th and 25th percentiles for each AUT threshold varied between OR 1.08 (99% CI 0.74 – 1.56) for the AUT based on MAP < 100 mmHg and OR 1.06 (99% CI 0.88 – 1.28) for the AUT based on MAP < 60 mmHg (*Table 2*).

The total AUTs for each defined threshold and duration of the procedure were higher in patients who underwent general anaesthesia compared to patients who underwent procedural sedation (*Supplementary table 1*). In other words, the total area under the threshold (consisting of depth and duration) for each MAP threshold was larger for patients who underwent general anaesthesia compared to procedural sedation. In addition to the main analyses which were adjusted for type of anaesthesia, we performed post-hoc sensitivity analyses in patients who underwent general anaesthesia (n = 128), and procedural sedation (n = 574). We did not find an association between MAP < 70 mmHg (general anaesthesia: scaled penalised OR 1.07 (99% CI 0.65 – 1.75), sedation: scaled penalised OR 0.99 (99% CI 0.79 – 1.25)) or MAP < 60 mmHg (general anaesthesia: scaled penalised OR 1.41 (99% CI 0.37 – 5.30), procedural sedation: scaled penalised OR 1.27 (99% CI 0.62 – 2.58)) and occurrence of POD after TAVR (*Supplementary table 2*).

Table 1 Patient and procedural characteristics

Age, years, median [IQR]
Sex, male, n (%)
Preoperative comorbidities, conditions and medication
EuroSCORE, median [IQR] [23,27]
Frailty, n (%)
Hypertension, n (%)
Diabetes mellitus, n (%)
Transient ischaemic attack, n (%)
Stroke, n (%) • No • Ischaemic • Haemorrhagic
Heart failure, NYHA class 3 or 4, n (%)
Atrial fibrillation, n (%)
Estimated glomerular filtration rate, ml·min·1,73 m^{-2}, median [IQR]
Procedure specific characteristics
Type of anaesthesia, general anaesthesia, n (%)
Duration of procedure, minutes, median [IQR]
Approach, transfemoral, n (%)
Aortic valve type, balloon expandable, n (%)
Intraoperative haemodynamic variables and medication
Area under the blood pressure threshold, mean blood pressure < 100 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 90 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 80 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 70 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 60 mmHg, mmHg·min, median [IQR]

Abbreviations: IQR: interquartile range

	All patients (n = 675)	Postoperative delirium (n = 93)	No postoperative delirium (n = 582)	Missings n (%)
	81 [77 – 85]	82 [79 – 85]	81 [76 – 85]	
	308 (46)	37 (40)	271 (47)	
	14 [10 – 21]	16 [12 – 25]	14 [10 – 20]	6 (1)
	304 (45)	47 (51)	257 (44)	
	425 (63)	66 (71)	359 (62)	
	202 (30)	30 (32)	172 (30)	
	97 (14)	12 (13)	85 (15)	
	592 (88)	84 (90)	508 (87)	
	75 (11)	6 (7)	69 (12)	
	8 (1)	3 (3)	5 (1)	
	361 (54)	55 (59)	306 (53)	
	233 (35)	34 (37)	199 (34)	
	59 [45 – 73]	58 [47 – 69]	59 [45 – 74]	1 (0)
	128 (19)	34 (37)	94 (16)	
	143 [124 – 164]	153 [135 – 182]	140 [123 – 160]	1 (0)
	574 (85)	63 (68)	511 (88)	
	551 (73)	70 (75)	414 (71)	
	2,310 [1,190 – 3,310]	2,530 [1,340 – 4,110]	2,050 [1,160 – 3,080]	14 (2)
	1,110 [505 – 2,080]	1,260 [643 – 2,760]	1,030 [487 – 1,960]	14 (2)
	414 [163 – 1,080]	536 [266 – 1,620]	395 [147 – 964]	14 (2)
	119 [31 – 402]	208 [69 – 701]	106 [26 – 358]	14 (2)
	26 [3 – 99]	75 [16 – 233]	23 [0.25 – 90]	14 (2)

Table 2 Intraoperative hypotension, area under various blood pressure thresholds and occurrence of postoperative delirium

Area under the blood pressure threshold, mean blood pressure < 100 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 90 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 80 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 70 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 60 mmHg, mmHg·min

Five separate logistic regression models were fitted for five mean blood pressure thresholds on the association between intraoperative hypotension and postoperative delirium. The results are expressed as a scaled adjusted odds ratio between the 75th and 25th percentile and as a scaled penalised adjusted odds ratio with 99% confidence intervals.

Index value/ category	Reference value/category	Adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)	Penalised adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)
1,190	3,310	0.96 (0.51 – 1.80)	1.08 (0.74 – 1.56)
505	2,080	1.00 (0.49 – 2.03)	1.08 (0.75 – 1.55)
163	1,080	1.13 (0.52 – 2.45)	1.08 (0.78 – 1.50)
31	402	1.38 (0.63 – 3.03)	1.08 (0.83 – 1.40)
3	99	1.65 (0.84 – 3.24)	1.06 (0.88 – 1.28)

The index value represents the 25th percentile of a continuous variable or index category of a categorical variable. The reference value represents the 75th percentile of a continuous variable or reference category of a categorical variable.
Abbreviations: CI: confidence interval

Supplementary table 1 Patient and procedure characteristics

Postoperative delirium, n (%)
Age, years, median [IQR]
Sex, male, n (%)
Preoperative comorbidities, conditions and medication
EuroSCORE, median [IQR] [23, 27]
Frailty, n (%)
Hypertension, n (%)
Atrial fibrillation, n (%)
Coronary artery disease, n (%)
Procedure specific characteristics
Duration of procedure, minutes, median [IQR]
Approach, transapical, n (%)
Aortic valve type, balloon expandable, n (%)
Intraoperative haemodynamic variables and medication
Area under the blood pressure threshold, mean blood pressure < 100 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 90 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 80 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 70 mmHg, mmHg·min, median [IQR]
Area under the blood pressure threshold, mean blood pressure < 60 mmHg, mmHg·min, median [IQR]
Heart rate, beats per minute, median [IQR]
Peripheral capillary oxygen saturation, %, median [IQR]
Intraoperative need for vasopressor therapy, yes, n (%)
Intraoperative need for inotrope therapy, yes, n (%)

Abbreviations: BMI: body mass index; NYHA: the New York Heart Association functional classification; IQR: interquartile range

	All patients (n = 675)	General anaesthesia (n = 128)	Procedural sedation (n = 547)	Missings n (%)
	93 (14)	34 (27)	59 (11)	
	81 [77 – 85]	80 [74 – 84]	81 [77 – 85]	
	308 (46)	71 (56)	237 (43)	
	14 [10 – 21]	17 [12 – 26]	14 [9 – 20]	6 (1)
	304 (45)	57 (45)	247 (45)	
	425 (63)	90 (70)	335 (61)	
	233 (35)	35 (27)	198 (36)	
	336 (50)	83 (65)	253 (46)	
	143 [124 – 164]	170 [153 – 189]	136 [120 – 155]	1 (0)
	574 (85)	100 (78)	1 (1)	
	551 (73)	116 (91)	368 (67)	
	2,080 [1,190 – 3,310]	4,150 [3,250 – 5,030]	1,720 [1,030 – 2,700]	14 (2)
	1,110 [505 – 2,080]	2,750 [1,990 – 3,530]	844 [424 – 1,580]	14 (2)
	414 [163 – 1,080]	1,540 [986 – 2,110]	301 [126 – 697]	14 (2)
	119 [31 – 402]	604 [359 – 1,000]	75 [23 – 229]	14 (2)
	26 [3 – 99]	162 [70 – 312]	15 [0 – 58]	14 (2)
	69 [62 – 79]	62 [54 – 72]	70 [64 – 80]	13 (2)
	97 [95 – 98]	98 [97 – 99]	97 [95 – 98]	13 (2)
	556 (82)	125 (98)	431 (79)	
	12 (2)	7 (6)	5 (1)	

Supplementary table 2 Association between area under the blood pressure thresholds and occurrence of postoperative delirium

General anaesthesia (n = 128)
Area under the blood pressure threshold, mean blood pressure < 70 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 60 mmHg, mmHg·min
Procedural sedation (n = 547)
Area under the blood pressure threshold, mean blood pressure < 70 mmHg, mmHg·min
Area under the blood pressure threshold, mean blood pressure < 60 mmHg, mmHg·min

The results are expressed as a scaled adjusted odds ratio between the 75th and 25th percentile and as a scaled penalised adjusted odds ratio with 99% confidence intervals. The index value represents the 25th percentile of a continuous variable or index category of a categorical variable.

DISCUSSION

In summary, IOH was common during TAVR, and patients who developed POD had higher AUTs based on all predefined five MAP thresholds. Patients who developed POD compared to those who did not had a higher operative risk, smaller aortic valve area, suffered more from carotid stenosis, and underwent frequently non-transfemoral TAVR with general anaesthesia. In the multivariable analyses, IOH was however not associated with POD after TAVR when adjusted for possible confounding factors, as the observed effects were clinically irrelevant. Neither was IOH associated with POD according to the type of anaesthesia: the effects were small with limited clinical relevance, but with very large uncertainties in their estimates.

Due to the lack of widely accepted uniform definition of IOH, and different settings and outcome, it is difficult to define a common 'cut-off' for IOH associated adverse postoperative outcomes [30,31]. In the 2012 ACCF/AATS/SCAI/STS expert consensus document on TAVR, maintenance of a MAP of > 75 mmHg (or systolic blood pressure of at least 120 mmHg) during TAVR has been advised [32]. In the current study we analysed data according to the five frequently used hypotension definitions pending a widely accepted definition of IOH [30,33].

Our findings, that IOH was not associated with POD, may be explained by adaptation in elderly with severe aortic valve stenosis to chronic reduced cardiac output and chronic cerebral hypoperfusion [34]. Recent studies show an immediate increase in cardiac output

	Index value/ category	Reference value/category	Adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)	Penalised adjusted scaled odds ratio between the 75th and 25th percentile (99% CI)
	359	1,000	1.41 (0.46 – 4.43)	1.07 (0.65 – 1.75)
	70	312	1.41 (0.37 – 5.30)	1.07 (0.71 – 1.62)
	23	229	1.17 (0.53 – 2.60)	0.99 (0.79 – 1.25)
	0	58	1.27 (0.62 – 2.58)	1.01 (0.86 – 1.19)

The reference value represents the 75th percentile of a continuous variable or reference category of a categorical variable. †: model fit not possible, only 1 patient with transapical approach in this group.
Abbreviations: CI: confidence interval

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and cerebral blood flow following TAVR, suggesting a reserved or even decreased cerebral blood flow pre-TAVR [7,35]. Our findings put forward the hypothesis that a chronic cerebral hypoperfusion pre-TAVR, may result into tolerance to an acute drop in IOH with a short duration during TAVR, a phenomenon called brain ischaemic pre-conditioning [36-38]. Another factor which may explain our findings is the alleviation of possible neurocognitive harmful effect of IOH due to physiologic cerebral autoregulation [39,40]. Future prospective studies are needed to investigate the above-mentioned hypothesis following TAVR.

According to the literature, non-transfemoral TAVR is a strong predictor of POD after TAVR [8,12,14,41]. Substantial impact of non-transfemoral access on the onset of POD, as compared to the less invasive transfemoral access, suggests that several factors can explain this difference: a more advanced cerebro- and cardiovascular pathology (i.e., atherosclerosis), the need for general anaesthesia during the non-transfemoral procedure, the intensive care unit stay, postoperative wound pain which goes together with increased use of opioids, and postoperative inflammatory response [42]. Our findings suggest that IOH during general anaesthesia is not a contributing factor for the increased risk of POD after a non-transfemoral procedure, and that other potential factors may explain this increased risk. Based on the literature findings, in order to reduce the burden of delirium after TAVR we recommend, if reasonable, to avoid non-transfemoral access, and decrease the use of periprocedural general anaesthesia and opioids.

A strength of this study is that we used continuous variables during TAVR in order to reduce loss of information, and analysed them with restricted cubic splines. Another strength is that a multiple imputation method was used for missing data. Furthermore, in order to minimise overfitting and optimise model performance, penalisation and bootstrapping methods were used [29].

There are however several important limitations of this study. First, this is an analysis of retrospectively collected data with inherent limitations. Therefore, our results should be interpreted as hypothesis generating. Second, in the majority of cases delirium was diagnosed using DOS scores combined with clinical features. According to the local protocol, DOS scores should be registered during every shift. However, in some patients, DOS scores were not reported or were missing. Moreover, by using DOS scores the hypoactive type of delirium may be easily overlooked. Third, we have excluded patients without POD assessment which could have led to an under- or overestimation of the number of delirium cases in this study. Fourth, there may have also been other time-dependent variables which could influence the incidence of delirium that we did not include in our analyses, such as blood pressure variability during rapid ventricular pacing. To facilitate precise prosthesis positioning and to reduce the risk of device embolisation and malpositioning, rapid ventricular pacing is required during valve deployment for temporary reduction in cardiac output, transvalvular flow, and cardiac motion [43]. Rapid ventricular pacing was found to be associated with transient IOH, cerebral perfusion disturbances, and POD after TAVR [19-22, 44-46]. Finally, our post-hoc sensitivity analysis was underpowered due to the small sample size of patients undergoing TAVR with general anaesthesia. Therefore, larger studies are needed to assess the effect of general anaesthesia on delirium occurrence after TAVR.

In conclusion, this study shows that IOH is frequent during TAVR. Our findings do not suggest an association between IOH during TAVR and delirium thereafter. Other potential factors rather than intraoperative hypotension may explain the development of delirium among the elderly undergoing this treatment.

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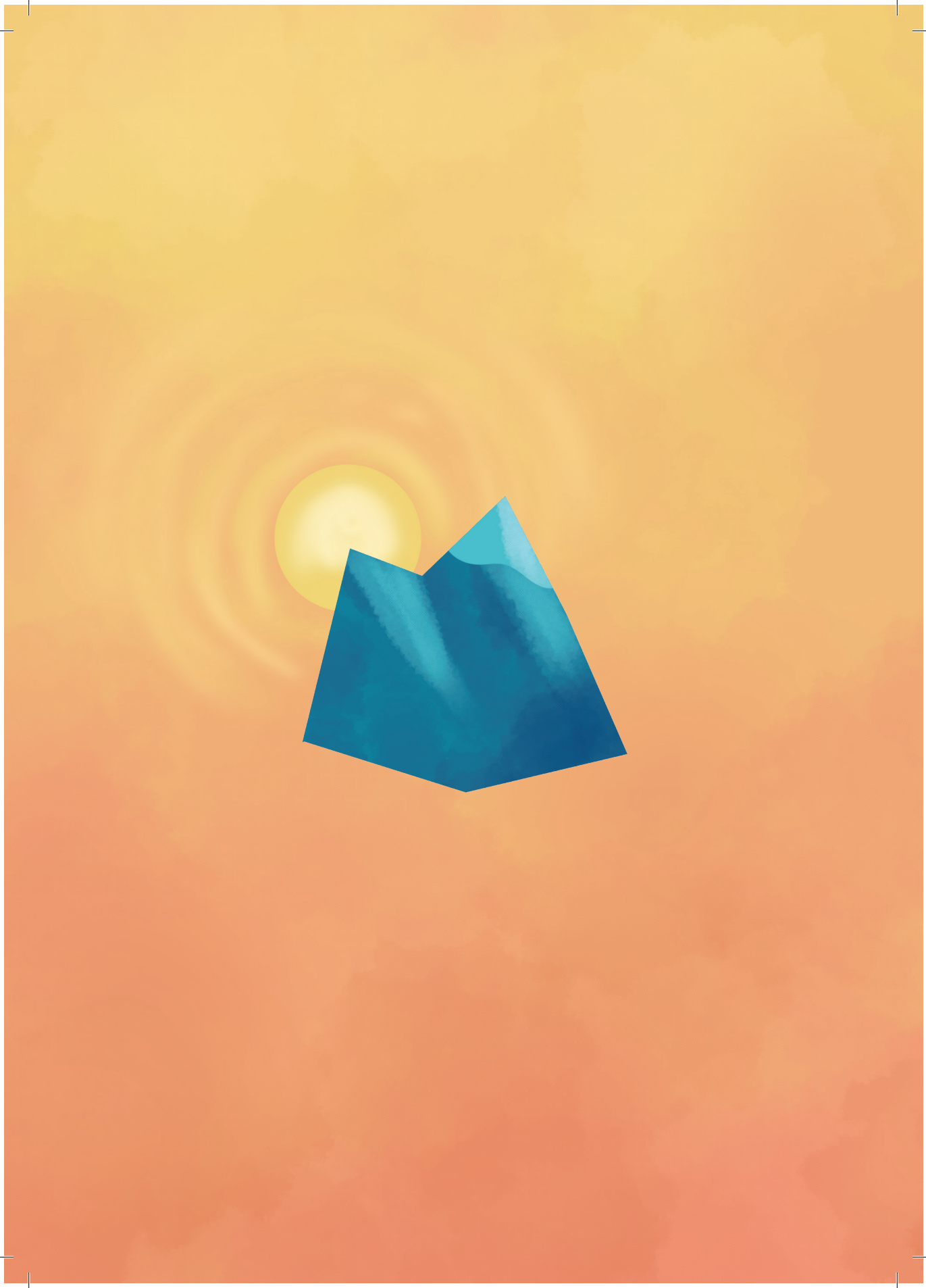

CHAPTER 3

β-BLOCKER SELECTIVITY IS NOT ASSOCIATED WITH CEREBRAL ISCHAEMIA DURING CAROTID ENDARTERECTOMY

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ABSTRACT

Purpose: Perioperative β-blocker use is common in patients undergoing carotid endarterectomy (CEA), but could impair cerebral perfusion. Differences in adrenergic receptor selectivity of β-blockers, i.e. imbalance between β1- and β2-mediated effects, may underly these effects. The present study aimed to estimate the association between β-blocker selectivity and intraoperative cerebral perfusion, by assessing the need for an intraluminal shunt during CEA.

Methods: A single center historical cohort study was conducted in participants of the AtheroExpress study who underwent CEA. The need for an intraluminal shunt was based on ischaemic changes with EEG monitoring or transcranial Doppler measurements All β-blockers were categorised into four groups: no β-blocker use, metoprolol and β-blockers with a higher (bisoprolol, atenolol) or lower (propranolol, labetalol, sotalol) β1/β2-selectivity ratio than metoprolol. The association between β-blocker selectivity ratio and the need for an intraluminal shunt was analysed.

Results: Of the 1,120 included patients, 151 patients (13%) were shunted (12 (21%) patients in the lower β1/β2 selectivity ratio group, 33 (11%) in the metoprolol group and 22 (18%) in the higher β1/β2 selectivity ratio group). β-blocker selectivity was not associated with the need for an intraluminal shunt (lower β1/β2 selectivity ratio: odds ratio (OR) 1.14 (95% confidence interval (95% CI) 0.70 – 1.86), metoprolol: OR 0.82 (95% CI 0.57 – 1.18), higher β1/β2 selectivity ratio: OR 1.14 (95% CI 0.75 – 1.72)). Preoperative β-blocker use, independent of selectivity was not associated with intraluminal shunting.

Conclusion: β-blocker selectivity was not associated with the need for an intraluminal shunt during CEA.

INTRODUCTION

Many patients scheduled for surgery chronically use β-blockers to lower their life-time risk of cardiovascular events. However, the initiation and continuation of β-blockers before noncardiac surgery remains a topic of debate for years [1]. The potentially favourable effects of β-blockers with regard to decreased risks of perioperative myocardial ischaemia might be counterbalanced by increased risks of postoperative stroke [2]. Variations in prescription indications and pharmacologic properties of β-blocker types make it difficult to compare the beneficial and harmful effects of the different β-blockers studied in the perioperative setting [3–5]. It has been suggested that differences in adrenergic receptor selectivity, i.e. an imbalance between β1- and β2-mediated effects on oxygen delivery to organs during periods of hypoxia and anaemia, are key to understand these perioperative effects [6]. It was shown that metoprolol decreases cardiac output predominantly by β1-antagonism and attenuates the compensatory β2-mediated vasodilation of isolated cerebral arteries in vitro [7].

Recent clinical studies support the theory that β-blockers with different selectivity have different effects on regional perfusion. If true, cerebral perfusion differences due to β-blockers should also be noticeable during carotid surgery. In a case-control study, perioperative β-blocker use was one of the perioperative risk factors associated with the need for intraluminal shunting during carotid endarterectomy (CEA) (odds ratio (OR) 2.5, 95% confidence interval 1.2 – 5.1) [8]. However, no additional information was provided on the clinical mechanisms of β-blockers on cerebral perfusion and this study did not provide details on the β1/β2-selectivity ratio of the β-blockers involved.

CEA is an effective intervention to prevent ischaemic stroke in patients with severe atherosclerosis of the carotid arteries. During CEA, cerebral perfusion is often monitored with electroencephalography (EEG) and transcranial Doppler (TCD). Changes in these monitoring signals after initial temporary carotid cross clamping, may indicate cerebral hypoperfusion. In such cases a temporary, intraluminal shunt is used during the procedure to provide collateral blood flow to the brain in order to prevent cerebral ischaemia [9].

The primary aim of our study was to analyse the association between β-blocker use and the need for intraluminal shunting during CEA, as a sign of compromised cerebral blood flow, taking into account the selectivity of the β-blocker. In previous studies, it has been shown that β-blocker use was associated with higher incidences of intraoperative hypotension in patients undergoing vascular surgery [10,11]. As the hypothetical negative effects of β-blockers with a lower β1/β2 selectivity ratio might be exerted by increased incidence of intraoperative hypotension, we also explored the effects of β-blockers and their selectivity on the occurrence of intraoperative hypotension.

METHODS

Patient population

This cohort study was performed using data from the AtheroExpress Biobank (AEB) study [12]. The inclusion criteria for this prospective cohort have previously been described, and patient inclusion and data collection are still ongoing. In short, the AEB study is a longitudinal biobank study conducted following Good Clinical Practice standards and national regulations. For the current study on preoperative β-blocker use and the need for an intraluminal shunt, the Medical Ethics Committee of the University Medical Center Utrecht waived the need to obtain separate informed consent (protocol number 15-286). The study includes blood and plaque specimens of patients undergoing carotid and/or iliofemoral endarterectomy in two tertiary vascular referral hospitals in The Netherlands: the St. Antonius Hospital in Nieuwegein and the University Medical Center Utrecht [13]. For the current historical cohort study on perioperative β-blocker use, their selectivity and the need for intraluminal shunting, a subgroup of adult patients was included. Patients with symptomatic carotid disease, underwent elective, emergent or re-do CEA between 4 January 2001 and 28 July 2016 at the University Medical Center Utrecht. No statistical power calculation was conducted prior to the study. We included all eligible patients in the prospective AEB cohort who met the inclusion criteria and did not meet the exclusion criteria. All patients gave informed consent to participate in the AEB study.

Data collection

Preoperative data were obtained from the AEB study dataset, including patient characteristics, comorbidities and medications. Intraoperative variables were derived from the anaesthesia information management system (AnStat; Carepoint, Ede, the Netherlands). All patients underwent general anaesthesia. The anaesthesia technique and treatment of intraoperative hypotension was left to discretion of the anaesthetist. Anaesthesia was typically initiated using boluses propofol and sufentanil. Rocuronium 0.6 $mg \cdot kg^{-1}$ was given to facilitate orotracheal intubation. For maintenance, inhalational anaesthesia with sevoflurane or isoflurane was applied together with boluses sufentanil i.v. Intraoperative hypotension was typically treated with fluids, noradenaline, phenylephrine or ephedrine.

The exposure of interest was the perioperative use of β-blockers and their selectivity for the β1-adrenoreceptor in comparison to the β2-adrenoreceptor. Perioperative β-blockers were continued in the perioperative period, including the day of surgery. As there is no uniform classification of β-blocker selectivity, we used the selectivity classification according to the β1/β2 selectivity ratios reported in a study using hamster

ovary cells expressing the human β1-adrenoreceptor or β2-adrenoreceptor [14]. Based on this study, we divided β-blockers into three exposure groups: metoprolol, β-blockers with higher β1/β2-selectivity ratio than metoprolol and β-blockers with lower β1/β2-selectivity ratio than metoprolol (*Box*).

Box Overview of β-blocker selectivity based on mammalian cells expressing human β-adrenoreceptor subtypes

	β1/β2 selectivity ratio	**β-blocker exposure group**
Bisoprolol	13.5	Higher β1/β2 selectivity compared to metoprolol
Atenolol	4.7	
Metoprolol	2.3	Metoprolol (β-blocker reference)
Labetalol	0.5	Lower β1/β2 selectivity compared to metoprolol
Propranolol	0.1	
Sotalol	0.1	

β-blocker selectivity was determined with whole cell-binding studies in Chinese Hamster Ovary cell lines expressing human β1-adrenoceptor or human β2-adrenoceptor [14].

Intraoperative hypotension was defined as duration and area under various, predefined thresholds based on the mean blood pressure (MAP) during surgery. Duration was expressed as the cumulative number of minutes below a MAP threshold and area under the threshold consisted of the combination of duration and depth under the MAP threshold, expressed in mmHg·min. Oscillometric non-invasive blood pressure measurements were used when intra-arterial blood pressures were not available at any time point.

The primary outcome under study was the insertion of an intraluminal shunt after cross-clamping of the carotid artery due to signs of cerebral ischaemia. According to our local protocol every patient is monitored with EEG and TCD recordings by a dedicated technician. Before cross-clamping, in close collaboration with the surgeon, the anaesthetist targets systolic or mean blood pressure to 30 - 40 mmHg above the preinduction blood pressure of the patient. After reaching this blood pressure target, a test cross-clamping of two minutes is performed. The results of this test phase are analysed by the dedicated technician under supervision of the neurologist-physiologist. Increase of asymmetry in EEG and/or a large decrease in the medial cerebral artery flow indicated by TCD are the most important considerations in shunt placement. The decision for shunt placement is based on the interpretation of the neurologist-

physiologist and is independent of the surgeon or anaesthesia provider. The anaesthesia information management system and hospital records were screened for the use of an intraluminal shunt during CEA by two independent researchers who were blinded for all other patient-related and perioperative variables.

As suggested in the introduction, intraoperative hypotension might be one of the potential mechanisms by which preoperative β-blockers might impair cerebral perfusion. We explored differences in duration and area-under-the-threshold of intraoperative hypotension among no β-blocker users and the three above described β-blocker exposure groups as a secondary outcome.

Missing variables and potential confounders

We used multiple imputation for all missing variables in *Table 1*. Twenty multiple complete datasets were created by multiple imputation with the 'aregImpute' function using predictive mean matching from the 'Hmisc' (release 4.1.1) in R (release 3.4.1; R foundation for Statistical Computing, Vienna, Austria). Missing blood pressure data was imputed based on a weighted average of a linear slope component (slope from last available blood pressure measurement to the next available measurement) [15]. Based on previously performed studies and clinical experience, the following possible confounders for the association between β-blocker selectivity and intraluminal shunting were selected a priori and included in all models: age, sex, hypertension, coronary artery disease, diabetes mellitus, history of stroke, preoperative renal function, degree of ipsilateral carotid stenosis, degree of contralateral carotid stenosis, haemoglobin level and low-density lipoprotein level. All potential confounders were used for both the primary analysis and sensitivity analyses. No potential effect modifiers were defined a priori, nor analysed.

Statistical analyses

All analyses were performed using R (release 3.4.1). Skewed continuous data are presented as medians with interquartile ranges (IQR). Categorical variables are expressed as frequencies (percentage). A preplanned multivariable logistic regression analysis was used to study the association between β-blocker selectivity and an intraluminal shunt during CEA (lrm function, 'rms'-package, release 5.1-2) and was expressed as penalised adjusted ORs with 95% confidence intervals (95% CI). No meaningful effect size was defined prior to the analyses. During the data analysis, collinearity was considered using variance inflation factors which were based on the covariance matrix of the fitted model.

Bootstrapping (n = 500 repetitions) and penalisation was used to determine and optimise model performance. Penalisation consisted of penalised maximum likelihood estimation ('pentrace' function) with the following penalties: 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24. Penalisation

is a shrinkage procedure to avoid overfitting of a model. Penalised regression coefficient estimates can substantially deviate from the unadjusted and adjusted estimates. The regression coefficient estimates after shrinkage are more likely to be close to the true values [16]. Based on assessment for nonlinearity, age, preoperative renal function, haemoglobin level and low-density lipoprotein were analysed in the regression model after transformation with restricted cubic splines. Statistical significance was defined as a two-sided α of 0.05.

Additional post hoc secondary analyses

The first post-hoc analysis was to explore the association between β-blocker use and an intraluminal shunt during CEA by multivariable logistic regression analysis with the confounders listed above. Based on the insight of different indications for different β-blockers, additional post-hoc analyses were performed. The sensitivity analyses include addition of a propensity score for all β-blocker groups, analysed with multivariable logistic regression analysis. The 20th multiple imputation set was used. The propensity models were initiated by adding all previously defined potential confounders (*Table 2 and Table 3*) to four logistic regression models with one of the four β-blocker groups (no preoperative β-blocker, lower β1/β2 selectivity ratio, metoprolol, higher β1/β2 selectivity ratio) as the dependent variable. Continuous variables were added with restricted cubic splines with three knots. After assessment of the balance using absolute standardised differences, high-density lipoprotein cholesterol level and an interaction term between age and Body Mass Index were added to all propensity score models. Nearest neighbour matching with a 1:3 ratio was performed using the logit of the propensity score models and the average treatment effect (ATE) was estimated (Match, Matching package release 4.9-6). Matching was performed with four calipers widths (0.10, 0.20, 0.30 and 0.40) to find the optimal balance. The optimal caliper width of 0.30 was used for all analyses.

RESULTS

This cohort included 1,141 patients who underwent CEA under EEG and TCD monitoring. Eleven patients (1%) were excluded because they used β-blockers (pindolol (n = 1), carvedilol (n = 2), celiprolol (n = 2), nebivolol (n = 6)) for which β-blocker selectivity could not be obtained according to the methods described. Ten patients (0.9%) could not be evaluated because of insufficient information to establish the connection between the AtheroExpress dataset and intraoperative anaesthesia data. Of the 1,120 remaining patients, 484 (43%) used a β-blocker. β-blocker users had more comorbidity compared to patients who did not use β-blockers (*Table 1*). Patients on β-blockers with higher β1/

β2 selectivity ratio than metoprolol (atenolol and bisoprolol) had less comorbidity compared to users of other β-blockers (*Table 1*). In *Supplementary table 1* (*Appendix 2*) patients were compared who received a shunt with those who did not.

One-hundred-fifty-one patients required intraluminal shunting (*Table 1*): 84 (13%) of the 636 patients not using β-blockers and 67 (14%) of the 484 patients on β-blockers. Higher degree of contralateral occlusion (OR 2.28 (95% CI 1.50 – 3.48)) and a lower estimated glomerular filtration rate (OR 1.43 (95% CI 1.07 – 1.90)) were associated with a higher risk for the need for an intraluminal shunt. We did not find an association between β-blocker selectivity and the need for an intraluminal shunt (*Table 2*).

To further explore the effects of different indications for different β-blockers, additional post hoc sensitivity analyses were performed among four β-blocker groups (no preoperative β-blocker, lower β1/β2 selectivity ratio than metoprolol, metoprolol, higher β1/β2 selectivity ratio than metoprolol). The results from the propensity matched analyses yielded similar results compared to the main analyses. The median standardised differences for the four β-blocker groups before matching were 0.13 (IQR 0.08 – 0.28), 0.19 (IQR 0.11 – 0.36), 0.10 (IQR 0.05 – 0.16) and 0.11 (IQR 0.04 – 0.13) before matching, respectively. The median standardised differences for the four β-blocker groups before matching were 0.02 (IQR 0.01 – 0.03), 0.12 (IQR 0.04 – 0.23), 0.03 (IQR 0.02 – 0.06) and 0.07 (IQR 0.03 – 0.10) after matching, respectively (*Supplementary tables 2 – 5 (Appendix 2)*). None of the four β-blocker groups was associated with the need for an intraluminal shunt. For patients not on a β-blocker therapy, the propensity matched absolute risk reduction was - 0.1% (95% CI 4.9% - 4.7%). For the groups lower β1/β2 selectivity ratio than metoprolol, metoprolol, and higher β1/β2 selectivity ratio than metoprolol the propensity matched absolute risk reduction was 10.7% (95% CI -0.9% - 22.3%), 2.1% (95% CI -3.1% - 7.3%) and - 1.7% (95% CI -9.5% - 6.1%), respectively (*Supplementary tables 2 – 5 (Appendix 2)*).

The incidence of intraoperative hypotension, expressed as both duration and area under various MAP thresholds, was comparable between β-blocker users and patients who did not receive preoperative β-blockers (*Figure 1a and Figure 1b*). In these analyses, no differences were found between β-blockers with lower β1/ β2 selectivity ratio compared to metoprolol, metoprolol and higher β1/β2 selectivity ratio compared to metoprolol.

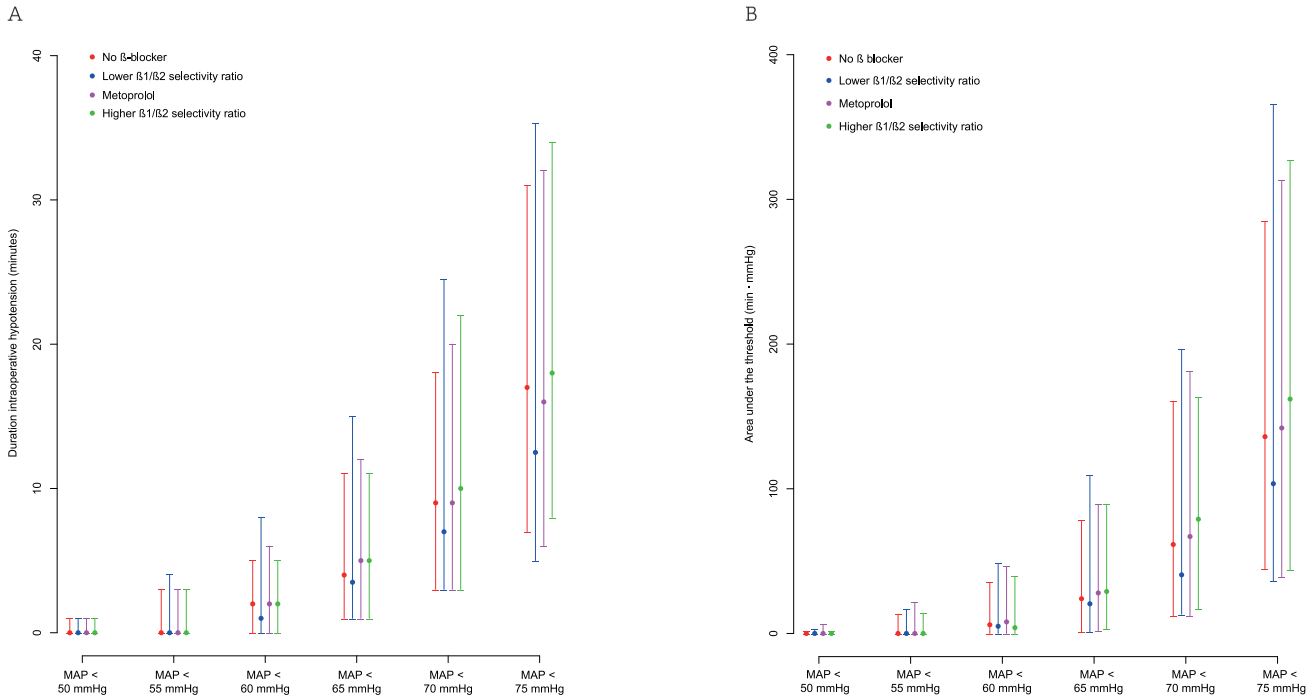

Figure 1 Duration and area various mean blood pressure thresholds by β-blocker exposure group

Hypotension duration and the areas under the threshold were compared between β-blocker users and patients who did not receive a β-blocker. No differences were found between patients who patients who did not receive preoperative β-blockers and patients who received preoperative metoprolol or β-blockers with lower or higher β1/β2 selectivity ratio compared to metoprolol.

Panel a: The incidence of intraoperative hypotension expressed as duration of mean blood pressure thresholds between 50 and 75 mmHg.

Panel b: The incidence of intraoperative hypotension expressed as the area under mean blood pressure thresholds between 50 and 75 mmHg.

Table 1 Patient and baseline characteristics for the overall cohort and according to β-blocker use

Age, years	
median [IQR]	
Sex, male, n (%)	
Carotid stenosis characteristics	
Stenosis type, n (%)	
De novo, n (%)	
Restenosis, n (%)	
Ipsilateral carotid stenosis, n (%)	
0 – 50%	
50 – 70%	
70 – 99%	
Contralateral carotid stenosis, n (%)	
0 – 50%	
50 – 70%	
70 – 99%	
100%	
Cardiovascular risk factors and comorbidities	
History of	
Hypertension, n (%)	
Hypercholesterolaemia, n (%)	
Coronary artery disease, n (%)	
History of coronary intervention, n (%)	
Diabetes mellitus, n (%)	
Previous transient ischaemic attack or stroke, n (%)	
Previous stroke, n (%)	
Estimated glomerular filtration rate according to Cockcroft-Gault equation, $ml \cdot min \cdot 1{,}73\ m^{-2}$ median [IQR]	
Haemoglobin level, $mmol \cdot l^{-1}$ median [IQR]	
Low-density lipoprotein cholesterol, $mmol \cdot l^{-1}$ median [IQR]	
Current smoker, n (%)	
Preoperative systolic blood pressure, mmHg, median [IQR]	
Preoperative diastolic blood pressure, mmHg, median [IQR]	
Preoperative medication use	
Diuretics, n (%)	
Calcium channel blocker, n (%)	
Angiotensin converting enzyme inhibitor, n (%)	
Angiotensin receptor blocker, n (%)	
Antiplatelet drugs, n (%)	
Intraluminal shunt, n (%)	
Intraoperative and surgical characteristics	

	No β-blocker (n = 636)	Lower β1/β2 selectivity † (n = 58)	Metoprolol (n = 301)	Higher β1/β2 selectivity † (n = 125)	Missings n (%) ‡
	69 [62 – 76]	72 [63 – 78]	69 [63 – 76]	69 [64 – 76]	0 (0)
	444 (70)	39 (67)	200 (66)	94 (75)	0 (0)
					26 (2)
	600 (94)	51 (88)	281 (93)	117 (94)	
	23 (4)	5 (9)	10 (3)	7 (6)	
					73 (7)
	6 (1)	1 (2)	1 (0)	2 (2)	
	49 (8)	3 (5)	25 (9)	10 (8)	
	540 (91)	51 (93)	255 (91)	104 (83)	
					158 (14)
	317 (59)	22 (42)	138 (54)	56 (45)	
	55 (10)	5 (10)	28 (11)	14 (11)	
	89 (17)	9 (17)	42 (16)	23 (18)	
	77 (14)	16 (31)	50 (19)	21 (17)	
	432 (69)	52 (90)	258 (87)	95 (76)	16 (1)
	407 (70)	40 (80)	204 (78)	78 (62)	110 (10)
	65 (11)	18 (36)	75 (27)	25 (20)	73 (7)
	91 (14)	23 (40)	111 (37)	33 (26)	9 (1)
	136 (21)	19 (33)	83 (28)	36 (29)	0 (0)
	514 (81)	49 (85)	248 (82)	91 (73)	0 (0)
	222 (35)	17 (29)	90 (30)	40 (3)	0 (0)
	69 [54 – 88]	68 [54 – 78]	70 [55 – 85]	65 [51 – 82]	117 (10)
	8.7 [8.1 – 9.3]	8.8 [8.0 – 9.6]	8.8 [8.1 – 9.3]	8.8 [8.3 – 9.4]	54 (5)
	2.5 [1.8 – 3.3]	2.3 [1.8 – 3.0]	2.4 [1.8 – 2.9]	2.4 [1.7 – 3.1]	662 (59)
	218 (35)	16 (28)	92 (31)	45 (36)	17 (2)
	150 [135 – 170]	151 [137 – 180]	150 [132 – 170]	150 [135 – 165]	178 (16)
	80 [70 – 90]	80 [70 – 92]	80 [73 – 90]	80 [70 – 90]	178 (16)
	186 (29)	33 (57)	119 (40)	49 (39)	4 (0)
	112 (18)	18 (31)	94 (31)	42 (34)	4 (0)
	146 (23)	29 (50)	114 (38)	47 (38)	4 (0)
	129 (20)	13 (22)	85 (28)	31 (25)	6 (1)
	557 (88)	35 (60)	263 (88)	109 (87)	7 (1)
	84 (13)	12 (21)	33 (11)	22 (18)	0 (0)

Table 1 Continued

Intraoperative
maintenance of anaesthesia ‡‡
Isoflurane, n (%)
Sevoflurane, n (%)
Propofol, n (%)
Intraoperative β-blocker bolus, n (%)
Metoprolol, n (%)
Esmolol, n (%)
Labetalol, n (%)
Intraoperative heart rate, beats per minute, median [IQR]
Intraoperative vasopressor pump use, n (%)
Phenylephrine, n (%)
Noradrenaline, n (%)
Intraoperative inotrope pump use, n (%)
Dobutamine, n (%)
Dopamine, n (%)
Milrinone, n (%)
Mean blood pressure before induction, mmHg, median [IQR]
Duration of mean blood pressure under the threshold, minutes, median [IQR]
< 75 mmHg
< 70 mmHg
< 65 mmHg
< 60 mmHg
< 55 mmHg
< 50 mmHg
Area-under-the-threshold based on mean blood pressure, mmHg·min, median [IQR]
< 75 mmHg
< 70 mmHg
< 65 mmHg
< 60 mmHg
< 55 mmHg
< 50 mmHg
Intraoperative fraction inspired oxygen, median [IQR]
Intraoperative end-tidal carbon dioxide, mmHg, median [IQR]
Duration of surgery, minutes, median [IQR]
Blood loss, milliliters, median [IQR]

‡ Number of missings before multiple imputation. Total numbers do not always add up to the number of patients in each β-blocker exposure group due to missing values. † compared to metoprolol. ‡‡

	No β-blocker (n = 636)	Lower β1/β2 selectivity † (n = 58)	Metoprolol (n = 301)	Higher β1/β2 selectivity † (n = 125)	Missings n (%) ‡
					0 (0)
	304 (48)	26 (45)	171 (57)	56 (45)	
	324 (51)	29 (50)	133 (44)	66 (53)	
	23 (4)	5 (9)	7 (2)	6 (5)	
					0 (0)
	25 (4)	2 (3)	19 (6)	3 (2)	
	5 (1)	0 (0)	10 (3)	0 (0)	
	1 (0)	0 (0)	1 (0)	0 (0)	
	61 [55 – 68]	57 [51 – 66]	57 [52 – 64]	54 [49 – 62]	9 (1)
	368 (58)	32 (55)	176 (59)	82 (66)	
	81 (13)	16 (28)	45 (15)	13 (10)	
					0 (0)
	2 (0)	3 (5)	3 (1)	0 (0)	
	3 (1)	2 (3)	2 (1)	0 (0)	
	1 (0)	0 (0)	0 (0)	0 (0)	
	115 [104 – 126]	118 [106 – 131]	116 [103 – 129]	118 [106 – 131]	273 (24)
					9 (1)
	17 [7 – 31]	13 [5 – 35]	16 [6 – 32]	18 [8 – 34]	
	9 [3 – 18]	7 [3 – 25]	9 [3 – 20]	10 [3 – 22]	
	4 [1 – 11]	4 [1 – 15]	5 [1 – 12]	5 [1 – 11]	
	2 [0 – 5]	1 [0 – 8]	2 [0 – 6]	2 [0 – 5]	
	0 [0 – 3]	0 [0 – 4]	0 [0 – 3]	0 [0 – 3]	
	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	0 [0 – 1]	
					9 (1)
	136 [45 – 285]	104 [36 – 165]	142 [39 – 313]	162 [44 – 327]	
	62 [12 – 161]	41 [13 – 196]	67 [12 – 181]	79 [17 – 163]	
	24 [1 – 78]	21 [1 – 109]	28 [2 – 89]	29 [3 – 89]	
	6 [0 – 35]	5 [0 – 48]	8 [0 – 46]	4 [0 – 39]	
	0 [0 – 13]	0 [0 – 16]	0 [0 – 21]	0 [0 – 14]	
	0 [0 – 2]	0 [0 – 3]	0 [0 – 6]	0 [0 – 2]	
	0.46 [0.42 – 0.51]	0.46 [0.42 – 0.53]	0.46 [0.42 – 0.50]	0.46 [0.42 – 0.52]	9 (1)
	34 [32 – 36]	34 [32 – 35]	33 [32 – 35]	33 [32 – 35]	9 (1)
	150 [134 – 171]	149 [140 – 176]	153 [133 – 174]	147 [129 – 163]	9 (1)
	300 [150 – 400]	325 [275 – 413]	200 [200 – 400]	250 [200 – 400]	998 (89)

Numbers do not add up to 1,120 as anaesthesia maintenance in 30 patients was established with a combination of propofol and/or isoflurane and/or sevoflurane.

Abbreviations: IQR: interquartile range

Table 2 Association between β-blocker selectivity and intraluminal shunt during carotid endarterectomy

β-blocker selectivity	
No β-blocker	
Lower β1/β2 selectivity ratio than metoprolol †	
Metoprolol	
Higher β1/β2 selectivity ratio than metoprolol ‡	
Age, years	
Sex, female	
Ipsilateral carotid stenosis, 70 - 100% ‡‡	
Contralateral carotid stenosis	
0 – 50%	
50 – 70%	
70 – 99%	
100%	
Hypertension	
Hypercholesterolaemia	
Coronary artery disease	
Diabetes mellitus	
Previous stroke	
Lower estimated glomerular filtration rate according to Cockcroft-Gault equation, $ml \cdot min \cdot 1{,}73\ m^{-2}$	
Haemoglobin level, $mmol \cdot l^{-1}$	
Antiplatelet drugs	
Low-density lipoprotein cholesterol, $mmol \cdot l^{-1}$	

◊ C-statistic for the adjusted model was 0.684 and for the penalised, adjusted model 0.678. † Propranolol, labetalol and sotalol were classified as β-blockers with a lower β1/β2 selectivity ratio than metoprolol. ‡ Bisoprolol and atenolol were classified as β-blockers with a higher β1/β2 selectivity ratio than metoprolol. ‡‡ Ipsilateral carotid stenosis consists of 0 – 50% and 50 -70% versus 70 - 100%. As a post-hoc sensitivity analysis, the multivariable adjusted analysis was repeated in the 484 β-blocker users with metoprolol users as a reference group.

Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ◊	Adjusted penalised odds ratio (95% CI) ◊
Reference		
1.71 (0.87 – 3.37)	1.35 (0.63 – 2.86)	1.14 (0.70 – 1.86)
0.81 (0.53 – 1.24)	0.69 (0.43 – 1.09)	0.82 (0.57 – 1.18)
1.40 (0.84 – 2.35)	1.21 (0.71 – 2.10)	1.14 (0.75 – 1.72)
1.18 (0.90 – 1.56)	0.97 (0.67 – 1.40)	0.95 (0.69 – 1.31)
0.99 (0.68 – 1.44)	1.05 (0.69 – 1.58)	0.98 (0.70 – 1.39)
0.64 (0.37 – 1.13)	0.65 (0.37 – 1.17)	0.78 (0.50 – 1.23)
Reference		
0.61 (0.24 – 1.56)	0.57 (0.23 – 1.42)	0.92 (0.56 – 1.49)
1.08 (0.60 – 1.95)	1.07 (0.60 – 1.90)	1.10 (0.72 – 1.69)
2.84 (1.76 – 4.58)	3.35 (1.99 – 5.63)	2.28 (1.50 – 3.48)
1.14 (0.75 – 1.74)	1.15 (0.73 – 1.81)	1.08 (0.75 – 1.56)
0.99 (0.66 – 1.49)	1.00 (0.64 – 1.55)	0.98 (0.68 – 1.41)
1.10 (0.69 – 1.76)	1.25 (0.77 – 2.03)	1.15 (0.78 – 1.69)
0.96 (0.64 – 1.44)	1.08 (0.70 – 1.65)	1.02 (0.71 – 1.45)
1.20 (0.84 – 1.71)	1.14 (0.78 – 1.67)	1.12 (0.81 – 1.55)
1.37 (1.05 – 1.78)	1.47 (1.04 – 2.07)	1.43 (1.07 – 1.90)
1.06 (0.84 – 1.33)	1.01 (0.82 – 1.24)	1.02 (0.90 – 1.15)
1.08 (0.65 – 1.81)	1.21 (0.70 – 2.10)	1.10 (0.72 – 1.68)
1.28 (0.87 – 1.87)	1.18 (0.82 – 1.70)	1.04 (0.80 – 1.35)

β-blockers with lower β1/β2 selectivity ratio compared to metoprolol (OR 1.34 (95% CI 0.85 – 2.11)) and β-blockers with higher β1/β2 selectivity ratio compared to metoprolol (OR 1.30 (95% CI 0.86 – 1.97)) were not associated with shunt need (*Table 3*).

Abbreviations: CI: confidence interval

Table 3 Association between β-blocker selectivity within the group of β-blocker users and intraluminal shunt during carotid endarterectomy

β-blocker selectivity
Metoprolol
Lower β1/β2 selectivity ratio than metoprolol †
Higher β1/β2 selectivity ratio than metoprolol ‡
Age, years
Sex, female
Ipsilateral carotid stenosis, 70 – 100% ‡‡
Contralateral carotid stenosis
0 – 50%
50 – 70%
70 – 99%
100%
Hypertension
Hypercholesterolaemia
Coronary artery disease
Diabetes mellitus
Previous stroke
Lower estimated glomerular filtration rate according to Cockcroft-Gault equation, $ml \cdot min \cdot 1{,}73\ m^{-2}$
Haemoglobin level, $mmol \cdot l^{-1}$
Antiplatelet drugs
Low-density lipoprotein cholesterol, $mmol \cdot l^{-1}$

◊ C-statistic for the adjusted model was 0.734 and for the penalised, adjusted model 0.713. † Propranolol, labetalol and sotalol were classified as β-blockers with a lower β1/β2 selectivity ratio than metoprolol. ‡ Bisoprolol and atenolol were classified as β-blockers with a higher β1/β2 selectivity ratio than metoprolol. ‡‡ Ipsilateral carotid stenosis consists of 0 – 50% and 50 -70% versus 70 - 100%.

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI) ◊	Adjusted penalised odds ratio (95% CI) ◊
	Reference		
	2.12 (1.02 – 4.40)	2.21 (0.96 – 5.10)	1.34 (0.85 – 2.11)
	1.73 (0.97 – 3.11)	1.87 (0.98 – 3.55)	1.30 (0.86 – 1.97)
	0.85 (0.54 – 1.34)	0.56 (0.32 – 0.98)	0.69 (0.45 – 1.04)
	0.93 (0.53 – 1.63)	0.99 (0.52 – 1.88)	0.96 (0.63 – 1.44)
	0.66 (0.29 – 1.50)	0.72 (0.29 – 1.81)	0.88 (0.55 – 1.43)
	Reference		
	0.70 (0.23 – 2.14)	0.71 (0.21 – 2.36)	0.99 (0.61 – 1.59)
	0.62 (0.24 – 1.58)	0.55 (0.20 – 1.49)	0.91 (0.57 – 1.43)
	2.40 (1.27 – 4.52)	2.45 (1.20 – 4.99)	1.42 (0.91 – 2.20)
	1.10 (0.52 – 2.30)	1.18 (0.50 – 2.78)	1.03 (0.65 – 1.62)
	1.03 (0.54 – 1.99)	0.86 (0.41 – 1.80)	0.95 (0.61 – 1.46)
	1.07 (0.59 – 1.92)	1.08 (0.56 – 2.12)	1.04 (0.68 – 1.57)
	0.91 (0.51 – 1.62)	1.12 (0.59 – 2.12)	1.00 (0.66 – 1.51)
	1.33 (0.78 – 2.29)	1.33 (0.72 - 2.44)	1.14 (0.76 – 1.70)
	1.88 (1.20 – 2.94)	2.37 (1.37 – 4.08)	1.77 (1.23 – 2.56)
	1.05 (0.73 – 1.51)	0.96 (0.63 – 1.47)	1.00 (0.73 – 1.37)
	1.07 (0.52 – 2.21)	1.00 (0.44 – 2.28)	1.01 (0.64 – 1.59)
	0.99 (0.65 – 1.49)	1.11 (0.69 – 1.80)	0.92 (0.71 – 1.19)

DISCUSSION

Independent of β1/β2 selectivity ratio, preoperative β-blocker use was not associated with the need for a temporary, intraoperative shunt during CEA. Only complete contralateral carotid artery occlusion and impaired renal function were associated with the need for an intraoperative shunt. No differences were found in the incidence of intraoperative hypotension between patients on β-blockers, independent of their β1/β2 selectivity ratio, and patients not using β-blockers.

Heterogeneity in β-blocker pharmacokinetic and pharmacodynamic properties makes it difficult to compare the risk of various β-blockers on adverse events after noncardiac surgery. Studies with different β-blockers are equivocal with regard to their effects on cerebral and cardiovascular events. The association between metoprolol, atenolol and bisoprolol on the incidence of postoperative strokes was studied in a propensity-matched cohort including more than 44,000 patients who underwent noncardiac and nonneurologic surgery. Bisoprolol, but not atenolol or metoprolol, was associated with a lower risk of postoperative stroke [2]. However, β-blocker selectivity was not associated with increased incidence of all-cause mortality and major cardiovascular events (including non-fatal ischaemic stroke) in a large Danish cohort, nor in subgroups with different cardiovascular comorbidities [17]. Comparable to our study, in all these studies metoprolol was the predominant β-blocker, its use varying from 55 – 67% among β-blocker users [2,17]. To make things even more complicated, many β-blockers are not only antagonists, but also exert agonist effects or some inverse agonist actions [18]. It is therefore difficult to determine to what extent desirable and undesirable cardiovascular effects of β-blockers can be attributed solely to β-adrenoreceptor responses. Another problem is variation in pharmacokinetic profiles and individual responses of β-blocker therapy. CYP enzyme polymorphisms lead to strongly varying molecular, cellular and physiologic intersubject responses [19]. Plasma concentrations and cardiovascular effects of metoprolol and propranolol are greatly influenced by various CYP2D6 polymorphisms [20,21]. Bisoprolol and atenolol however are not metabolised and thus not influenced by CYP2D6 metabolism [18].

These different β-blockers have different indications that may have resulted in confounding by indication. The possibility of confounding by indication is supported by differences in baseline characteristics of the patients. Patients who used β-blockers with a lower β1/β2 selectivity ratio had more often complete contralateral carotid stenosis, high degree ipsilateral carotid stenosis and cardiovascular risk factors and comorbidities compared to patients using β-blockers with a higher β1/β2 selectivity ratio. Although we performed multivariable logistic regression analyses, residual confounding cannot be ruled out.

In two studies, preoperative β-blocker use has been associated with the need for an intraluminal shunt during CEA. In contrast to a case-control study, our results suggest that there is no association between β-blocker use, regardless of the β1/β2 selectivity ratio and the need for an intraluminal shunt [8]. Age, sex and comorbidities were comparable to our study population; except for higher incidences of coronary artery disease, more antihypertensive drug use and lower numbers of high degree ipsilateral and contralateral stenosis in their patients. No information was provided about the distribution of preoperative β-blocker use and results were not adjusted for β-blocker selectivity [8]. Ipsilateral moderate carotid stenosis (60 - 80%) was also independently associated with the need for an intraluminal shunt during CEA. In a cohort study, preoperative β-blocker use was an independent predictor of intraoperative cerebral monitoring changes, as indicated by EEG or somatosensory evoked potentials changes. However, β-blocker use was not associated with cross-clamp related cerebral monitoring changes [22]. This study population had lower number of males and higher incidences of hypertension, diabetes mellitus and coronary artery disease compared to our study population. Comparable to the study of Florea et al, preoperative β-blockers were not specified, classified or analysed according to their selectivity ratio in this study [8]. Contralateral carotid occlusion, symptomatic stenosis, diabetes mellitus, and female sex were associated with cross clamp-induced changes in cerebral monitoring and the need for an intraluminal shunt in that study. In our study, results were adjusted for previously determined confounders, for example haemoglobin level, degree of contralateral stenosis [22] and degree of ipsilateral stenosis [8,23,24]. However, we could not confirm associations between haemoglobin level and degree of ipsilateral stenosis in our analysis.

Our study has some limitations. Due to limited numbers of the outcome, we did not adjust for other antihypertensive drugs than β-blockers in our analysis. Treatment with β-blockers in combination with other antihypertensive drugs has been associated with increased incidence of major adverse cardiovascular events, including non-fatal ischaemic stroke, after noncardiac surgery [25]. Due to low number of patients who used other β-blockers than metoprolol, various β-blockers had to be combined in three groups and some β-blockers were excluded due to low number of users in this cohort. In both the lower and higher β1/β2 selectivity ratio group as well as in the metoprolol group, this resulted in wide 95% confidence intervals. In addition to these limited variation in β-blockers, several pharmacological problems could have played a role. For example, no information on β-blocker use with regard to the moment of initiation and dose titration was available. Different β-blockers have different half-lives which might have been a confounding factor as well. However, β-blocker therapy was not interrupted during the perioperative period and the majority of the prescribed β-blockers in this cohort were

prolonged-release formulations. It is also possible that that (chronic) β-blocker use might provoke changes in small vessels and microcirculation, not detected by blood pressure measurement or by EEG and TCD changes. Therefore, it is possible that residual confounding might play a role in the unexpected direction of point estimates within the group of β-blocker users. The clinical relevance of shunt insertion as an outcome variable might be limited compared to the clinical relevance of postoperative stroke. However, it is not possible to study the causal relation between preoperative β-blocker use and postoperative stroke within the current historical cohort without studying the decision for a temporary shunt. The hypothesised causal mechanism is that β-blockers influence cerebral perfusion, and the cerebral perfusion during cross-clamping drives the decision for a temporary shunt. The cerebral perfusion and the subsequent insertion of a temporary shunt alter the risk of postoperative stroke. β-blockers are assumed to only influence stroke through cerebral perfusion and insertion of the shunt. Thus, the cerebral perfusion and insertion of a temporary shunt are intermediate variables in the relation between preoperative β-blocker use and the occurrence of postoperative stroke. Hence, the main variable of interest to study the effect of β-blockers should be either cerebral perfusion or shunt insertion as a proxy of cerebral perfusion.

In this historical cohort study in patients who underwent CEA, we did not find an association between β-selectivity and cerebral hypoperfusion indicated by the need for an intraluminal shunt. Preoperative β-blocker use, independent of β1/β2 selectivity ratio was not associated with occurrence of intraoperative hypotension.

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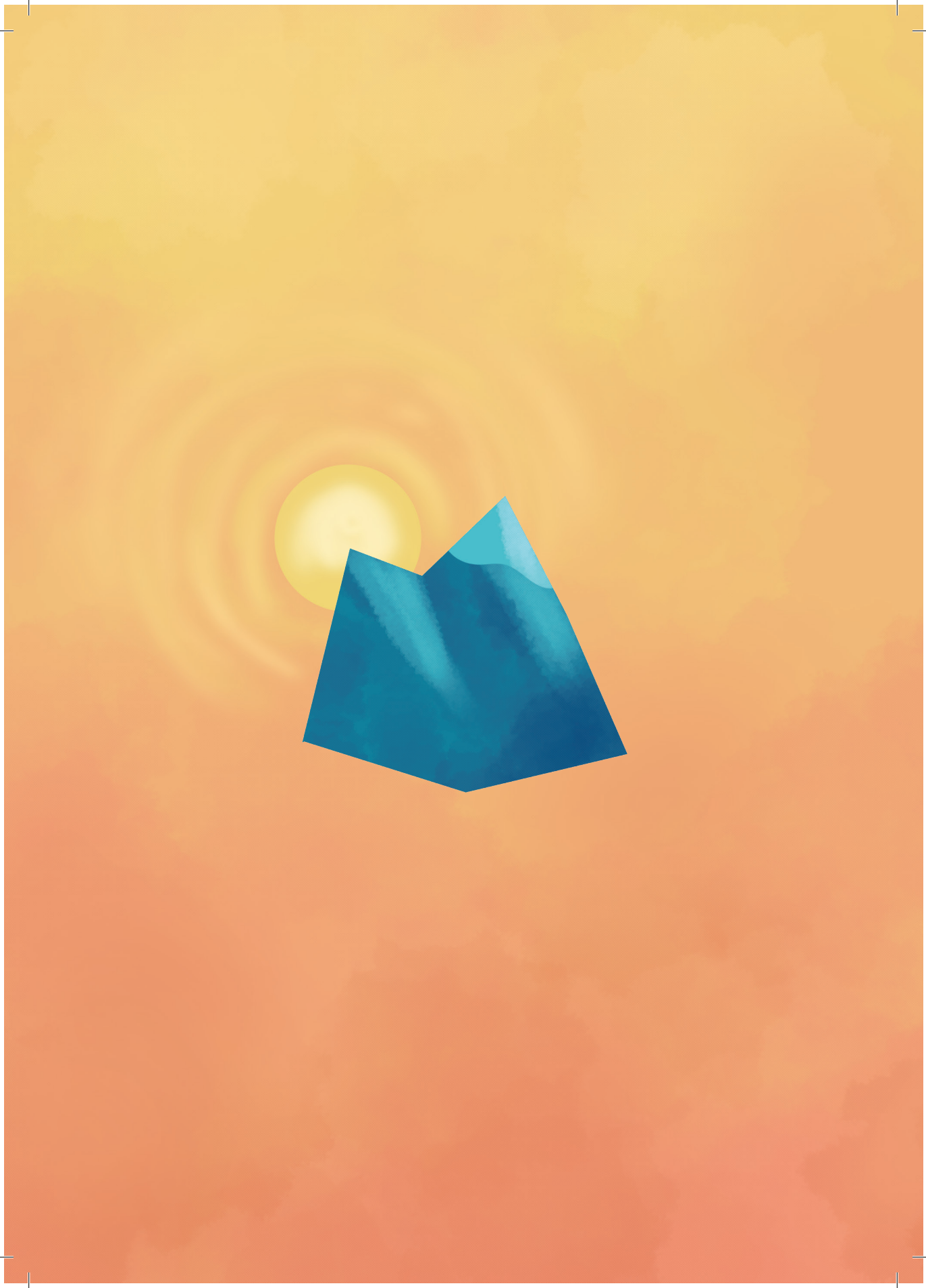
PART 3

INTRAOPERATIVE BLOOD PRESSURE ANALYSIS AND HYPOTENSION MECHANISMS IN INDIVIDUAL PATIENTS



CHAPTER 6

CONTINUOUS ASSOCIATIONS BETWEEN INTRAOPERATIVE BLOOD PRESSURE, DURATION OF SURGERY AND POSTOPERATIVE MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY

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ABSTRACT

Background: Intraoperative hypotension (IOH) analysis methods are often based on thresholds which are not biologically plausible. We hypothesised that intraoperative mean arterial pressures (MAP) have a continuous association with postoperative myocardial injury (PMI) and in-hospital mortality, rather than a threshold-based effect. To this aim, two new hypotension analysis methods were developed, and were compared to more traditional IOH analysis methods.

Methods: A historical cohort study was conducted in 15,452 patients aged ≥ 60 years who underwent intermediate to high risk noncardiac surgical procedures. The association between IOH exposure, defined by 5th and 50th MAP percentiles, depth- and duration-weighted area under the normal blood pressure threshold (AUT), and the outcomes PMI and in-hospital mortality were analysed. Troponin I levels were routinely measured within the first three postoperative days. PMI was defined as troponin I level above the clinical cut-off level.

Results: PMI occurred in 1,812 patients (12%) and 554 patients died during hospital stay (3.6%). Using interquartile range (IQR), the 5th MAP percentile (median of all patients 64 mmHg [IQR 58 – 70 mmHg]) (OR 1.3, 95% CI 1.2 – 1.4, $p < 0.05$) and depth-weighted AUT (OR 4.4, 95% CI 2.6 – 7.4. $p < 0.05$) were associated with PMI. The 50th MAP percentile (median 80 mmHg [IQR 73 – 87 mmHg]) (OR 1.4, 95% CI 1.2 – 1.7, $p < 0.05$) and depth-weighted AUT (OR 11.6, 95% CI 3.8 – 34.9, $p < 0.05$) were associated with in-hospital mortality.

Conclusions: MAP has a continuous association with PMI and in-hospital mortality. The depth of IOH seems to contribute more to these outcomes than the duration of IOH, although no MAP threshold was identified that clearly increased the risks.

INTRODUCTION

Several studies reported associations between intraoperative hypotension (IOH) and postoperative myocardial injury (PMI) after noncardiac surgery [1–3]. A complicating factor in the interpretation of the relationship between IOH and postoperative organ injury is the dependence on the definition of IOH and analysis methods [4]. The currently used methods to analyse IOH are likely insufficient. There are three main issues in analysing the relationship between IOH and organ injury: the use of a threshold-based analysis, inadequate incorporation of depth and duration of low blood pressures and the strong relationship between IOH and the duration of surgery [5,6] (*Supplementary table 1*).

Using a threshold in the analysis is problematic from a clinical viewpoint. Such a boundary effect is not very plausible: e.g. an intraoperative mean arterial pressure (MAP) of 65 mmHg would cause no injury, whereas a MAP of 64 mmHg would. Moreover, a patient with any MAP below 65 mmHg is more likely to have a prolonged period of lower MAP. Current IOH analysis methods do not include both depth and duration as separate variables, making it difficult to unravel the exact contribution of depth and duration. In commonly applied methods as the area-under-the-threshold (AUT) method and the time-weighted average (TWA) method a short but severe dip in blood pressure exhibits the same AUT or TWA as a long-lasting blood pressure just below a threshold [3]. In addition, longer surgical time inevitably leads to increased risk of exposure to IOH, and was associated with higher risk of postoperative events[7]. Moreover, an increased duration of IOH was associated with an increased risk of PMI [2,8,9].

Thus, analyses with additional intraoperative blood pressure characteristics, other than depth and duration under a certain threshold, are necessary to provide better insight in the association between IOH and postoperative organ injury. We hypothesised that intraoperative blood pressure has a continuous association with postoperative organ injury, rather than a threshold effect. Therefore, the aim of this study was to explore new methods of modelling intraoperative blood pressure in relation to the occurrence of PMI. To this aim, we developed two methods to model intraoperative blood pressure. In addition, we compared the associations of these two intraoperative blood pressure analysis methods to more traditional IOH analysis methods.

METHODS

Study design and study population

This cohort study included inpatients aged 60 years or older who underwent intermediate to high risk noncardiac surgery between 1 January 2012, and 1 June 2017 at the University Medical Center Utrecht, Utrecht, the Netherlands. Only patients with at least one postoperative troponin I measurement during the first three postoperative days were included [2,10]. Patients with pre-existing end-stage renal disease (defined as renal replacement therapy), American Society of Anesthesiologists (ASA) physical status equal or more than 5, duration of anaesthesia less than 20 minutes or when intraoperative blood pressure measurements were not available were excluded. If patients underwent another surgical procedure, then this procedure was considered as a novel patient (3.8% of the patients underwent another intermediate or high-risk surgery £ 3 days after the first surgical procedure). The local ethics committee waived the need for informed consent as only routinely collected data were used (protocol number 16-552).

Data collection

Intraoperative data from the patient monitor and anaesthesia machine were collected from the electronic anaesthesia information management system (AnStat, CarePoint Nederland BV, Ede, the Netherlands). Most intraoperative variables were stored as the median for each minute. Non-invasive oscillometric blood pressure measurements were stored at measurement intervals, typically every 3-5 minutes. Demographic and postoperative data were collected from the electronic hospital information system (HiX, ChipSoft, Amsterdam, the Netherlands). The anaesthesia technique and management of intraoperative blood pressure was left to the discretion of the anaesthetist. Intraoperative blood pressure was typically treated with fluids, norepinephrine, phenylephrine or ephedrine but these treatments were not included in analysis.

Blood pressure

The exposure of interest in this study was intraoperative blood pressure, defined as all blood pressure measurements between start of induction of anaesthesia and time of patient emergence. If the timestamp of emergence was not available; the time when the patient left the operation room was considered as the end of the surgical procedure. MAPs of both continuous invasive measurements and non-invasive measurements were extracted. Invasive blood pressure measurements were excluded if these represented < 10% of all blood pressure data during the procedure. Blood pressure artefacts (defined as MAP < 0 mmHg; diastolic blood pressure > MAP > systolic blood pressure; pulse pressure < 5 mmHg; diastolic blood pressure < 0 mmHg; 20 mmHg < systolic blood

pressure > 300 mmHg) were only removed prior to the analyses when MAP measures were outside twice the standard deviation range of average case MAP to prevent correct measurements from being deleted only based on incorrect systolic and/or diastolic but correct MAP values.

When both invasive and non-invasive blood pressure measurements were present at given time points, only the invasive value was included in the analysis. When multiple blood pressure measurements of the same type (multiple invasive blood pressure or non-invasive blood pressure measurements) were available at the same minute, the average value of these multiple MAPs was calculated. With the aim of a per minute analysis, missing blood pressure data were imputed based on a weighted average of both a linear slope component (slope from last available blood pressure measurement to the next available measurement) and the last-known slope component (slope of the two last known blood pressure values) (*Supplementary figure 1*). Because only 0.03% of the measurements showed a gap between blood pressure values of more than 5 minutes, this imputation method has only been tested for an interval of missing value up to 5 minutes, and found to be accurate.

To provide more insight in the blood pressure course during surgery, hypotension thresholds were not used – i.e. no thresholds were used to define low blood pressure. Instead, intraoperative blood pressures were related to a physiologic normal blood pressure. To avoid that hypertension was included in the analyses, a MAP cut-off of 100 mmHg was used to demarcate a normal intraoperative blood pressure. As we assumed that blood pressure levels above this value could not compensate for the harmful effects of IOH, only intraoperative MAPs < 100 mmHg were used for the IOH calculations.

In our search for an analysis method that does not use a threshold, we developed two different methods. The first one, a percentile-based method, did not include a blood pressure threshold but did include a time-based threshold, which was therefore considered imperfect. Nonetheless, it provided valuable insight into the three problems of IOH analyses described in the introduction, and led to the development of the second method that does not include a depth-based nor a time-based threshold for low blood pressure. Both methods are described below with the emphasis on the second method.

Supplementary table 1 Evolution and comparison of intraoperative hypotension analysis methods

Hypotension analysis method
Number of hypotension episodes, count [25]
Duration under an absolute blood pressure threshold, minutes [2,7,8]
Minimum mean blood pressure, mmHg [19]
Lowest mean blood pressure for various cumulative minutes, mmHg [3]
Lowest mean blood pressure for sustained minutes, mmHg [3]
Area under an absolute mean blood pressure threshold, mmHg·min [26]
Time-weighted average under absolute mean blood pressure threshold [3]

Overview of various intraoperative hypotension analysis methods categorised by the use of blood pressure threshold, considering depth and/or duration of hypotension and/or duration. The last column indicates whether duration of surgery is used as a covariable or as interaction in the intraoperative hypotension analysis method.

The first method for an intraoperative blood pressure course analysis was to summarise all blood pressures by percentiles (percentile-based method). Therefore, in each patient all intraoperative blood pressures were sorted on increasing value and the 5th and 50th mean blood pressure percentiles were calculated. In this, the 5th percentile represents the depth of hypotensive episodes and the 50th percentile represents the 'typical' intraoperative blood pressure value (*Box: dashed green and orange lines*). The association between these two MAP percentiles and PMI was analysed. As we found a strong interaction between intraoperative mean blood pressure percentiles and duration of surgery, this emphasised the need to include an interaction term between these percentiles and duration of surgery in the analysis to study the association with PMI. Further, blood pressure outliers might contribute particularly to the value of low blood pressure percentiles during short procedures. This is in part dependent on the number of intraoperative blood pressure measurements. For example, during a procedure of 60 minutes and a blood pressure measurement interval of 3 minutes, 20 measurements will be obtained (assuming non-invasive measurements). In contrast, during a procedure of 360 minutes, 120 blood pressure measurements are collected. Therefore, the 5th and 50th MAP percentiles represent a different time interval depending on the duration of surgery.

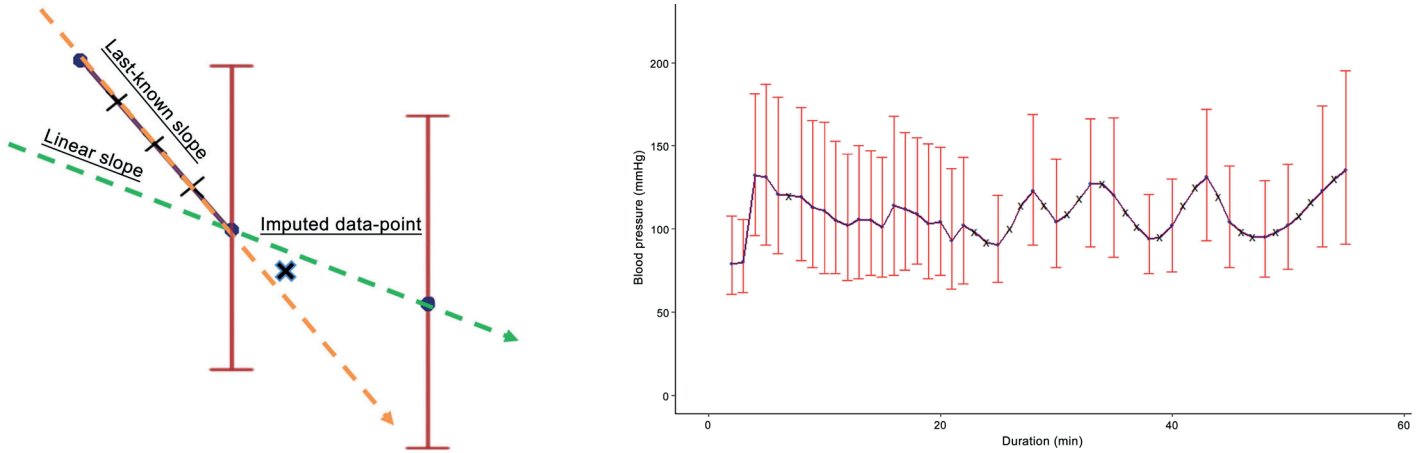
As the time interval between non-invasive blood pressure measurements varied between 1 and 5 minutes, we used an interpolation method to obtain one blood pressure value per minute, and performed a per minute analysis. The interdependence between the duration of surgery and the blood pressure percentiles made it impossible to fully

Absence of a blood pressure threshold	Depth	Duration	Depth and duration	Duration of surgery
-	+/-	+/-	-	Covar
-	+/-	+	-	Covar
+	+	-	-	Covar
+	+	+/-	-	Covar
+	+	+/-	-	Covar
-	+	+	+	Covar
-	+	+	+	Covar and Int

Abbreviations: Covar: duration of surgery as a covariable necessary in the analysis; Int: duration of surgery as interaction necessary in the analysis.

understand the effect modification. We thus searched for another analysis method that could separate on the duration of surgery from the individual contributions of depth and duration of intraoperative low blood pressures.

The second method was to calculate an overall effect for the blood pressure below a normal blood pressure, as well as effects that were weighted for either depth or duration of low blood pressures. This method was based on the notion that patients with different intraoperative blood pressure courses may have the same total area-under-the-normal-blood-pressure curves. The areas under a normal MAP threshold of 100 mmHg were calculated, expressed as mmHg·min. Two additional depth- and duration-weighted variables were derived from the area-under-the-normal-blood-pressure. In these variables, the depth, respectively the duration of the area-under-the-normal-blood-pressure were squared and resulted in depth^2·duration (depth-weighted AUT) (mmHg^2·min) and depth·duration^2 (duration-weighted AUT) (mmHg·min^2) variables. These variables were used to distinguish between patients with short episodes of very low blood pressures and patients with sustained episodes of slightly low intraoperative blood pressures and occurrence of PMI. As this weighted-AUT method explicitly models the effect of the duration of IOH, the duration of surgery only needed to be modelled as a covariate and not as an interaction term with IOH (*Box: blue and grey bars*).



A B

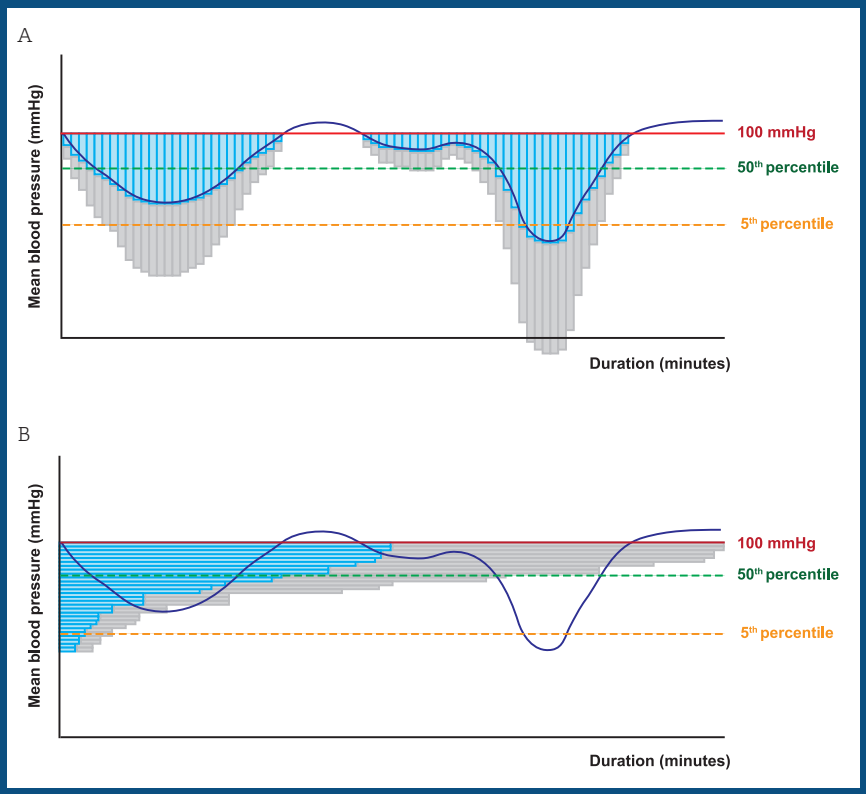
Supplementary figure 1 Strategy for the imputation of missing intraoperative blood pressure values between two recorded datapoints, intended to use for a per minute analysis

Both previous and following blood pressure measurements were used for imputation of missing intraoperative blood pressure values.

Panel a: Imputation of missing blood pressures was an iterative process using previous imputed values for the next imputation step. The weighted average of both a linear slope component (slope from last available measurement to the next available measurement) and a last-known slope component (slope of the two last known blood pressure values) were used for imputation.

Panel b: An example of the effect of the imputation strategy (black crosses represent imputed blood pressure values).

Box Graphical representation of the percentile-based method and weighted area-under-the-threshold parameters.



In this study, two continuous intraoperative blood pressure analysis methods were used.

- Method 1: Percentile-based method: mean blood pressure percentiles (*panel a and panel b: dashed green and orange lines*). All intraoperative mean blood pressures were sorted for every patient and the 5th and 50th mean blood pressure percentiles were analysed.
- Method 2: Weighted area-under-the-threshold method: a mean blood pressure of 100 mmHg (*panel a and panel b: red line*) was used as a reference for normal blood pressure and used for the calculation of the area < 100 mmHg (*panel a and b: grey bars*). Two additional area-weighted parameters were derived:
    1. The depth-weighted area (*panel a: blue and grey bars*) was calculated by squaring the depth part of the area < 100 mmHg for every minute ($depth^2 \cdot duration$, $mmHg^2 \cdot min$).
    2. The duration-weighted area (*panel b: blue and grey bars*) was calculated by squaring the duration part of the area for every mmHg mean blood pressure < 100 mmHg ($depth \cdot min^2$, $mmHg \cdot min^2$).

6

Outcomes

PMI after noncardiac surgery was used as the primary outcome in this exploratory study. According to our local clinical postoperative protocol, troponin I levels were routinely measured and analysed using a third-generation enhanced AccuTnI assay (Beckman Coulter, Brea, CA, USA) during the first three postoperative days [2, 10]. PMI was defined as a troponin I level within the first three postoperative days of more than 60 $ng \cdot l^{-1}$, which is the above the 99th percentile upper reference limit [2, 10]. The secondary outcome was in-hospital mortality during the same admission of the surgical procedure.

Potential confounders and missing data

Based on previously performed studies and clinical experience, the following possible confounders in the association between intraoperative blood pressure and PMI were selected a priori: age, sex, ASA physical status, presence of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, non-end-stage renal disease, usage of any chronic preoperative medication, surgical specialty and priority of surgery (elective surgery, emergency surgery within respectively 2, 8 and 24 hours). Multiple complete datasets were created with the multiple imputation method with the 'aregImpute' function using predictive mean matching from the 'rms'-package (release 5.1-2) in R (release 3.5.1; R foundation for Statistical Computing, Vienna, Austria). Patients without any postoperative troponin I measurements during the first three postoperative days were excluded from the final analyses, but were used for optimisation of the imputation procedure [11].

Statistical analysis

All analyses were performed using R (release 3.5.1; R foundation for Statistical Computing, Vienna, Austria). Continuous data were presented as medians with interquartile ranges (IQR). Categorical variables were expressed as frequencies with percentages. Blood pressure percentiles were added as an interaction term with duration of surgery. Based on visual assessment for nonlinearity of all continuous variables, age, mean blood pressure percentiles, IOH depth·duration, IOH depth^2·duration and IOH depth·duration^2 were transformed using restricted cubic splines with three knots. The association between intraoperative blood pressure and PMI was analysed with a multivariable logistic regression model (lrm function, 'rms'-package (release 5.1-2)) and was expressed as penalised, scaled adjusted odds ratios (OR) between the 75th and 25th percentile with 95% confidence intervals (CI). The scaled odds ratios for the continuous variables compare the third quartile with the first quartile and for the categorical variables each group with the reference group. Penalisation is a shrinkage procedure to avoid overfitting of the model and consisted of penalised maximum likelihood estimation (pentrace function, 'rms'-package (release 5.1-2)) with the following penalties: 0.5, 1,

2, 3, 4, 6, 8, 12, 16 and 24. Statistical significance was determined by p-value based on penalised adjusted odds ratios and 95% confidence intervals after bootstrapping [12] and defined as a two-sided α of 0.05.

The performance of the above described IOH analyses methods was compared to previously described IOH analysis methods with and without thresholds. Consistent with the main analyses, non-linear variables were transformed using restricted cubic splines with three knots. The results were adjusted for the same potential confounders as in the main analyses and penalisation was performed. Bootstrapping (n = 500 repetitions) and penalisation were used to determine model performance for all IOH analysis methods. Index-corrected R^2- and c-index values were calculated and compared.

RESULTS

Of the 32,026 surgical procedures during the study period, a total of 11,565 procedures were excluded due to surgery related exclusion criteria. In addition, 5,009 patients were excluded due to patient-related exclusion criteria (n = 1,299), missing intraoperative blood pressure measurements (n = 5) and missing outcomes (n = 3,705). Overall, 15,452 surgical procedures (i.e. 48% of the initial cohort) in 11,376 unique patients were analysed (*Figure 1*).

Included patients were more often male (56%), with a median age of 69 years (IQR 65 – 75 years) and were mostly classified as ASA physical status 2 (57%). Hypertension (54%) and cardiac disease (40%) were the most common reported comorbidities. The median duration of surgery was 132 minutes (IQR 82 – 208 minutes). Neurosurgery (21%), ear, nose and throat surgery/oral and maxillofacial surgery (19%) and vascular surgery (13%) were to most common surgical procedures (*Table 1*). The outcome PMI occurred in 1,812 patients (12%) and 554 patients (3.6%) died during their hospital stay.

All intraoperative MAP values were sorted on increasing value and the 5th and 50th percentiles were calculated for every patient. The median 5th MAP percentile was 64 mmHg (IQR 58 – 70 mmHg) and the median 50th percentile was 80 mmHg (IQR 73 – 87 mmHg). The 5th MAP percentile value was associated with PMI (penalised adjusted OR 1.3, 95% CI 1.3 – 1.4). No significant association was found between the 50th MAP percentile and occurrence of PMI (OR 1.0, 95% CI 0.9 – 1.1) (*Table 2*). The effect estimates of duration of surgery (OR 1.7, 95% CI 1.6 – 1.8) and the other covariables are listed in *Table 2*. For in-hospital mortality, the 50th MAP percentile (OR 1.4, 95% CI 1.2 – 1.7), but not the 5th MAP percentile (OR 1.0, 95% CI 0.9 – 1.2) was associated with the outcome. Duration of surgery (OR 1.6, 95% CI 1.4 – 1.8) was associated with this outcome as well (*Table 2*).

Table 1 Characteristics of included patients and surgical characteristics

	n = 15,542	**Missings n (%)** †
Age, years, median [IQR]	69 [65 – 75]	0 (0)
Sex, male, n (%)	8,671 (56)	0 (0)
Hypertension, n (%)	8,273 (54)	3,724 (24)
Diabetes mellitus, n (%)	2,961 (19)	3,853 (25)
Renal disease, n (%)	2,872 (19)	3,781 (25)
Cardiac disease, n (%)	6,134 (40)	3,707 (24)
Cardiovascular disease, n (%)	2,254 (15)	4,552 (29)
Chronic medication use, n (%)	14,447 (93)	4,121 (27)
ASA physical status, n (%)		1,712 (11)
1	1,386 (9)	
2	8,834 (57)	
3 or 4	5,232 (34)	
Median mean blood pressure 5th percentile, mmHg, median [IQR]	64 [58 – 70]	0 (0)
Median mean blood pressure 50th percentile, mmHg, median [IQR]	80 [73 – 87]	0 (0)
Area-under-the-normal-blood-pressure, depth·duration, mmHg·min, median [IQR]	2,274 [1,180 – 4,283]	0 (0)
Depth-weighted area-under-the-normal-blood-pressure, depth^2·duration, mmHg^2·min, median [IQR]	60,644 [28,351 – 121,797]	0 (0)
Duration-weighted area-under-the-normal-blood-pressure, depth·duration^2, mmHg·min^2, median [IQR]	178,588 [53,188 – 597,320]	0 (0)
Surgical specialty, n (%)		
Ear, nose, throat surgery/ oral and maxillofacial surgery	2,887 (19)	
General surgery	1,126 (7)	0 (0)
Gastroenterological and oncological surgery	1,741 (11)	
Gynaecology	782 (5)	
Neurosurgery	3,264 (21)	
Orthopaedic surgery	1,713 (11)	
Plastic surgery	269 (2)	
Trauma surgery	565 (4)	
Urology	1,053 (7)	
Vascular surgery	2,052 (13)	

Table 1 Characteristics of included patients and surgical characteristics

	n = 15,542	**Missings n (%) †**
Priority of surgery, n (%)		
Elective surgery	11,576 (75)	0 (0)
Emergency surgery, within 24 hours	1,553 (10)	
Emergency surgery, within 8 hours	1,718 (11)	
Emergency surgery, within 2 hours	605 (4)	
Duration of surgery, median [IQR]	132 [82 – 208]	0 (0)
Number of surgical procedures for every patient, n (%)		
1	8,813 (77)	0 (0)
2 – 5	2,484 (22)	
6 – 15	79 (1)	

† Number and percentage of missing values related to 15,542 surgical procedures (in 11,376 unique patients).
Abbreviations: ASA: American Society of Anesthesiologists; IQR: interquartile range; SD: standard deviation

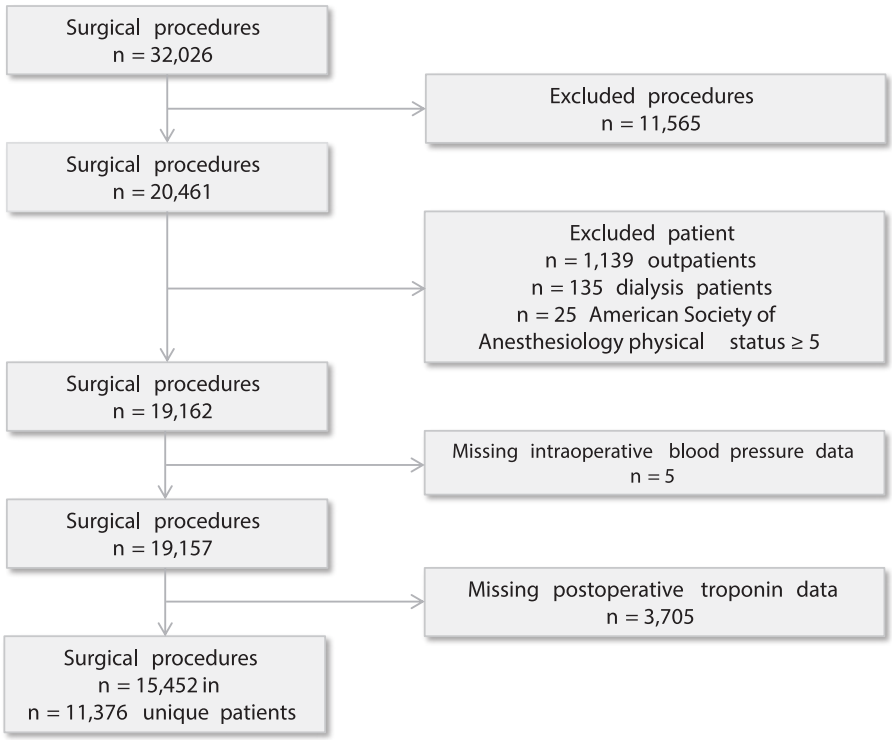


Figure 1: Flow chart of patient and surgical procedure selection

Table 2 Association between intraoperative mean blood pressure percentiles and postoperative myocardial injury and in-hospital mortality after noncardiac surgery

	Index value/ category †	**Reference value/ category ‡**
5th mean blood pressure percentile, mmHg	58	70
50th mean blood pressure percentile, mmHg	73	87
Age, years	75	65
Sex	Male	Female
Hypertension		
Diabetes mellitus		
Renal disease		
Cardiac disease		
Cardiovascular disease		
Chronic medication use		
ASA physical status		
1		
2		
3		
4		
Surgical specialty		
General surgery		
Ear, nose, throat surgery/oral and maxillofacial surgery		
Gastroenterological and oncological surgery		
Gynaecology		
Neurosurgery		
Orthopaedic surgery		
Plastic surgery		
Trauma surgery		
Urology		
Vascular surgery		
Priority of surgery		
Elective surgery		
Emergency surgery, within 24 hours		
Emergency surgery, within 8 hours		
Emergency surgery, within 2 hours		
Duration of surgery, minutes	208	82

PMI Adjusted odds ratio (95% CI)	PMI Penalised adjusted odds ratio (95% CI)	p-value	In-hospital mortality Adjusted odds ratio (95% CI)	In-hospital mortality Penalised adjusted odds ratio (95% CI)	p-value
1.29 (1.17 – 1.41)	1.29 (1.18 – 1.41)	< 0.05	1.04 (0.88 – 1.24)	1.05 (0.89 – 1.24)	0.56
1.04 (0.93 – 1.15)	1.03 (0.93 – 1.14)	0.58	1.42 (1.17 – 1.71)	1.40 (1.16 – 1.69)	< 0.05
1.44 (1.31 – 1.58)	1.44 (1.31 – 1.58)	< 0.05	1.09 (0.92 – 1.28)	1.09 (0.93 – 1.28)	0.31
0.95 (0.85 – 1.06)	0.95 (0.85 – 1.06)	0.37	1.09 (0.90 – 1.32)	1.08 (0.89 – 1.31)	0.43
1.17 (1.03 – 1.34)	1.17 (1.03 – 1.34)	< 0.05	1.02 (0.74 – 1.41)	1.02 (0.74 – 1.41)	0.89
1.19 (1.01 – 1.40)	1.19 (1.01 – 1.40)	< 0.05	1.30 (0.93 – 1.81)	1.30 (0.94 – 1.81)	0.12
1.29 (1.11 – 1.49)	1.29 (1.11 – 1.49)	< 0.05	1.57 (1.05 – 2.35)	1.57 (1.05 – 2.34)	< 0.05
1.38 (1.18 – 1.61)	1.38 (1.18 -1.61)	< 0.05	0.96 (0.70 – 1.31)	0.96 (0.70 – 1.31)	0.81
1.23 (1.03 – 1.46)	1.23 (1.03 – 1.46)	< 0.05	1.22 (0.74 – 2.01)	1.22 (0.74 – 2.00)	0.45
1.16 (0.78 – 1.71)	1.16 (0.79 – 1.72)	0.46	0.80 (0.40 – 1.60)	0.81 (0.41 – 1.62)	0.57
1.00	1.00		1.00	1.00	
1.47 (1.07 – 2.04)	1.47 (1.06 – 2.02)	< 0.05	1.52 (0.81 – 2.85)	1.47 (0.80 – 2.69)	0.22
1.90 (1.35 – 2.67)	1.89 (1.35 – 2.64)	< 0.05	3.46 (1.80 – 6.66)	3.32 (1.76 – 6.26)	< 0.05
3.83 (2.54 – 5.78)	3.79 (2.52 – 5.71)	< 0.05	8.48 (4.13 – 17.4)	8.08 (4.02 – 16.2)	< 0.05
1.00	1.00		1.00	1.00	
0.37 (0.29 – 0.47)	0.37 (0.29 – 0.47)	< 0.05	0.26 (0.16 – 0.44)	0.27 (0.16 – 0.44)	< 0.05
0.70 (0.56 – 0.88)	0.71 (0.57 – 0.88)	< 0.05	1.37 (0.97 – 1.94)	1.37 (0.97 – 1.94)	0.07
0.41 (0.28 – 0.60)	0.42 (0.29 – 0.61)	< 0.05	0.11 (0.03 – 0.49)	0.15 (0.05 – 0.50)	< 0.05
0.57 (0.46 – 0.70)	0.57 (0.46 – 0.70)	< 0.05	1.05 (0.75 – 1.47)	1.05 (0.75 – 1.46)	0.78
0.58 (0.46 – 0.73)	0.58 (0.46 – 0.73)	< 0.05	0.58 (0.37 – 0.91)	0.58 (0.37 – 0.91)	< 0.05
0.25 (0.13 – 0.49)	0.26 (0.13 – 0.49)	< 0.05	§	§	
0.77 (0.57 – 1.04)	0.77 (0.57 – 1.04)	0.09	0.97 (0.59 – 1.58)	0.96 (0.59 – 1.56)	0.88
0.38 (0.27 – 0.52)	0.38 (0.28 – 0.52)	< 0.05	0.30 (0.15 – 0.61)	0.31 (0.16 – 0.62)	< 0.05
0.79 (0.64 – 0.97)	0.79 (0.64 – 0.98)	< 0.05	0.51 (0.35 – 0.74)	0.51 (0.35 – 0.75)	< 0.05
1.00	1.00		1.00	1.00	
1.83 (1.53 – 2.19)	1.83 (1.53 – 2.18)	< 0.05	2.23 (1.59 – 3.12)	2.24 (1.61 – 3.13)	< 0.05
2.95 (2.53 – 3.43)	2.94 (2.53 – 3.43)	< 0.05	4.45 (3.41 – 5.81)	4.46 (3.42 – 5.82)	< 0.05
6.60 (5.34 – 8.15)	6.57 (5.32 – 8.11)	< 0.05	17.2 (12.8 – 23.1)	17.0 (12.7 – 22.8)	< 0.05
1.69 (1.57 – 1.83)	1.68 (1.56 – 1.81)	< 0.05	1.63 (1.41 – 1.87)	1.59 (1.39 – 1.82)	< 0.05

Table 2 Continued

Odds ratios represent an increase in the odds comparing the 25th percentile († index value/category) and 75th percentiles (‡ reference value/category). Blood pressure percentiles (after transformation with restricted cubic splines) were added as an interaction term with duration of surgery. Results were adjusted for the following confounders: age, sex, ASA physical status, usage of any chronic preoperative medication, presence of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, non-end-stage renal disease, surgical specialty and priority of surgery.
p-values were based on penalised adjusted odds ratios and 95% confidence intervals after bootstrapping (n = 500). Due to the lack of events in particular groups, not all odds ratios could be calculated (§ no value available).
Abbreviations: ASA: American Society of Anesthesiologists; CI: confidence interval; PMI: postoperative myocardial injury

There was a strong interaction between the MAP percentiles and duration of surgery and their relation to PMI (*Figure 2*). The interaction was most notable for the 5th MAP percentile, where the association between 5th MAP percentile and risk of PMI depended on the duration of surgery (*Figure 2, panel a: different slopes for different durations of surgery, marked by different line colours*). For a patient with a duration of surgery of 156 minutes (60th percentile) whose 5th MAP percentile was 70 mmHg, the risk of PMI of was 3.5%. When that patient's 5th MAP percentile was 50 mmHg rather than 70 mmHg, the risk of PMI would be 6.2%. In contrast, the interaction between the 50th MAP percentile and duration of surgery in relation to PMI was mostly neglible (*Figure 2, panel b: the slopes are almost horizontal*). For the same patient with a duration of surgery of 156 minutes, the risk of PMI with a 50th MAP percentile of 85 mmHg was 3.9% and only increased to 4.1% with a 50th MAP percentile of 65 mmHg (*Figure 2, panel b*).

The interaction between MAP percentiles and duration of surgery emphasised the need to explore additional characteristics of the intraoperative blood pressure course. Especially the deflecting line for lower 50th MAP percentiles at a duration of surgery of 406 minutes (*Figure 2: panel b: yellow line*) is difficult to interpret as the the 5th MAP percentile, 50th MAP percentile, and duration of surgery are interdependent. Depth- and duration- weighted AUT variables were created additionally to the 'normal area-under-the-normal-blood-pressure' variable for every patient. Depth-weighted AUT (OR 4.4, 95% CI 2.6 – 7.4), but not duration-weighted AUT (OR 0.9, 95% CI 0.6 – 1.3), was associated with PMI (*Table 3*). For example, two patients with similar procedures and comparable total hypotension area (AUT of 2,186 and 2,196) but differences in depth- and duration-weighted AUT, have different risks to develop PMI. The risk of PMI for the patient with a relative low depth-weighted AUT but relative high duration-weighted AUT was 9%, and for the patient with a high depth-weighted AUT but relative low duration-weighted AUT was 15%. The depth-weighted AUT (OR 12, 95% CI 3.8 – 34), but not the

duration-weighted AUT was significantly associated with in-hospital mortality (*Table 3*). The effect estimates for duration of surgery (OR 1.5, 95% CI 1.1 – 2.1) and the results of the other covariables are listed in *Table 3*.

To enhance the interpretation of the results of the weighted-AUT method, the associations listed in *Table 3* are plotted in *Figure 3*. These continuous associations are shown for two groups of blood pressure courses (*Figure 3: panel a and panel b: steady blood pressure course; panel c and panel d: patient with dipping blood pressure course*) and variable cumulative AUTs (red, blue and green lines). Patients with dipping blood pressure course (*Figure 3: panel d: depth-weighted AUT*) had higher associated risk for occurrence of PMI compared to patients with a steady low blood pressure (*Figure 3: panel b: duration-weighted AUT*). In addition, patients with substantial intraoperative hypotension (*Figure 3: panel b and panel d: green lines*) and/or longer duration of surgery had higher associated risks for occurrence of PMI compared to patients with minimal intraoperative hypotension (*Figure 3: panel b and panel d: red lines*) and/or shorter duration of surgery.

The overall model performance, indicated by R^2, showed comparable values for the new intraoperative blood pressure analysis methods compared to traditional IOH analysis methods (*Table 4*). Similar to R^2 values, the c-statistic values were comparable with traditional intraoperative blood pressure analysis methods. AUT and TWA analysis methods and the above described new IOH analysis methods showed the best model performance.

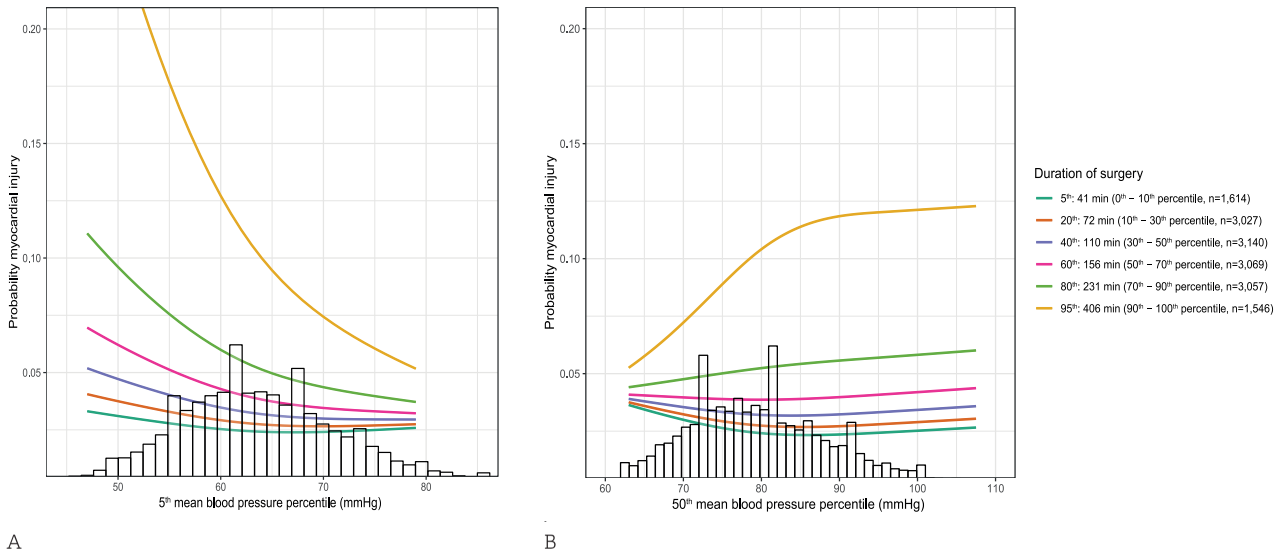


Figure 2 Adjusted, continuous associations between 5th and 50th mean blood pressure percentiles, duration of surgery and postoperative myocardial injury after noncardiac surgery

Panel a: 5th mean blood pressure percentile.

Panel b: 50th mean blood pressure percentile.

Both panels are the graphical representation of the effect estimates for the percentile mean blood pressures, duration of surgery and their interaction as estimated by the percentile-based regression model for postoperative myocardial injury (*Table 2: column 'Penalised adjusted odds ratio'*). All other variables were held constant at either their overall incidence or their median value. Histograms show the distribution of the 5th and 50th percentile mean blood pressure. Duration of surgery was categorised according to the 5th, 20th, 40th, 60th, 80th and 95th percentile with the number of patients for various durations of surgery.

For example, a 5th percentile mean blood pressure of 60 mmHg corresponds to a risk of 2.5% postoperative myocardial injury if duration of surgery is short (5th percentile of duration of surgery: 41 min) (*panel a: dark green line*). The risk of occurrence of postoperative myocardial injury increases to 12.7% if the duration of surgery is long (95th percentile of duration of surgery: 406 min) (*panel a: orange line*).

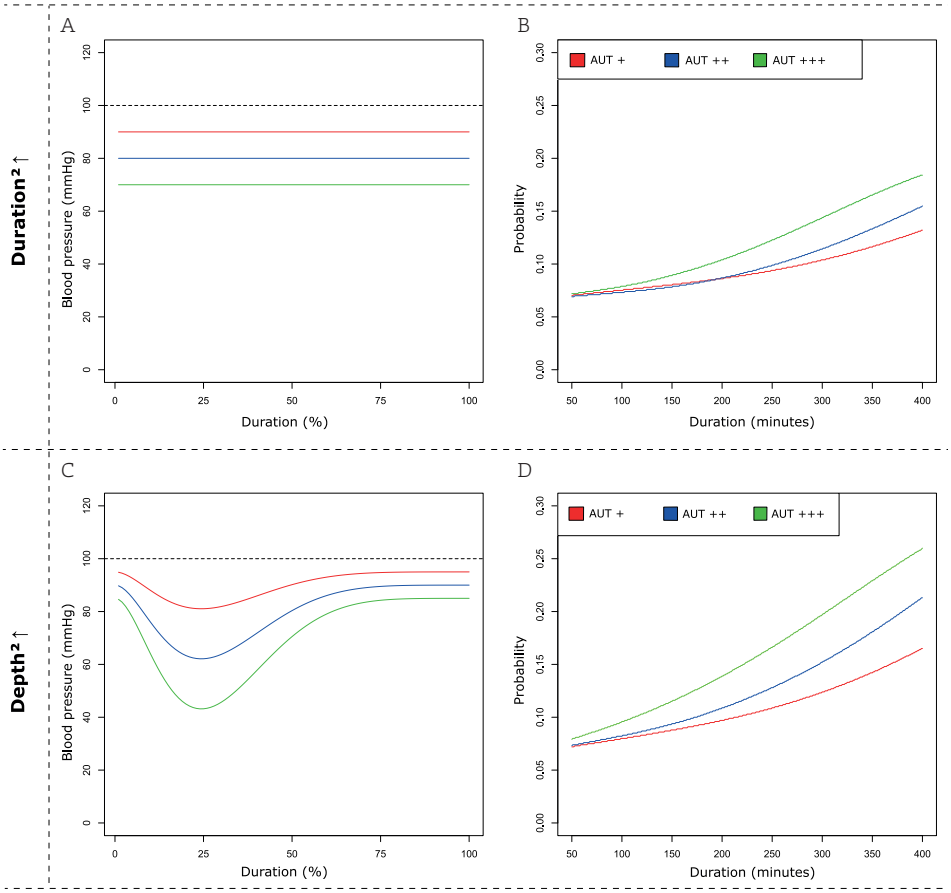


Figure 3 Association between patients with a steady blood pressure course and patients with dipping blood pressure course and occurrence of postoperative myocardial injury after noncardiac surgery

Panel a: Simplified example of patients with a steady mean blood pressure course during surgery and variable relative duration of surgery (%).

Panel b: Graphical representation of the association between mean blood pressure course of patients with a steady blood pressure course and occurrence of postoperative myocardial injury.

Panel c: Simplified example of patients with dipping blood pressure course during surgery and variable relative duration of surgery (%).

Panel d: Graphical representation of the association between mean blood pressure course of patients with dipping blood pressure course and occurrence of postoperative myocardial injury.

Patients with dipping blood pressure course (*panel d*) have higher risk for occurrence of postoperative myocardial injury compared to patients with a steady low blood pressure (*panel b*) while the total area under the normal mean blood pressure is equal. In addition, patients with substantial intraoperative hypotension (green lines compared to red line) and/or longer duration of surgery have higher risks for occurrence of postoperative myocardial injury.

Table 3 Association between intraoperative area under the normal blood pressure variables and postoperative myocardial injury and in-hospital mortality after noncardiac surgery

	Index value/ category†	**Reference value/ category‡**
Area-under-the-normal-blood-pressure, depth·duration, mmHg·min	4,283	1,180
Depth-weighted area-under-the-normal-blood-pressure, depth^2·duration, mmHg^2·min	121,800	28,351
Duration-weighted area-under-the-normal-blood-pressure, depth·duration^2, mmHg·min^2	597,320	53,188
Age, years	75	65
Sex	Male	Female
Hypertension		
Diabetes mellitus		
Renal disease		
Cardiac disease		
Cardiovascular disease		
Chronic medication use		
ASA physical status		
1		
2		
3		
4		
Surgical specialty		
General surgery		
Ear, nose, throat surgery/oral and maxillofacial surgery		
Gastroenterological and oncological surgery		
Gynaecology		
Neurosurgery		
Orthopaedic surgery		
Plastic surgery		
Trauma surgery		
Urology		
Vascular surgery		

PMI Adjusted odds ratio (95% CI)	PMI Penalised adjusted odds ratio (95% CI)	p-value	In-hospital mortality Adjusted odds ratio (95% CI)	In-hospital mortality Penalised adjusted odds ratio (95% CI)	p-value
0.14 (0.05 – 0.35)	0.26 (0.12 – 0.53)	< 0.05	0.08 (0.01 – 0.40)	0.08 (0.01 - 0.40)	< 0.05
7.02 (3.74 – 13.2)	4.38 (2.60 – 7.36)	< 0.05	11.6 (3.82 – 34.9)	11.6 (3.82 - 34.9)	< 0.05
1.02 (0.62 – 1.70)	0.89 (0.61 – 1.31)	0.57	1.27 (0.53 – 3.02)	1.27 (0.53 - 3.02)	0.61
1.44 (1.31 – 1.59)	1.44 (1.31 – 1.59)	< 0.05	1.07 (0.91 – 1.25)	1.07 (0.91 - 1.25)	0.42
0.94 (0.84 – 1.05)	0.94 (0.84 – 1.05)	0.29	1.06 (0.87 – 1.29)	1.06 (0.87 - 1.29)	0.57
1.17 (1.03 – 1.34)	1.17 (1.03 – 1.34)	< 0.05	1.02 (0.74 – 1.42)	1.02 (0.74 - 1.42)	0.89
1.20 (1.02 – 1.41)	1.20 (1.02 – 1.41)	< 0.05	1.32 (0.95 – 1.83)	1.32 (0.95 - 1.83)	0.10
1.29 (1.11 – 1.49)	1.29 (1.12 – 1.49)	< 0.05	1.58 (1.06 – 2.35)	1.58 (1.06 - 2.35)	< 0.05
1.37 (1.18 – 1.60)	1.37 (1.18 – 1.60)	< 0.05	0.96 (0.71 – 1.32)	0.96 (0.71 - 1.32)	0.83
1.21 (1.02 – 1.43)	1.21 (1.02 – 1.43)	< 0.05	1.16 (0.71 – 1.91)	1.16 (0.71 - 1.91)	0.56
1.16 (0.79 – 1.71)	1.16 (0.79 – 1.72)	0.45	0.81 (0.40 – 1.64)	0.81 (0.40 - 1.64)	0.58
1.00	1.00		1.00	1.00	
1.48 (1.07 – 2.04)	1.47 (1.07 – 2.02)	< 0.05	1.52 (0.81 – 2.86)	1.52 (0.81 - 2.86)	0.19
1.91 (1.36 – 2.68)	1.90 (1.36 – 2.66)	< 0.05	3.50 (1.82 – 6.74)	3.50 (1.82 - 6.74)	< 0.05
3.88 (2.57 – 5.85)	3.85 (2.57 – 5.79)	< 0.05	8.78 (4.28 – 18.0)	8.78 (4.28 - 18.0)	< 0.05
1.00	1.00		1.00	1.00	
0.37 (0.29 – 0.47)	0.38 (0.30 – 0.48)	< 0.05	0.23 (0.14 – 0.38)	0.23 (0.14 - 0.38)	< 0.05
0.70 (0.57 – 0.88)	0.71 (0.57 – 0.88)	< 0.05	1.36 (0.96 – 1.91)	1.36 (0.96 - 1.91)	0.08
0.42 (0.29 – 0.61)	0.42 (0.29 – 0.61)	< 0.05	0.12 (0.03 – 0.51)	0.12 (0.03 - 0.51)	< 0.05
0.55 (0.45 – 0.67)	0.55 (0.45 – 0.67)	< 0.05	1.00 (0.72 – 1.39)	1.00 (0.72 - 1.39)	0.98
0.57 (0.45 – 0.72)	0.57 (0.45 – 0.72)	< 0.05	0.58 (0.37 – 0.90)	0.58 (0.37 - 0.90)	< 0.05
0.25 (0.13 – 0.50)	0.27 (0.14 – 0.51)	< 0.05	§	§	
0.78 (0.58 – 1.06)	0.79 (0.58 – 1.06)	0.12	0.98 (0.61 – 1.59)	0.98 (0.61 - 1.59)	0.94
0.38 (0.27 – 0.52)	0.38 (0.27 – 0.52)	< 0.05	0.30 (0.15 – 0.60)	0.30 (0.15 - 0.60)	< 0.05
0.78 (0.63 – 0.96)	0.78 (0.63 – 0.96)	< 0.05	0.49 (0.34 – 0.72)	0.49 (0.34 - 0.72)	< 0.05

Table 3 Continued

	Index value/ category†	Reference value/ category‡
Priority of surgery		
Elective surgery		
Emergency surgery, within 24 hours		
Emergency surgery, within 8 hours		
Emergency surgery, within 2 hours		
Duration of surgery, minutes	208	82

Odds ratios represent an increase in the odds comparing the 25th percentile († index value/category) and 75th percentiles (‡ reference value/category). Age, depth²·duration and depth·duration² were transformed with restricted cubic splines. Results were adjusted for the following confounders: age, sex, ASA physical status, usage of any chronic preoperative medication, presence of hypertension, diabetes mellitus, cardiac disease, cerebrovascular disease, non-end-stage renal disease,

Table 4 Comparison of different intraoperative hypotension analysis methods

Hypotension analysis methods	**Blood pressure thresholds**
Number of hypotension episodes, n [25]	MAP < 65 mmHg
Duration under an absolute blood pressure threshold, minutes [2,7,8]	MAP < 100 mmHg MAP < 65 mmHg
Minimum mean blood pressure, mmHg [19]	Lowest MAP, mmHg
Lowest mean blood pressure for various cumulative minutes, mmHg [3]	Lowest MAP for at least ≥ 3 minutes
Lowest mean blood pressure for sustained minutes, mmHg [3]	Lowest sustained MAP ≥ 3 minutes
Area under an absolute mean blood pressure threshold, mmHg · min [26]	MAP < 100 mmHg MAP < 65 mmHg
Time-weighted average under absolute mean blood pressure threshold, mmHg [3]	MAP < 100 mmHg MAP < 65 mmHg
This article	
Mean blood pressure percentiles [19]	5th MAP percentile & 50th MAP percentile, mmHg
Depth- and duration weighted area under the normal blood pressure	depth·duration & depth²·duration & depth·duration²

Both new IOH analysis methods were applied to the study cohort and the c-index and R^2 values were compared to the results of some previously published IOH analysis methods. Odds ratios represent an increase in the odds comparing the 25th percentile († index value/category) and 75th percentiles

PMI Adjusted odds ratio (95% CI)	PMI Penalised adjusted odds ratio (95% CI)	p-value	In-hospital mortality Adjusted odds ratio (95% CI)	In-hospital mortality Penalised adjusted odds ratio (95% CI)	p-value
1.00	1.00		1.00	1.00	
1.90 (1.58 – 2.28)	1.91 (1.60 – 2.29)	< 0.05	2.12 (1.51 – 2.98)	2.12 (1.51 - 2.98)	< 0.05
3.01 (2.59 – 3.51)	3.02 (2.59 – 3.51)	< 0.05	4.54 (3.48 – 5.94)	4.54 (3.48 - 5.94)	< 0.05
6.90 (5.59 – 8.52)	6.94 (5.62 – 8.57)	< 0.05	17.9 (13.3 – 24.0)	17.9 (13.32 - 24.0)	< 0.05
2.11 (1.78 – 2.52)	1.99 (1.68 – 2.36)	< 0.05	1.49 (1.05 – 2.10)	1.49 (1.05 - 2.10)	< 0.05

surgical specialty and priority of surgery. P-value was based on penalised adjusted odds ratios and 95% confidence intervals after bootstrapping (n = 500). Due to the lack of events in particular groups, not all odds ratios could be calculated (§ no value available).
Abbreviations: ASA: American Society of Anesthesiologists; CI: confidence interval; PMI: postoperative myocardial injury

6

c-index	R^2	Index value/ category †	Reference value/ category ‡	Odds ratio myocardial injury (95% CI)
0.773	0.195	5	1	1.35 (1.21 – 1.49)
0.771	0.192	184	61	1.18 (0.92 – 1.50)
0.774	0.199	23	1	1.45 (1.30 – 1.62)
0.773	0.197	48	63	1.20 (1.12 – 1.28)
0.775	0.199	53	66	1.25 (1.18 – 1.33)
0.775	0.199	54	67	1.25 (1.18 – 1.33)
0.772	0.194	4,283	1,180	1.41 (1.22 – 1.63)
0.775	0.201	144	3	1.46 (1.31 – 1.62)
0.772	0.196	24.9	13.0	1.22 (1.13 – 1.32)
0.775	0.200	1.02	0.03	1.36 (1.21 – 1.53)
0.775	0.201			Table 2
0.775	0.199			Table 3

(‡ reference value/category).
Abbreviations: CI: confidence interval; MAP: mean arterial pressure

DISCUSSION

In this retrospective observational cohort study, two new intraoperative hypotension analysis methods were introduced: a percentile-based method and a weighted-AUT method. In both analysis methods duration of surgery was incorporated, but blood pressure thresholds were not used. The results suggest that intraoperative MAP has a continuous association with PMI. No MAP threshold that clearly increased the risk of PMI was identified. The depth of IOH seems to contribute more to the association with PMI or in-hospital mortality than the duration of IOH, as indicated by the results of the weighted-AUT method.

Blood pressure management is one of the main tasks of the anaesthetist as part of intraoperative homeostasis maintenance. During surgery, low blood pressures are common and often caused by a combination of mechanisms, such as vasodilation, hypovolaemia and/or decreased cardiac function [13]. In various observational studies an association has been found between IOH and occurrence of PMI and other organ injury after noncardiac surgery [2,7,9]. In most of these studies arbitrarily chosen and sometimes data driven blood pressure thresholds were analysed. However, from a physiological perspective it is questionable whether one blood pressure cut-off 'fits all' and causality cannot be proven in observational studies [14]. The individual risk of occurrence of IOH and occurrence of postoperative organ injury differs between patients as well as between organs, a result of organ-specific autoregulation and a combination of preoperative comorbidity, medication, type of surgery and haemodynamic changes. Therefore, individualised intraoperative blood pressure management to prevent organ dysfunction seems more promising than continuation for the quest of one universal blood pressure threshold. A few interventional studies on prevention of IOH and postoperative adverse events have been performed [15,16,17]. In only one of these trials, maintenance of an individualised blood pressure was associated with a lower risk of postoperative organ dysfunction compared to standard care, i.e. maintenance of one universal blood pressure threshold [17].

Although it is still unclear whether prevention of IOH improves postoperative outcomes, the question remains which minimum blood pressure is allowable for an individual patient (and for a specific organ) and how to deal with these low intraoperative blood pressures. More insight in the complexity and cohesion of depth and duration of low intraoperative blood pressure might lead to more insight in IOH mechanisms and better-informed decisions in blood pressure treatment. In this exploratory study, we gradually obtained more insight in the importance and contribution of duration of surgery, depth and duration of intraoperative hypotension and their association with PMI and in-

hospital mortality. The results of the percentile-based method showed that duration of surgery should be attributed in hypotension analysis methods. Surgical procedures with a longer duration inevitably increase the risk of exposure to IOH. However, inclusion of both procedures with short and longer duration of surgery and therefore differences in the possible exposure to IOH might suggest occurrence of a MAP threshold (*Figure 2*). In few studies, duration of surgery was one of the covariables, but it was not added as an interaction when analysing associations between time-weighted definitions of intraoperative hypotension and postoperative PMI or mortality [3,18] Both here presented percentile-based and weighted-AUT analysis methods incorporate duration of surgery.

The use of a threshold in IOH analysis creates a boundary effect which is not plausible from a biological point of view. Therefore, we hypothesised that IOH analysis methods without a threshold may better resemble the clinical situation. For example, the 5th and 25th lowest MAP percentiles on the first seven postoperative days were significantly associated with occurrence of the composite endpoint of PMI and mortality after noncardiac surgery [19]. The weighted AUT variables in our study are a first attempt to split the contribution of depth and duration of intraoperative blood pressure and their associations with postoperative adverse events. Performance of models with mean blood pressure percentiles and weighted AUT were comparable to previously described IOH analysis methods. This indicates that the above described methods might be a more biologically plausible alternative to current IOH analysis methods for identification of relevant components of intraoperative blood pressure for prediction of adverse postoperative outcomes [20].

Our study has some limitations. First, the main analysis (weighted AUT analysis) was a post-hoc analysis due to the exploratory character of this study. The different IOH analysis methods were subsequently developed and applied to patients from a single centre. The performance of both IOH analysis methods should be analysed in different patient populations and for other postoperative outcomes. Second, although hypotension thresholds were avoided in the new IOH analysis methods, a reference for normal intraoperative blood pressure, i.e. MAP < 100 mmHg, was necessary. This 'normal' blood pressure was included in the analysis methods to avoid that intraoperative hypertension might compensate for adverse effects of intraoperative hypotension. We considered a MAP < 100 mmHg as a reference, which may be considered arbitrarily. However, several studies have shown that the risk for postoperative organ injury already increases with prolonged durations of MAP < 80 mmHg and for shorter durations of lower mean blood pressures [21]. Third, other intraoperative factors, for example heart rate and anaemia also can influence intraoperative blood pressure and occurrence of postoperative myocardial injury. These and other factors were not included in the analyses. Fourth, the

results were not adjusted for occurrence of postoperative hypotension. Postoperative hypotension is common and not always detected by routine vital sign assessment [22]. Although postoperative hypotension is probably less severe than intraoperative hypotension [19], it is nevertheless associated with PMI after noncardiac surgery [23,24]. Fifth, the results of the IOH analysis methods are not directly applicable in clinical practice. Percentiles and weighted AUT variables can only be determined after the end of the procedure.

In this study, we presented two new IOH analysis methods to study the association between IOH and occurrence of PMI and in-hospital mortality after noncardiac surgery. The performance of both IOH analysis methods is comparable to traditional IOH analysis methods. The results of both analyses show that duration of surgery should be incorporated in the IOH analysis methods and that depth of low MAP contributes to a greater extent to occurrence of PMI and in-hospital mortality compared to duration of low MAP after noncardiac surgery. We obtained more insight in IOH, showing the importance of these aforementioned factors in a continuous association of blood pressure and outcome, rather than a boundary effect, i.e. applying a specific threshold.

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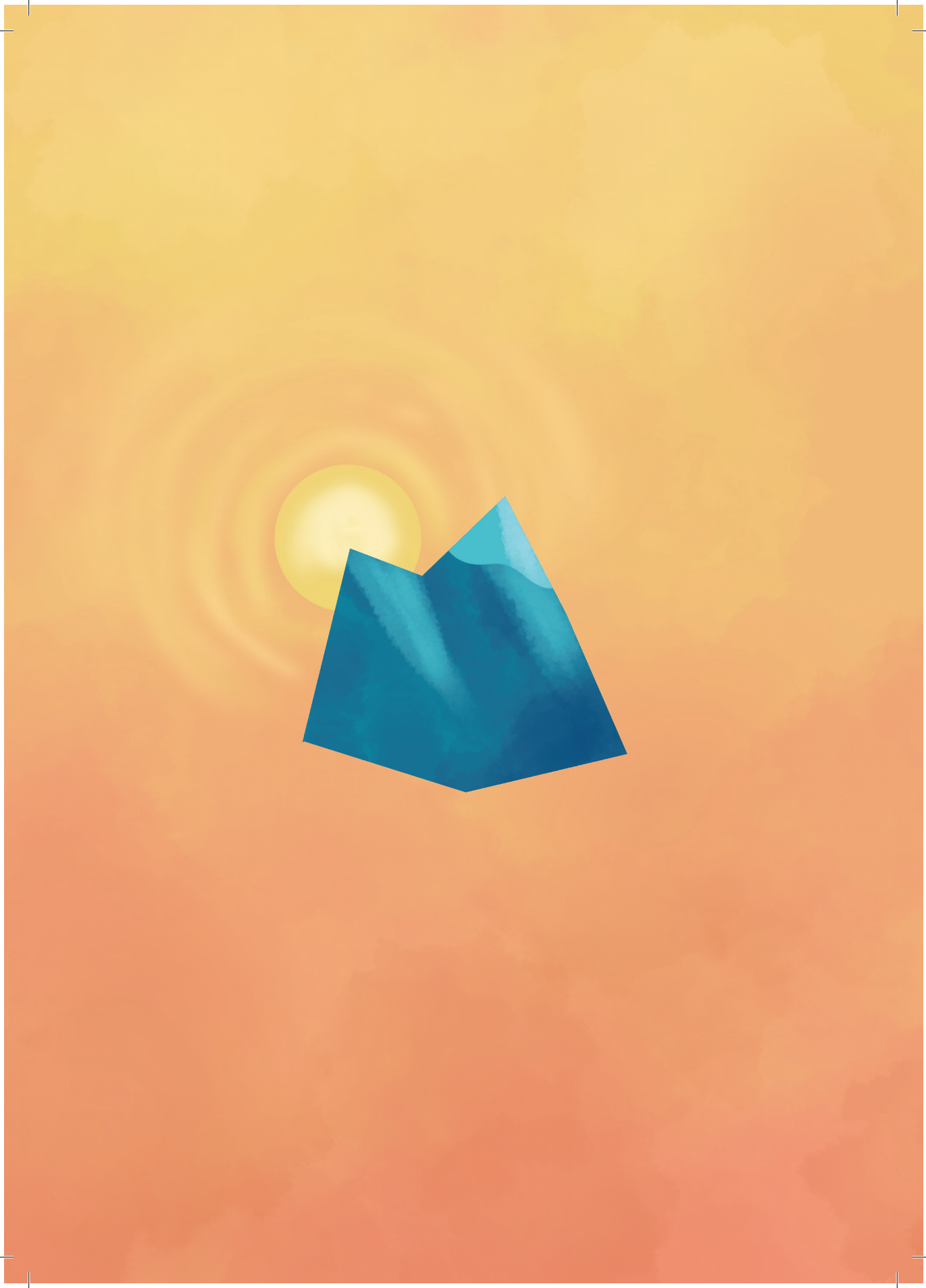

CHAPTER 7

RELATION BETWEEN ARTERIAL WAVEFORM PARAMETERS AND MEAN ARTERIAL PRESSURE CHANGES AFTER A BOLUS PHENYLEPHRINE OR EPHEDRINE: AN EXPLORATORY STUDY

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ABSTRACT

Background*:* Patients undergoing general anaesthesia often experience intraoperative hypotension (IOH). IOH is associated with postoperative injury and prevention of IOH might improve patient outcomes. Arterial waveform parameter (AWP) analysis might provide useful diagnostic information regarding the underlying hypotension mechanisms. We hypothesised that AWP can distinguish between underlying causes of hypotension and predict the most effective intervention – without quantifying the cardiac output.

Methods*:* Patients undergoing elective, noncardiac surgery with invasive blood pressure monitoring were eligible. IOH episodes were treated with boluses of the vasopressors phenylephrine or ephedrine at the discretion of the attending anaesthetist. Two trained research assistants observed procedures live and registered the exact time of vasopressor administration. Arterial waveform data of ten minutes before and after the vasopressor bolus were extracted and analysed. The primary outcome was the mean arterial pressure (MAP) before and after a vasopressor bolus.

Results*:* 88 surgical procedures were observed and in 26 procedures (30%) a vasopressor bolus was administered during the observation period. 41 boluses of phenylephrine ($n = 24$) and ephedrine ($n = 17$) were analysed. MAP decreased with 2 mmHg ($p < 0.001$) after administration of phenylephrine, whereas MAP increased with 9 mmHg ($p < 0.001$) after administration of ephedrine. All AWP increased after administration of ephedrine, except for the duration of the diastolic phase. On the contrary, all AWP parameters decreased after administration of phenylephrine, except for the duration of the diastolic phase. A linear mixed-effects model showed that MAP is in varying degrees dependent on different AWP.

Conclusions*:* MAP is in varying degrees dependent on AWP and the relation between AWP and MAP differed whether phenylephrine or ephedrine was administered. Furthermore, the relation between AWP and the MAP varied between the most likely underlying IOH mechanism.

INTRODUCTION

During surgery, the most vital job of an anaesthetist is to maintain homeostasis for optimal oxygen and nutrients supply and removal of waste products. For that purpose, the anaesthesia team continuously monitors their patient to estimate the adequacy of the cardiac output and organ perfusion. As haemodynamic disturbances are common during surgery, continuous monitoring allows the anaesthesia team to timely identify such disturbances [1]. Nonetheless, identification of such events is not enough to restore circulatory homeostasis. The anaesthetists need to have (patho-)physiological situation awareness to understand the cause of the of the disturbance and make appropriate course corrections.

The pulmonary artery catheter is one of the available monitoring devices that can be used to obtain a direct estimate of cardiac output, filling pressures and other haemodynamic parameters [2]. However, the use of this device decreased over the years, because it is an invasive technique accompanied by the risk of severe complications such as arrhythmias, infections, pulmonary artery rupture and thrombosis [3-7]. Therefore, less invasive intraoperative haemodynamic monitoring as blood pressure measurements, heart rate and -rhythm are routinely used to maintain awareness of the haemodynamic state of an individual patient.

Although not the same, blood pressure measurements are often used as a surrogate to estimate the adequacy of cardiac output and organ perfusion [8]. Both non-invasive oscillometric and invasive arterial blood pressure measurements are frequently used [9]. Low blood pressures – or intraoperative hypotension – have been associated with inadequate organ perfusion postoperative organ injury [13-15]. Timely identification and appropriate treatment might improve patient outcomes [16].

There are various causes of intraoperative hypotension, for example hypovolaemia, vasodilation and impaired cardiac function [1,17]. It is difficult to determine the underlying cause – or multiple causes – directly from the blood pressure values. Blood pressure is related to blood flow, but they are not the same. That is why new techniques to estimate cardiac output are being developed, ideally with similar or even better results than a pulmonary artery catheter, but with lower risks of severe complications.

Most of these techniques rely on the shape of the arterial waveform as measured by invasive blood pressure measurement devices [10]. The basic concept is that pulse pressure is proportional to stroke volume. However, over the years more sophisticated estimations have replaced this simple assumption. Modern techniques use various components – or parameters – of the arterial waveform as proxies for either contractility

or stroke volume [10,11]. These waveform-based parameters help estimate the change in cardiac output and systemic vascular resistance, dependent on the underlying cause, for example intraoperative hypotension due to vasodilation [12].

As pressure is not the same as flow, estimating stroke volume from pressure-based waveform parameters requires a translational step, as the relationship between vascular tone, pulse pressure and stroke volume is not constant [18,19]. Some devices directly measure the relation pressure and flow using transpulmonary thermodilution, and use the relation to calibrate their stroke volume estimates. Other devices indirectly estimate the relationship between pressure and flow through an algorithm that uses various waveform parameters and patient demographics to predict how vascular tone affects pulse pressure. Both direct and indirect methods accurately estimate stroke volume and cardiac output under normal haemodynamic conditions in which their underlying assumptions remain constant [18,20]. However, when their underlying assumptions do not hold, especially in large changes in vascular tone, the accuracy of their stoke volume and cardiac output estimates decline [5, 7-9, 18,19,21,22].

When treating intraoperative hypotension, the goal of these cardiac output monitoring devices is to understand its underlying cause and – most of all – select the most effective treatment to restore the haemodynamic balance. For example, phenylephrine and ephedrine are two commonly-used short-acting cardiovascular drugs with partial differences in their effects on the cardiovascular system [23-26]. Both are a_1-adrenergic receptor agonists producing arterial – and venous – vasoconstriction, but ephedrine also has b_1-adrenergic activity [17,27,28]. This means that their ability to restore the haemodynamic balance depends on the clinical situation, i.e. the underlying cause of the hypotension. Consequently, it may suffice for anaesthetists to understand the pathophysiological situation in a qualitative way and identify which drug they should administer to their patients for an optimal effect. Perhaps it then becomes superfluous to have a formal estimate of the cardiac output, especially when based on so many assumptions.

The present study serves as a pilot to test our hypothesis that arterial waveform parameters (AWP) can distinguish between underlying causes of hypotension and predict the most effective intervention – without quantifying the cardiac output. We will analyse the relationship between various arterial waveform parameters and the mean arterial pressure (MAP) observed at the same points in time, for the periods both before and after a bolus of either phenylephrine or ephedrine in patients who underwent noncardiac surgery. Even though it is not yet the goal of this study to actually predict the haemodynamic effects of these interventions, the AWP should be strongly correlated to the MAP in all circumstances: both before and after the boluses of either phenylephrine

or ephedrine. Observing that correlation would provide preliminary support for our hypothesis that using the changes over different interventions can help leverage arterial waveform analysis as a tool to better understand intraoperative haemodynamics.

METHODS

Study design and study population

This study was carried out according to Good Clinical Practice standards and national regulations. The Medical Ethics Committee of the University Medical Center Utrecht waived the need to obtain informed consent for this study (protocol number 19-629). This cohort study included adult patients who underwent elective, noncardiac surgery and had invasive blood pressure measurements with an arterial catheter at the University Medical Center Utrecht, Utrecht, the Netherlands between July 2019 and October 2019.

Every day, one researcher (EW) screened all surgical procedures for the next day and identified the procedures with planned invasive blood pressure monitoring. Inclusion criteria were duration of surgery > 60 minutes, general anaesthesia and the estimation that the patients required at least one bolus ephedrine or phenylephrine during the observation period (details regarding the observation period are described below). Exclusion criteria were emergency or cardiac surgery, no invasive blood pressure measurements during anaesthesia or when the research assistants were unable to perform live observations during the procedure due to logistical reasons. We included all eligible patients who met the inclusion criteria and did not meet the exclusion criteria. No statistical power calculation was performed prior to the study.

The anaesthesia techniques performed and IOH treatment were left to the discretion of the attending anaesthetist. Anaesthesia was typically induced by boluses propofol, sufentanil or remifentanil and maintained with inhalational anaesthesia (isoflurane or sevoflurane) or propofol infusion. A bolus of rocuronium (0,6 $mg \cdot kg^{-1}$) was administrated to facilitate orotracheal intubation. IOH was treated with fluids, phenylephrine or norepinephrine pumps and/or boluses phenylephrine (50 – 100 µg i.v.) and/or ephedrine (2.5 – 7.5 mg i.v.).

Data collection and live observations

Data on patient-, procedure and intraoperative characteristics were collected from the electronic patient record and the anaesthesia information management system (Anstat, version 2.1, 2019; Carepoint, Ede, The Netherlands). Parts of the methods with regard to the live observations were previously described in a previous publication, as data collection was combined for both studies [29]. In summary, two research assistants (sixth year medical

students) were trained prior to the study by an anaesthetist to recognise and register vasopressor administration in the operating room. During a time period of 11 weeks the assistants attended and observed (parts of) the noncardiac procedures. Each observation period covered a part of the procedure of at least one hour. To ensure that a mix of procedures was sampled, the procedures were visited in sequence (i.e. the assistant identified the next eligible procedure to visit when a measurement session was finished).

The assistants used a special software package, the Behavioral Observation Research Interactive Software to record live observations [30]. The assistants were instructed on the exact timing of the observation period. The start of the observation period was marked by the registration of a flush of the arterial blood pressure measurement system. Data collected with live observation registration software was afterwards synchronised with the data points from the anaesthesia information management system, based on the flush event in the stored waveform data.

Arterial wave parameter extraction

Arterial waveform data of ten minutes before and after the vasopressor bolus were extracted from the database and analysed. Raw arterial waveform data was reviewed and analysed with in-house developed software (SignalBase, version 10.0.0; legal copyright UMC Utrecht, Utrecht, the Netherlands). The fragmentation process of the arterial blood pressure in SignalBase and calculation of AWP were based on algorithms as described previously [31].

First, arterial waveform data was fragmented into so-called snippets, i.e. separated, individual arterial waves. The fragmentation process consisted of the following steps: the arterial waveforms were resampled and the maximum (top) and minimum (valley) values of the signal were detected. Thereafter, segments were found if a top existed between two valleys. For each segment six landmarks were determined, namely diastolic pressure (start of the snippet), maximum rate of arterial pressure increase during the systolic phase pressure (dP/dt_{max}), anacrotic notch pressure, systolic pressure, dicrotic notch pressure and diastolic pressure (end of the snippet). Second, other variables such as time derived parameters, area under the curve (AUC) parameters, slope parameters and pressure parameters were calculated from the six arterial waveform landmarks. In order to prevent an overlapping effect of vasopressor boluses on the morphology of the arterial waveform and AWP, there had to be a minimum period of 5 minutes between each administration.

Arterial waveform parameter selection

The selection of AWP was made a priori, and based on their relation with specific parts of the cardiac cycle [31-34]. The following AWP were selected for analysis: heart rate (HR), pulse pressure (PP), dicrotic notch pressure, the standard deviation (SD)

of the sampled mean blood pressure points, duration of systolic phase corrected for HR, duration of diastolic phase corrected for HR, dP/dt_{max} corrected for HR and systolic upstroke time corrected for HR. The assumed consequences of changing values of the selected APW parameters on the cardiac cycle are briefly discusses below.

- PP: proportional to the stroke volume (SV). A narrow PP can reflect a drop in left ventricular SV due to insufficient preload, elevated afterload, or a reduced contractility [20]. The most likely basis of a (consistently) wide value of the PP is stiffness of the arteries [35].
- Dicrotic notch pressure: the magnitude of the dicrotic notch is determined by a patient's arterial compliance, systemic vascular resistance and arteriolar vasodilatation. Low intravascular volume and increased peripheral vascular resistance are related to less elastic recoil and decreased wave reflection transmitted to the circulation, possibly leading to a lower dicrotic notch pressure [36].
- SD: The SD is related to the PP and is proportional to the SV. So, the SD is indicative of the SV [18,37].
- dP/dt_{max}: when adjusted for heart rate, preload and aortic pressure, the maximum rate of left ventricular pressure during isovolumetric contraction (dP/dt_{max}) has been considered as a marker of contractility [38]. Although peripheral measurement of dP/dt_{max} tends to underestimate ventricular dP/dt_{max}, peripherally measured values have appeared to accurately reflect changes in left ventricular dP/dt_{max} if adequate vascular filling is achieved [34,39,40].
- Duration of systolic and diastolic phases and systolic upstroke time: all three time-derived parameters highly depend on heart rate. It is thought that ventricular filling time depends mostly on the duration of the diastolic phase.

Outcome assessment

The outcome was the mean arterial pressure (MAP) at the same time point as the AWP during the ten minutes before and after a vasopressor bolus. Invasive blood pressures were measured with Spacelabs patient monitors (type Xprezzon, Spacelabs Healthcare, Snoqualmie, WA, U.S.A.). Artefacts were removed based on the following filters: duration of systolic phase < duration of diastolic phase, systolic blood pressure > 20 mmHg & < 250 mmHg, diastolic blood pressure > 10 mmHg, PP > 5 mmHg, diastolic pressure < MAP, dicrotic notch pressure < systolic blood pressure, systolic blood pressure > MAP, difference between top and systolic blood pressure < 20 mmHg, difference between valley and diastolic blood pressure < 20 mmHg.

Statistical analysis

Statistical analyses were performed using R (Version 4.0.2 for Mac, the R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were visually assessed for a normal distribution using qq-plots and tested with the Kolmogorov-Smirnov test. Normally distributed data were presented as means with SD. Skewed continuous data were presented as medians with interquartile ranges (IQR) and evaluated using Wilcoxon signed rank tests. Categorical variables were expressed as numbers (percentage). The Wilcoxon rank sum test was used to assess the median difference in AWP before and after the administration of either phenylephrine or ephedrine.

To study the relation between each APW parameter and the absolute MAP at the same time point, before or after a bolus of either phenylephrine or ephedrine, two linear mixed-effects models were fitted. The basic model had MAP as the dependent variable and the selected APW parameters as fixed effects. The full model included fixed effects for the 'After bolus' period (versus the 'Before bolus' period), for use of a phenylephrine bolus (versus use of ephedrine), for the interaction between period and phenylephrine (versus the 'After bolus' period using ephedrine), and for the two-way and three-way interactions between the AWP, the 'After bolus' period and the use of phenylephrine.

As patients could have multiple observation episodes a random intercept per patient was included in each model to account for within-patient variance and a random slope for the choice of vasopressor was included to account for individual sensitivity to a particular drug. In addition, a random intercept per unique episode and a random intercept for the time period (before versus after the bolus) were included in each model to account for within-episode (-within-patient) variances in the blood pressure course. A restricted maximum likelihood (REML) approach was used constructing the model. p-values < 0.05 were considered statistically significant and 95% confidence intervals (CI) were reported. Regression coefficients were reported for the full model. The prediction errors of the models were compared in Bland-Altman plots, using the observed (measured) MAP on x-axis, rather than the average of the observed and estimated MAP, as the observed MAP by definition reflects the truth over the estimated MAP.

RESULTS

Patient characteristics

Eighty-eight patients were observed during the inclusion period. Twenty-six patients (30%) received at least one vasopressor bolus during the live observations. In total, 41 administrations of phenylephrine (n = 24) and ephedrine (n = 17) were administered.

Eight patients (31%) received two or more boluses of either phenylephrine (n = 4) or ephedrine (n = 4). Six patients (23%) received both phenylephrine and ephedrine. Hypertension (50%), renal disease (31%) and diabetes mellitus (24%) were the most common comorbidities. Most patients underwent abdominal surgery (31%). Additional characteristics with regard to the patients and procedures are presented in *Table 1*.

Blood pressure change before and after administration of phenylephrine or ephedrine
The MAP decreased with 2 mmHg within 10 minutes after administration of phenylephrine, whereas MAP increased with 9 mmHg within 10 minutes after administration of ephedrine. The change in heart rate differed between patients after both phenylephrine and ephedrine (*Figure 1*).

All AWP decreased after administration of phenylephrine, except for the duration of the diastolic phase. On the contrary, all AWP increased after administration of ephedrine, except for the uncorrected systolic upstroke time, uncorrected duration of the systolic phase and the duration of the diastolic phase. The absolute changes in the six AWP after the administration of phenylephrine and ephedrine are presented in *Table 2*. The association between the AWP and MAP change after a bolus phenylephrine or ephedrine were analysed with a linear mixed-effects model (*Table 3*).

The pulse pressure is positively related to the MAP: an increase of 1 mmHg in pulse pressure results is a MAP increase of 0.15 mmHg (95% CI 0.09 – 0.22). After administration of a vasopressor bolus, the MAP changes more after ephedrine (0.08 (95% CI -0.05 – 0,20) compared to phenylephrine per mmHg increase of the PP. For each unit increase in the value of the SD of the arterial waveform pressure, the MAP decreases by 0.22 mmHg (95% CI -0.42 – -0.02). This effect more pronounced after a bolus of phenylephrine compared to ephedrine. When a bolus of phenylephrine is administered, for each unit increase in the value of the SD, the value of the MAP would be 1.12 mmHg (95% CI -1.48 – -0.71) lower compared to ephedrine. When the dicrotic notch pressure increases by 1 mmHg the value of the MAP increases by 0.68 mmHg (95% CI 0.66 – 0.71). After administration of phenylephrine, the MAP increases more per mmHg dicrotic notch pressure increase compared to ephedrine (0.21 mmHg (95% CI 0.17 – 0.25)). After an increase of dP/dt_{max} ($mmHg \cdot s^{-1}$), MAP changes minimally compared to the other AWP (0.01 mmHg (95% CI 0.01 – 0.01). The effect of dP/dt_{max} after a vasopressor bolus on MAP hardly change between phenylephrine or ephedrine.

Table 1 Characteristics of included patients and surgical procedures

Patient characteristics
Male, n (%)
Age, years, median [IQR]
Body mass index, $kg \cdot m^{-1}$, median [IQR]
ASA physical status, n (%)
ASA 1
ASA 2
ASA 3
Hypertension, n (%)
Atrial fibrillation, n (%)
Ischaemic heart disease, n (%)
Heart failure, n (%)
Cerebrovascular accident, n (%)
Diabetes mellitus, n (%)
Peripheral artery disease, n (%)
Renal disease (eGFR < 70), n (%)
Anticoagulants, n (%)
Diuretics, n (%)
Beta blockers, n (%)
Renin-angiotensin-aldosterone system inhibitors, n (%)
Calcium antagonists, n (%)
Statins, n (%)
Preoperative systolic, mean and diastolic blood pressure, mmHg, median [IQR]
Intraoperative characteristics *
Surgical specialty, n (%)
Abdominal surgery, n (%)
Gynaecology, n (%)
Maxillofacial surgery, n (%)
Neuro-oncology, n (%)
Neurosurgery, n (%)
Plastic surgery, n (%)
Urology, n (%)
Vascular, n (%)

	All patients (n = 26)	Patients who received ≥ 1 bolus phenylephrine (n = 13)	Patients who received ≥ 1 bolus ephedrine (n = 7)	Patients who recieved both phenylephrine and ephedrine (n = 6)
	8 (31)	3 (23)	2 (29)	3 (50)
	70 [55 - 76]	71 [53 - 76]	69 [56 - 76]	73 [64 - 80]
	27 [24 - 31]	28 [24 - 32]	27 [24 - 32]	24 [24 - 28]
	3 (12)	2 (15)	1 (14)	0 (0)
	15 (58)	7 (54)	3 (43)	5 (83)
	8 (31)	4 (31)	3 (43)	1 (17)
	13 (50)	5 (39)	3 (43)	5 (83)
	3 (12)	2 (15)	0 (0)	1 (17)
	3 (12)	2 (15)	1 (14)	0 (0)
	1 (4)	1 (8)	0 (0)	0 (0)
	2 (8)	1 (8)	1 (14)	0 (0)
	6 (23)	5 (39)	0 (0)	1 (17)
	3 (12)	1 (8)	1 (14)	1 (17)
	8 (31)	4 (31)	1 (14)	3 (50)
	10 (39)	5 (39)	1 (14)	3 (50)
	5 (19)	3 (23)	1 (14)	1 (17)
	6 (23)	3 (23)	1 (14)	2 (33)
	8 (31)	3 (23)	1 (14)	4 (67)
	5 (19)	3 (23)	1 (14)	2 (33)
	7 (27)	4 (31)	1 (14)	2 (33)
	138 [122 - 149]	140 [121 - 153]	134 [129 - 143]	127 [114 - 138]
	97 [89 - 108]	100 [87 - 108]	96 [90 - 112]	90 [84 - 100]
	75 [70 - 81]	77 [68 - 86]	73 [71 – 96]	75 [61 - 81]
	8 (31)	3 (23)	3 (43)	2 (33)
	3 (12)	1 (8)	2 (29)	0 (0)
	3 (12)	3 (23)	0 (0)	0 (0)
	4 (15)	3 (23)	1 (14)	0 (0)
	1 (4)	1 (8)	0 (0)	0 (0)
	1 (4)	1 (8)	0 (0)	0 (0)
	5 (19)	1 (8)	0 (0)	4 (67)
	1 (4)	0 (0)	1 (14)	0 (0)

Table 1 Continued

Intraoperative maintenance of anaesthesia at time of vasopressor bolus, n (%)
Sevoflurane
Isoflurane
Propofol
Intraoperative phenylephrine pump, n (%)
Intraoperative norepinephrine pump, n (%)

* Based on preoperative assessments and assessment of intraoperative anaesthesia records.
Abbreviations: ASA: American Society of Anesthesiologists; eGFR: estimated glomerular filtration rate; IQR: interquartile range

Table 2 Change in arterial waveform parameters after administration of phenylephrine or ephedrine

Mean arterial blood pressure, mmHg, median [IQR]
Heart rate, beats per minute, median [IQR]
Pulse pressure**,** mmHg, median [IQR]
Dicrotic notch pressure**,** mmHg, median [IQR]
dP/dt_{max}, mmHg·s^{-1} median [IQR]
dP/dt_{max} corrected for heart rate, mmHg·s^{-1}, median [IQR]
Duration systolic phase, seconds, median [IQR]
Duration systolic phase corrected for heart rate, seconds, median [IQR]
Duration diastolic phase, seconds, median [IQR]
Duration diastolic phase corrected for heart rate, seconds, median [IQR]
Systolic upstroke time, seconds, median [IQR]
Systolic upstroke time corrected for heart rate, seconds median [IQR]
Standard deviation of the arterial pressure wave, mmHg, median [IQR]

Time related parameters were corrected for heart rate as duration of (parts of) the cardiac cycle depends on the heart rate.

	All patients (n = 26)	Patients who received ≥ 1 bolus phenylephrine (n = 13)	Patients who received ≥ 1 bolus ephedrine (n = 7)	Patients who recieved both phenylephrine and ephedrine (n = 6)
	5 (19)	0 (0)	3 (43)	2 (33)
	2 (8)	1 (8)	0 (0)	1 (17)
	19 (73)	12 (92)	4 (57)	3 (50)
	19 (73)	10 (77)	4 (57)	5 (83)
	9 (35)	3 (23)	4 (57)	2 (33)

	Phenylephrine			Ephedrine		
	Before the bolus	After the bolus	Change	Before the bolus	After the bolus	Change
	75 [70 – 81]	73 [66 – 79]	-1.9	70 [63 – 81]	78 [68 – 92]	8.7
	67 [60 – 74]	67 [59 – 73]	-0.3	59 [56 – 65]	64 [58 – 69]	4.5
	58 [45 – 70]	55 [44 – 70]	-2.9	56 [42 – 65]	64 [51 – 79]	8.0
	77 [69 – 89]	76 [68– 79]	-1.2	76 [66 – 88]	83 [72 – 95]	6.5
	688 [550 – 916]	680 [530 – 847]	-7.9	577 [472 – 754]	696 [564 – 903]	118
	724 [570 – 1094]	694 [571 – 1058]	-30	564 [482 – 746]	755 [576 – 888]	191
	0.35 [0.31 – 0.38]	0.34 [0.29 – 0.37]	-0.01	0.37 [0.34 – 0.36]	0.36 [0.34 – 0.39]	-0.01
	0.38 [0.32 – 0.42]	0.37 [0.31 – 0.41]	-0.01	0.36 [0.32 – 0.41]	0.39 [0.33 – 0.42]	0.03
	0.55 [0.47 – 0.70]	0.56 [0.49 – 0.67]	0.01	0.63 [0.54 – 0.71]	0.57 [0.50 – 0.69]	-0.06
	0.61 [0.56 – 0.68]	0.61 [0.57 – 0.68]	0.01	0.62 [0.57 – 0.67]	0.61 [0.56 – 0.66]	-0.01
	0.15 [0.13 – 0.19]	0.15 [0.13 – 0.18]	-0.0023	0.17 [0.15 – 0.20]	0.16 [0.15 – 0.20]	-0.01
	0.17 [0.15 – 0.20]	0.17 [0.15 – 0.20]	-0.0013	0.18 [0.16 – 0.20]	0.18 [0.16 – 0.21]	0.0012
	18 [13 – 21]	17 [13 – 21]	-1.4	17 [13 – 20]	20 [15 – 24]	2.7

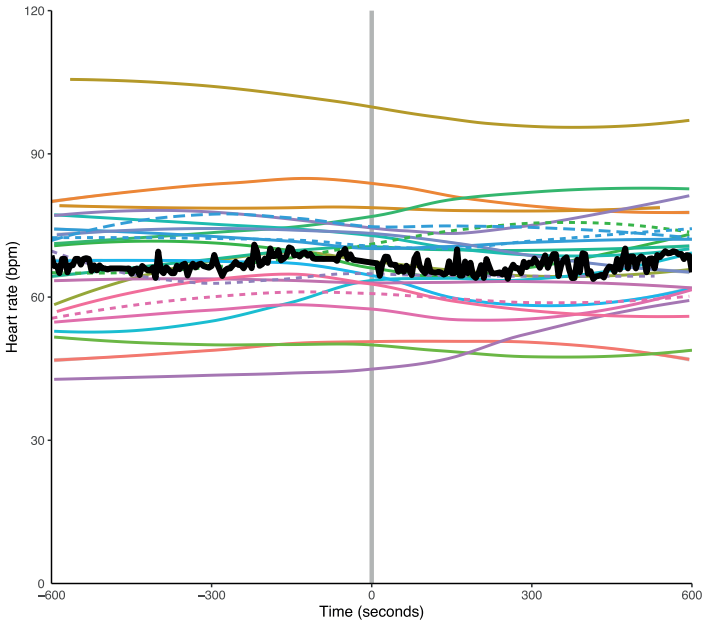
Table 3 Full linear mixed-effects model based on restricted maximum likelihood

Random effects
PeriodID
PatientID
Residuals
Fixed effects
Intercept
After bolus, intervention = 1
Phenylephrine group
Standard deviation of the arterial pressure wave
Pulse pressure, mmHg
Dicrotic notch pressure, mmHg
Systolic upstroke time corrected for heart rate, seconds
Duration diastolic phase corrected for heart rate, seconds
Duration systolic phase corrected for heart rate, seconds
dP/dt_{max} corrected for heart rate, $mmHg \cdot s^{-1}$
After bolus:phenylephrine group
After bolus:standard deviation of the arterial pressure wave
Phenylephrine group:standard deviation of the arterial pressure wave
After bolus:pulse pressure
Phenylephrine group:pulse pressure
After bolus:dicrotic notch pressure
Phenylephrine group:dicrotic notch pressure
After bolus:systolic upstroke time corrected for heart rate
Phenylephrine group:systolic upstroke time corrected for heart rate
After bolus:duration diastolic phase corrected for heart rate
Phenylephrine group:duration diastolic phase corrected for heart rate
After bolus:duration systolic phase corrected for heart rate
Phenylephrine group:duration systolic phase corrected for heart rate
After bolus:dP/dt_{max} corrected for heart rate
Phenylephrine group:dP/dt_{max} corrected for heart rate
After bolus:phenylephrine group:standard deviation of the arterial pressure wave
After bolus:phenylephrine group:pulse pressure
After bolus:phenylephrine group:dicrotic notch pressure
After bolus:phenylephrine group:systolic upstroke time corrected for heart rate
After bolus:phenylephrine group:duration diastolic phase corrected for heart rate
After bolus:phenylephrine group:duration systolic phase corrected for heart rate
After bolus:phenylephrine group:dP/dt_{max} corrected for heart rate

Abbreviations: CI: confidence interval; ID: identification number; IQR: interquartile range; MAP: mean arterial pressure; SD: standard deviation

	Variance	SD	Correction
Intercept	4.11	2.03	
After bolus	6.43	2.54	-0.07
Intercept	11.06	3.33	
Phenylephrine group	10.98	3.31	1.00
	6.67	2.56	
Estimate MAP	**Standard error**	**T value**	**95% CI**
18.9	2.09	9.04	14.8 – 23.0
-7.30	2.30	-3.17	-11.8 – -2.78
1.29	2.50	0.52	-3.62 – 6.18
-0.22	0.10	-2.26	-0.42 – -0.02
0.15	0.034	4.48	0.09 – 0.22
0.68	0.012	58.3	0.66 – 0.71
-82.2	3.79	-21.7	-89.6 – -74.4
-26.3	1.57	-16.8	-29.4 – -23.3
57.8	2.66	21.8	52.4 – 62.9
0.009	0.001	8.25	0.007 – 0.011
1.54	2.72	0.56	-3.77 – 6.87
0.24	0.15	1.62	-0.07 – 0.52
1.58	0.14	11.3	1.28 – 1.85
0.13	0.05	2.60	0.03 – 0.22
-0.24	0.05	-4.95	-0.32 – -0.14
-0.07	0.02	-4.59	-0.10 – -0.04
-0.23	0.02	-14.2	-0.26 – -0.19
44.4	4.78	9.29	34.4 – 53.5
41.2	4.57	9.03	31.8 – 50.1
-0.29	1.87	-0.16	-3.96 – 3.34
9.06	1.66	5.44	5.79 – 12.3
-3.25	3.17	-1.03	-9.34 – 3.29
-16.3	3.13	-5.20	-22.3 – -9.76
-0.008	0.001	-6.57	-0.01 – -0.005
-0.006	0.001	-4.65	-0.009 – -0.004
-1.12	0.19	-5.83	-1.48 – -0.71
0.08	0.06	1.19	-0.05 – 0.20
0.21	0.02	10.4	0.17 – 0.25
-51.8	6.04	-8.58	-63.4 – -39.2
-3.63	2.07	-1.76	-7.66 – 0.44
16.9	3.87	4.37	8.73 – 24.3
0.005	0.002	2.87	0.001 – 0.008

A



B

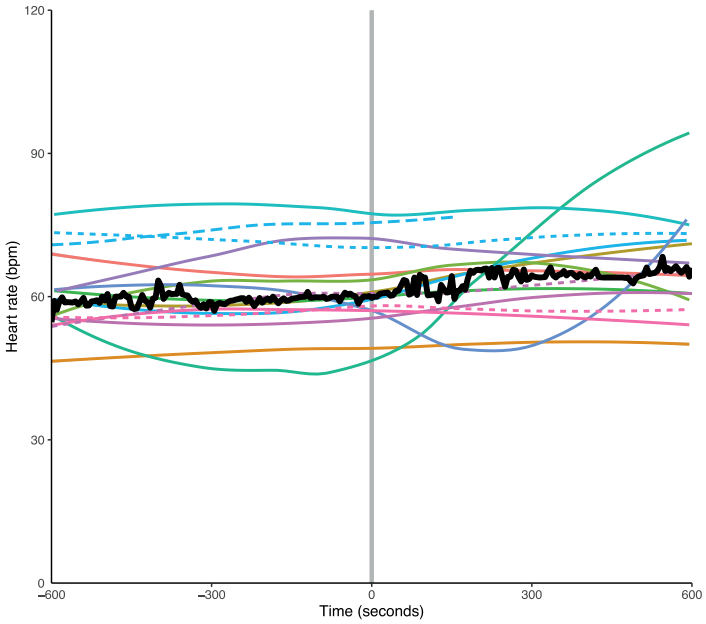
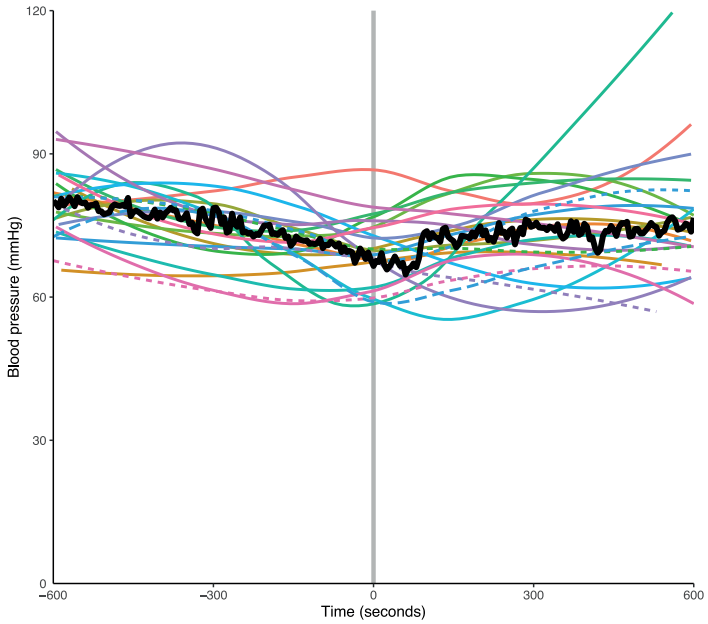


Figure 1 Spaghetti plot for change in heart rate and mean arterial pressure

Panel a: Heart rate change after phenylephrine administration at time = 0.

Panel b: Heart rate change after ephedrine administration at time = 0.

C



D

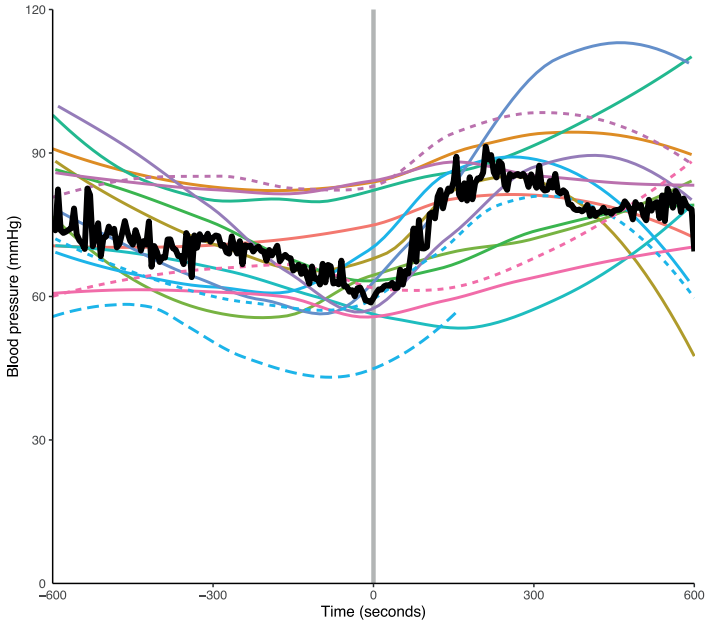


Figure 1 Continued

Panel c: Mean arterial pressure change after phenylephrine administration at time = 0.

Panel d: Mean arterial pressure change after ephedrine administration at time = 0.

If the systolic upstroke time increases by 1 msec, the MAP decreases by 0.08 mmHg (95% CI -0.09 – -0.07) mmHg. However, after a bolus of phenylephrine or ephedrine is administered, the MAP increases by 0.04 mmHg (95% CI 0.03 – 0.05) per 1 msec increase in the duration of the systolic upstroke time. After administration of phenylephrine, the MAP is 0.05 mmHg (95% CI -0.06 - -0.04) lower per msec systolic upstroke time compared to ephedrine. For each msec increase in the duration of the systolic phase, the MAP increases by 0.06 mmHg (95% CI 0.05 – 0.06). When compared to ephedrine, the value of the MAP would be 0.02 mmHg (95% CI 0.01 – 0.02) higher per msec increase of the systolic phase after administration of phenylephrine. When the duration of the diastolic phase increases the MAP decreases by 0.03 mmHg (95% CI -0.03 – -0.02) per msec. If a bolus of phenylephrine is administered, the MAP would be minimally lower per msec increase of diastole duration compared to ephedrine (0.004 mmHg (95% CI -0.008 – 0.0004).

All Bland-Altman plots (*Figure 2*) show a mean error of zero mmHg (as expected from a regression analysis). The limits of agreement for the overall Bland-Altman plots are +/- 5 mmHg (*Figure 2: top row*). For the 'Before bolus' period (*Figure 2: middle row*) the limits of agreement are closer to zero at +/- 4 mmHg, whereas for the 'After bolus' period (*Figure 2: bottom row)* the limits of agreement are also +/- 5 mmHg. The limits of agreement and even the shapes of the clouds are very similar between the plots of the basic model (*Figure 2: left column*) and the full model (*Figure 2: right column*).

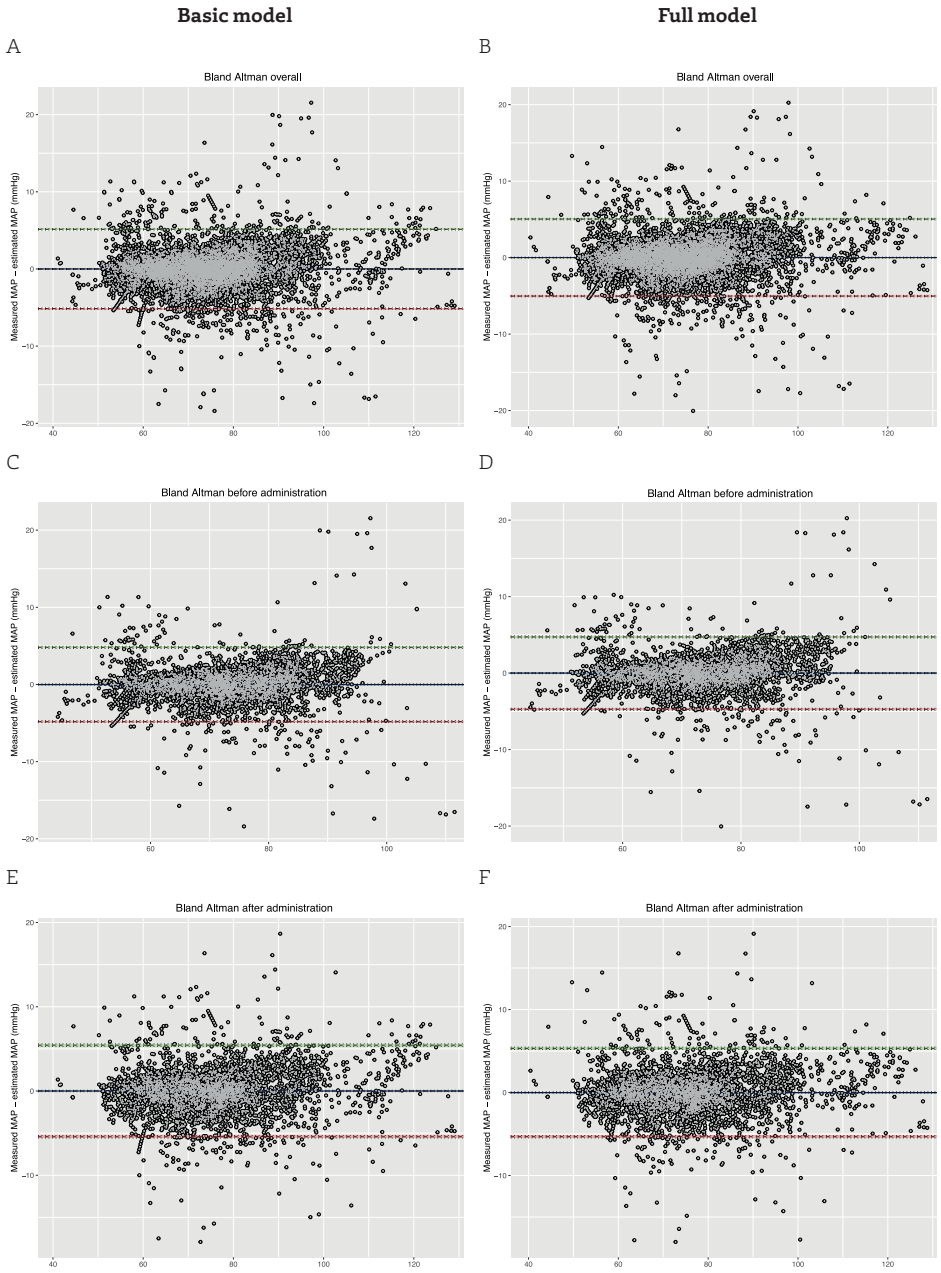


Figure 2 Bland-Altman plots showing the absolute prediction errors (y-axis) dependent on the mean arterial pressure

The left column (*panel a, panel c, and panel e*) shows the plots for predictions of the basic regression model, the right column (*panel b, panel d and panel f*) for the full model. The top rows (*panel a and panel b*) indicate the overall prediction error, the middle rows (*panel c and panel d*) the prediction error before the bolus, the bottom rows (*panel e and panel f*) the prediction error after the bolus. The blue lines indicate the mean bias, the green lines the upper limit of agreement, the red lines the lower limit of agreement.

DISCUSSION

In this pilot study, we analysed the relationship between arterial waveform parameters (AWP) and the mean arterial pressure (MAP) as measured at same points in time. There were strong correlations between several of the parameters and the MAP, both during the periods before and after the bolus (*Table 3*) and the prediction errors from the linear mixed effects regression models were small, with limits of agreement of +/- 5 mmHg MAP. The prediction errors are very similar between the basic model and the full model that includes all interaction terms between the before- and after periods and the type of intervention (phenylephrine versus ephedrine). As the haemodynamic situation changes from before the bolus to the bolus for individual patients, we would expect a change in predictive performance between the basic model and the full model if the AWP do not contain most of the information necessary to predict the MAP. Further, as the mechanism of action differs between phenylephrine and ephedrine, we would expect a difference in the predictive performance of the basic model and the full models within either the before-period and the after-period. Hence, the results of this pilot provide a very preliminary indication that arterial waveform parameters can be used to distinguish between underlying causes of hypotension and predict the most effective intervention – without quantifying the cardiac output.

The results of this study by no means prove our hypothesis. Our analysis only correlates the AWP to the MAP at their shared point in time; we have not yet analysed whether the AWP before the bolus predict how the choice for either phenylephrine or ephedrine will change the haemodynamic situation and thus the AWP after the bolus. This was simply not part of the scope of the current analysis. Neither did we yet make any effort to interpret the regression coefficients from the full model, although the high number of statistically significant regression coefficients – even for some three-way interaction terms – also confirm that there appears to be plenty of predictive information in the AWP to understand the haemodynamic situation in individual patients. Our current analysis should therefore be seen as a preliminary proof-of-concept for using changes over time before and after different interventions to analyse AWP and their interpretation.

Arterial waveform analysis has gained a large interest and is a promising tool in the haemodynamic assessment of perioperative situation [41]. In various studies, the relation between AWP and blood pressure has been studied and related to the cardiac cycle. AWP can be categorised according to parts of the cardiac cycle, for example related to preload, stroke volume, contractility, afterload. However, this classification of AWP is not so clear cut as AWP are related to multiple parts of the cardiac cycle.

PP (variation) and SD have been associated with preload [8,31]. The linear mixed-effects model showed that an increase of the MAP is depended on increase of the PP. In case of a reduced afterload, the value of the MAP seemed to be more sensitive to small changes in PP when compared to a reduced preload. This is consistent with the theory that a widening value of the PP demonstrates increasing stiffness of the blood vessels and that in case of a reduced afterload (decreased stiffness of the blood vessels) MAP can decrease considerably when a minimal decrease in PP occurs [35]. In line with PP, SD had comparable effects on the MAP. Phenylephrine and ephedrine showed both a positive effect on the increase of MAP after increasing PP and SD. This is in line with previous reports regarding the preload increasing effects of phenylephrine [27,42]. However, it also has been suggested that phenylephrine decreases cardiac output, for example an increase of afterload in preload-dependent patients [17,23,42].

Under the assumption of an adequate intravascular state (pulse pressure variation < 11%), dP/dt_{max} showed good correlation with left ventricular contractility [31,34,39,40,43]. Unlike phenylephrine, ephedrine is known for its positive inotrope effects. However, our results did not show a larger increase of dP/dt_{max} by ephedrine compared to phenylephrine. This is in line with the results from various animal-studies that phenylephrine can increase dP/dt_{max} in a dose-dependent manner and normal haemoglobin level [44-47].

Dicrotic notch pressure has been associated with MAP and afterload. The amplitude of the dicrotic notch may vary due to changes in peripheral vascular resistance and vasopressors [48,49]. In addition, the relative dicrotic notch pressure (dicrotic notch pressure – diastolic pressure) was also related to MAP: lower relative dicrotic notch pressures were related to lower IOH during general anaesthesia [50]. Phenylephrine can increase both dicrotic notch pressure and MAP [50]. The effects of ephedrine on (relative) dicrotic notch pressure are unclear.

Systolic upstroke time, duration of diastolic and systolic phase are related to heart rate. One would expect that phenylephrine would increase duration of the cardiac cycle due to decrease of the heart rate. So far, there are no relevant studies that investigated the relation between systolic upstroke time, duration of diastolic and systolic phases and MAP change. In one study, high systolic upstroke was related to the presence of coronary artery disease [51]. The results are inconclusive about the influence of duration of the corrected systolic and diastolic phase on MAP after administration of phenylephrine or ephedrine after correction of heart rate. The same applies to the relation between systolic upstroke time and MAP.

Despite the association between IOH and various postoperative adverse events, reliable assessment or prediction of altering haemodynamic conditions and present IOH mechanisms remains difficult. An enormous amount of data can be yield from the monitoring modalities applied in patients undergoing surgery and subtle changes, hardly visible by the eye or by blood pressure values changes, may be useful to predict and consequently prevent IOH by proactive treatment instead of empiric treatment when IOH already occurred [16]. Recently, in multiple papers introduction of invasive and non-invasive cardiac output devices new concepts on (machine) learning algorithms based on arterial waveforms have been introduced [16,52-56]. Multiple commercial invasive and non-invasive devices are available [56-58]. However, commercial devices can be difficult to use, invasive, expensive and not available in every hospital. In addition, the use of algorithms to monitor a patients' haemodynamic condition also has its drawbacks, for example loss of the physiologic meaning and no assessment or conclusion regarding hypotension mechanisms. Recently, several efforts have been made to obtain additional haemodynamic parameters. There promising results show that for example relative dicrotic notch pressure and cardiac output can be derived from arterial waveforms or photoplethysmographic signal [50,59].

This study has several strengths. First, the registration of the exact time of administration of boluses provided us the opportunity to analyse AWP before and after the administration of phenylephrine or ephedrine reliably. Second, patients with various comorbidities, perioperative medication and procedures were included. In a heterogeneous study population, clear differences in MAP change and heart rate could be observed. We suspect that this form arterial waveform assessment in the future might be used in a variety of patients.

Nevertheless, this study has several obvious limitations. First, the quality of our data could possibly be suboptimal due to inadequate damping of the arterial blood pressure signal and flaws in the fragmentation process of the signal. It was tried to remove possible wrong estimations of segments and landmarks by means of multiple filters. After this process, about 10% of our data was removed. However, it cannot be stated with certainty that there were no artefacts left in our data. Second, missing or removed values were not imputed and replaced. Third, due to the simultaneous use of vasopressor pumps and possible administration of multiple boluses of phenylephrine or ephedrine before the bolus we analysed, the effect of either phenylephrine or ephedrine on MAP and APW parameters may be distorted. We tried to took this into account by a minimum period of 5 minutes between vasopressor boluses. Fourth, the choice of AWP selection was limited due to suboptimal extraction of some relevant AWP, for example area under the systolic and diastolic phase, in early versions of the SignalBase software. This

limited the choice of AWP that we could analyse. Fifth, only patients with an arterial catheter in the radial artery were included. It is well known that the catheter site can influence arterial waveform and contour [9]. Sixth, the exact contribution of AWP to IOH mechanisms and the interplay with phenylephrine and ephedrine should be explored to more detail before it can be implemented in clinical practice. Several steps should be taken to convert these hypothesis-generating results into a physiologically relevant model, for example additional AWP exploration and selection, model optimisation and determination of agreement should be explored.

In conclusion, MAP is in varying degrees dependent on APW parameters, and the degree of this dependence can change when a bolus of phenylephrine or ephedrine is administered. The relation between AWP and the MAP seems to be different between patients and vasopressors. SD, PP, dicrotic notch pressure and dP/dt_{max} and their relation with MAP are probably dependent on the underlying mechanism of IOH. The preliminary results of this study may contribute to development of physiology-related arterial waveform analysis without the need for commercial devices or complex algorithms. Future studies should explore if these and other AWP could be used to predict IOH, reveal its underlying mechanism, and enable anaesthetists to apply appropriate treatment and reduce the exposure to low intraoperative blood pressures for individual patients.

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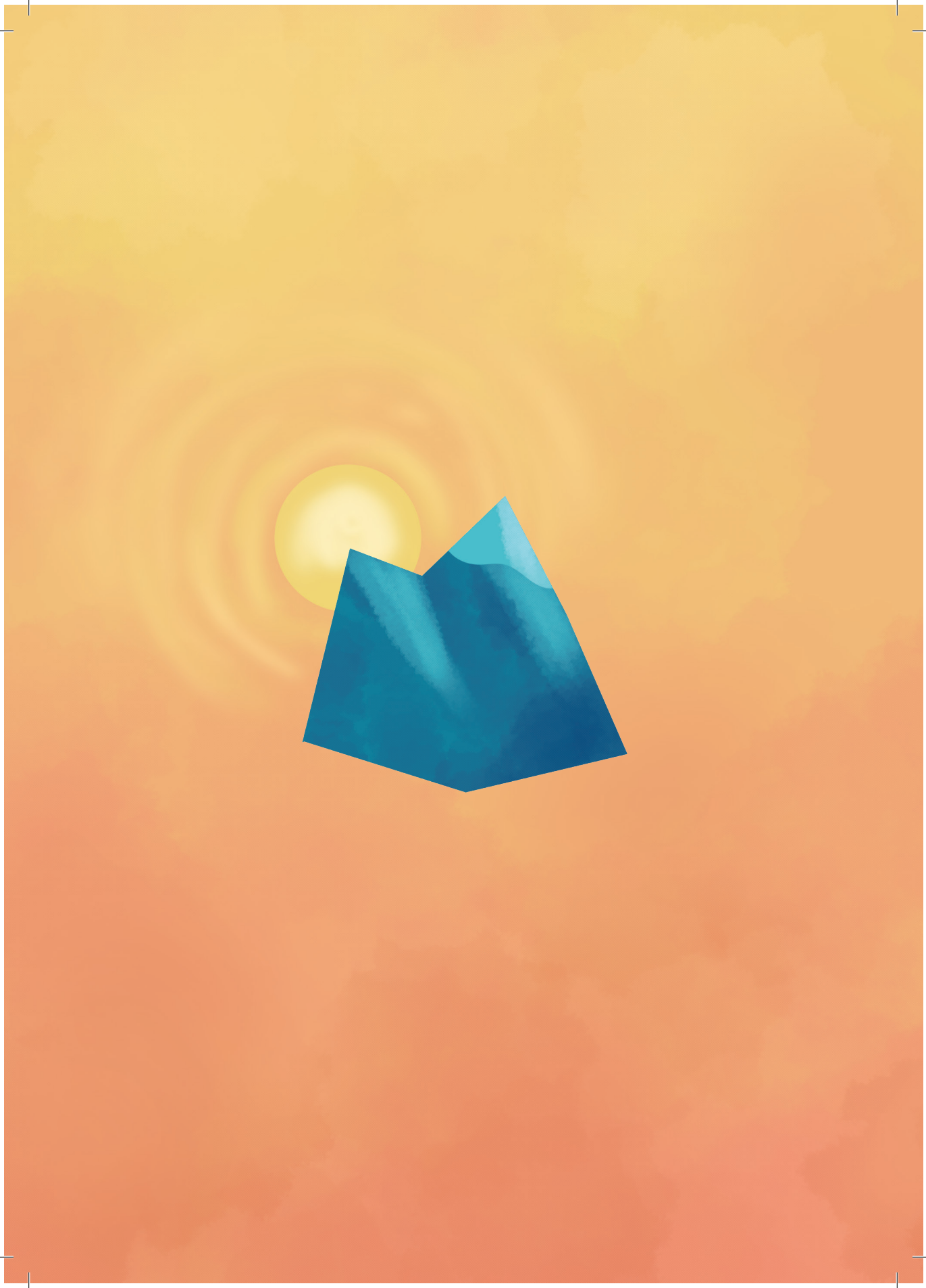
PART 4

GENERAL DISCUSSION AND SUMMARY



GENERAL DISCUSSION

GENERAL DISCUSSION

Evaluating the impact of intraoperative blood pressures on organ perfusion in the complex clinical context

Blood pressure measurements are often used as a surrogate measurement for blood flow. Although blood pressure and flow are not the same, there is no blood flow and organ perfusion without (adequate) blood pressure. Intraoperative hypotension (IOH) has received much attention in the past decade due to its frequent occurrence and presumed adverse consequences [1, 2]. Various associations have been found between IOH and postoperative organ injury between low intraoperative blood pressure and postoperative organ dysfunction [3-8]. Despite extensive research, we still don't know which blood pressure is necessary for adequate blood flow and organ perfusion. In this chapter we start with a summary of literature: what is known about the relation between intraoperative hypotension and organ injury after surgery. We identified several knowledge gaps, mainly on cerebral outcomes. We then discuss the results of the studies that we performed that were set up to fill these gaps. Finally, we put the studies in a larger perspective with a focus on the clinical context and methodology of intraoperative hypotension analysis.

Lessons learned from previous literature

We recently performed a systematic review on intraoperative hypotension and postoperative organ injury (**Chapter 2**). Various observational studies on intraoperative hypotension suggest that it has a relation with postoperative organ injury and mortality. Despite abundant associations, no minimal or target blood pressure value has been identified [6-8]. More specifically, prolonged exposure (≥ 10 min) to mean blood pressure < 80 mmHg and for shorter durations < 70 mmHg was associated with mildly elevated risks of any end-organ injury [9]. Increased durations for mean blood pressure < 65 – 60 mmHg or for any exposure < 55 – 50 mmHg were associated with elevated risks for myocardial injury and acute kidney injury [9], but not with occurrence of postoperative delirium [10-13] or ischaemic stroke [14,15].

During the review process, we noticed two issues: a huge variation in hypotension definitions and mechanisms and un unclear relationship between IOH and postoperative cerebral outcomes. First, little is known about the causal mechanisms of intraoperative hypotension and postoperative organ injury. Based on the results of the review we noticed that lower intraoperative blood pressures of longer duration were associated with postoperative hypotension. However, we could not extract which blood pressures are too low for organ perfusion. Variation in hypotension definitions and mechanisms makes it difficult to compare the results of studies:

- *Hypotension definition and analysis methods:* there is not one uniform hypotension definition [15]. Most intraoperative hypotension definitions are based on an absolute of relative blood pressure threshold for a certain duration. Blood pressures below these thresholds are considered hypotension. Furthermore, occurrence, incidence and magnitude of intraoperative hypotension all depend on the chosen hypotension definition and analysis method [16,17].
- *Hypotension mechanisms*: during anaesthesia and surgery it is not uncommon that a combination of hypotension mechanisms is present. For example, vasodilation (due to antihypertensive drugs, anaesthetics), hypovolaemia (due to diuretics, fasting before surgery, blood loss), depression of cardiac function (due to a medical history with cardiac disease). Preoperative condition and comorbidities of the patient, administration of intraoperative medication, type and duration of surgery all can influence occurrence of certain hypotension mechanisms.

The interpretation of the results of the included studies in the review is further hindered by large variation in study population (comorbidities, perioperative medication, type and duration of surgery) and outcome assessments (outcome definition, measurement and follow-up periods) [9]. There are too many IOH definitions and mechanisms to differentiate between the impact of IOH on various organs in individual patients and to determine which intraoperative blood pressures are too low.

Second, the relation between low intraoperative blood pressures and cerebral outcomes is not clear. Limited studies (of good methodological quality) are available to provide evidence for the relation between intraoperative hypotension and postoperative delirium or stroke. The lack of insight in the relation between intraoperative blood pressure and cerebral perfusion gives rise to concern. One explanation for the lack of association between IOH and postoperative cerebral outcomes is that the incidence of postoperative myocardial injury and acute kidney injury is higher than for example ischaemic stroke [18,19]. Another explanation could be that larger part of the patients suffer from less pronounced signs of cerebral dysfunction. Keeping the relation between cerebral blood pressure, blood flow and autoregulation in mind, we probably have to look to more a subtle expression of cerebral dysfunction. So, the inconclusive results and the lack of evidence for cerebral outcomes encouraged us to perform various studies on low intraoperative blood pressures and more subtle signs of postoperative cerebral hypoperfusion. One can argue that there is no association, however absence of evidence is not evidence of absence. It is highly unlikely that there is no relation as it is well known that the brain is very vulnerable for hypoperfusion [20-23].

Cerebral dysfunction: complex but not clear

Cerebral perfusion can be compromised when a patient experiences low blood pressure despite the presence of cerebral autoregulation. Autoregulation is an important mechanism to prevent suboptimal perfusion during episodes of fluctuating blood pressures. Intersubject variability (for example in Circle of Willis anatomy, carotid stenosis), age, comorbidities and preoperative medication are examples of these factors [24-28]. The range of an intact cerebral autoregulation varies great between patients. Age and (poorly-controlled) hypertension for example may influence the autoregulatory range making some patients more vulnerable for cerebral hypoperfusion than others. It has been hypothesised that temporary, suboptimal brain perfusion may cause delirium. So, postoperative delirium could be a less prominent sign, but a more frequent expression of organ dysfunction compared to ischaemic stroke.

Delirium is characterised by acute disturbance in consciousness, attention and cognitive function [29-31]. The pathophysiology of postoperative delirium is complex and multifactorial [32,33]. Delirium is common after surgery and has typically the highest incidence during the first three postoperative days [11, 34, 35]. It can be detected by clinical assessment guided by delirium assessment tools [36, 37]. Occurrence of delirium is associated with prolonged stay on the intensive care unit and in the hospital [38]. We performed two studies on the occurrence of delirium after cardiac surgery and transcatheter aortic valve implantation (**Chapters 3 and Chapter 4**). No association was found between any of the mean blood pressure thresholds and occurrence of postoperative delirium. It should be noted however, that delirium assessment in **Chapter 4** and other studies is not always optimal. Various validated screening tools for delirium exist and are thoroughly assessed and all of these tools are suitable for accurate delirium measurement [39-41]. Proper and complete delirium detection with validated assessment tools results in valid and reliable delirium diagnosis [39, 42]. However, in daily clinical practice knowledge and the perceived time-consuming nature of delirium assessment may hamper delirium assessment [43]. Prehabilitation, intraoperative use of antipsychotics, BIS-guidance, (single-channel) electroencephalography monitoring and dexmedetomidine treatment might decrease postoperative delirium [44-47].

The question was raised whether specific hypotension mechanisms increase the risk of cerebral dysfunction after surgery. Therefore, we explored the effects of one specific, potentially modifiable hypotension mechanism on postoperative cerebral outcomes (**Chapter 5**). β-blockers are popular class of β-adrenergic receptor antagonists. This class is widely used mainly for the regulation of heart rate and blood pressure [48]. Although this class of medication has similar (cardiovascular) targets, they differ in their selectivity for different β-adrenergic receptor subtypes [48-50]. However, there is growing evidence

that the wanted cardiovascular effects are sometimes accompanied by unwanted effects on cerebral perfusion [51]. In the third study, we characterised perioperative β-blockers according to their selectivity for the β1- and β2-adrenergic receptors. We studied the association between perioperative β-blocker selectivity and the need for a temporarily shunt during carotid endarterectomy. Again, we could not demonstrate an effect of perioperative β-blockers, independent of β-blocker receptor selectivity, on occurrence of IOH or the need for a temporarily shunt during carotid endarterectomy. So far, analysis of a predictable mechanism for reduced blood flow did not gain more insight in the relation between intraoperative blood pressures and cerebral hypoperfusion. Even very low blood pressures, for example mean blood pressures < 50 mmHg could not be related to cerebral outcomes which surprised us. Due to these improbable absence of results on cerebral outcomes, it deemed necessary to carefully look at the (traditional) intraoperative hypotension definitions and analysis methods.

From pressure to perfusion

Despite the lack of a relation with cerebral dysfunction, several studies do show a relation between intraoperative hypotension and myocardial injury or acute kidney injury. Based on the results of the review, one could suggest that a mean blood pressure < 65 mmHg is a turning point for organ hypoperfusion. This does not mean that there is not a limit to low blood pressures that can be accepted regarding organ perfusion. Critical analysis of the results of the review from a clinical perspective provided us the following three insights: 1. One particular blood pressure threshold is unlikely, 2. The contribution of blood pressure depth and duration is unclear and 3. Knowledge of the IOH mechanisms is essential.

1. *There probably is a limit for acceptable intraoperative blood pressures, but not one particular blood pressure cut-off:* In some studies, this threshold is presented as the lower blood pressure limit [1, 7, 52]. However, on second thoughts the existence of threshold becomes less likely considering the physiology. If, for example a mean blood pressure threshold of 65 mmHg as lower limit would exist, then a mean blood pressure of 66 mmHg wouldn't cause organ injury, whereas a mean blood pressure of 64 mmHg would. One possibility for the effects of intraoperative hypotension on postoperative organ injury is that the suggestion for a blood pressure threshold is based on methodological shortcomings or statistical phenomena instead of a physiological basis.
2. *The contribution of depth and duration of hypotension is unclear*. The exact contribution of the depth and duration of low intraoperative blood pressures has not been elucidated yet. In some way, the duration of low intraoperative blood pressures is incorporated in threshold-based analyses. In most hypotension definitions

duration is incorporated. Examples of hypotension definitions are duration under the blood pressure threshold, area under the threshold (depth·duration under a threshold) and time-weighted average (area under the threshold / duration of surgery) [1, 7, 52]. In addition, the exposure to low intraoperative blood pressure is intrinsically linked to the duration of surgery. Short procedures can only result in a relatively short duration of hypotension. For example, during a 60-minute procedure, a maximum of 60 minutes with low intraoperative blood pressures can occur. In contrast, during a 360-minute procedure, duration of IOH theoretically can increase to 360 minutes.

3. *Understanding the role of different hypotension mechanisms is essential to explain the effects of blood pressure on organ perfusion.* During the study on β-blocker selectivity and the need for a shunt, a predictable mechanism underlying low blood pressure. Focus on hypotension mechanisms can help to unravel the complex relation between intraoperative hypotension and organ (hypo)perfusion.

We developed two alternative hypotension analysis methods (**Chapter 6**) without blood pressure thresholds but with emphasis on the effects of depth, duration and course of intraoperative blood pressures on postoperative myocardial injury. In this study, no mean blood pressure threshold was identified, but intraoperative blood pressures had a continuous relation with postoperative myocardial injury after noncardiac surgery. In more detail, short blood pressure dips, indicated by the 5th mean blood pressure percentile and depth-weighted area under the normal blood pressure, were strongly related to postoperative myocardial injury. In contrast, the relation between a steady intraoperative blood pressure course indicated by the 50th mean blood pressure percentile and duration-weighted area under a normal blood pressure and postoperative myocardial injury was unclear. An important limitation of these new intraoperative hypotension analysis methods, is that they can only be performed after surgery when all intraoperative blood pressure measurements are available. Real-time appraisal of the haemodynamic situation of a patient might aid to timely determination and adequate treatment of intraoperative hypotension mechanisms.

In another study (**Chapter 7**), we continued with understanding the relation and causality between blood pressure and blood flow. This was accompanied by a different approach: with a shift from low blood pressures in the in the light of underlying comorbidity and medication to mechanism of action. In this study, changes of various arterial wave form parameters and blood pressures after a bolus of phenylephrine and ephedrine were analysed. The advantage of waveform analysis compared to cardiac out measurements by Swan Ganz monitoring is that the hypotension mechanisms become clearer after a blood pressure intervention (vasopressor bolus). The results of this exploratory

study are promising. Although not fully understood so far, some arterial waveform parameters are related to mean blood pressure changes. Therefore, administration of phenylephrine or ephedrine might expose the underlying cause of hypotension, for example preload reduction of decreased systemic vascular resistance. In other words, different pharmacodynamic effects of phenylephrine and ephedrine might provide more insight in present intraoperative hypotension mechanisms. The question remains whether this is a causal explanation rather than a mechanistic finding.

Future perspectives

Most studies included in the review and in this thesis had an observational study design and had primarily a hypothesis generating approach. Interventional studies are required to demonstrate a causal relation between IOH and postoperative organ injury. Although the need for randomised study designs to show causality has been emphasised years ago [53], the insights above show that development of a proper study in intraoperative hypotension is not easy. A few randomised studies have been published in the past years or are upcoming and can be summarised in three categories: 1. Goal-directed therapy algorithms, 2. Medical devices and 3. Individual blood pressure targets.

- *Goal directed therapy*: despite a large number of clinical trials, the evidence available for prevention of postoperative acute kidney injury or mortality remains inconclusive [54-57].
- *Medical devices*: several trials focused on the prevention of low intraoperative blood pressures (and combinations with deep hypnosis indicated by bispectral index or low minimal alveolar anaesthetic concentration) by automated alerts during noncardiac surgery. 90-day mortality or hospitalisation were not affected [58-60]. A machine learning-derived early warning system, intra-arterial blood pressure or continuous non-invasive blood pressure measurements [61-64] can help to limit the exposure to intraoperative hypotension but not clearly improve patient outcomes.
- *Individual intraoperative blood pressure targets*: higher intraoperative blood pressures might limit occurrence of acute kidney injury, but not delirium after surgery [13, 65].

An important limitation of these trials is that presence of hypotension mechanisms was ignored. New clinical trials should focus on differences in hypotension mechanisms and organ injury risk between patients. After determination of a causal relation between IOH and postoperative organ injury, more focus on prevention of IOH might improve patient outcomes. In clinical practice, prevention of IOH is not so straightforward. Currently, the blood pressure is treated reactive: when the blood pressure rapidly drops or approaches the minimal acceptable blood pressure threshold. Proactive blood

pressure management and identification of patients at risk for deep and/or prolonged hypotension are interesting future research topics. So far, in various studies machine-learning algorithms were developed to predict intraoperative hypotension [66-68].

Concluding remarks

Intraoperative hypotension is a common side effect of anaesthesia. Therefore, intraoperative hypotension is a problem of major concern. Evaluating the relation between intraoperative hypotension and postoperative organ injury requires insight in the complex clinical context. Low intraoperative blood pressures have been associated with postoperative cardiac and kidney injury, but the relation with cerebral outcomes remains unclear. From a clinical point of view, existence of a mean blood pressure lower limit of 65 mmHg becomes less likely after introduction of hypotension analysis methods that better resemble normal physiology. However, organ perfusion has to be impaired in absence of adequate blood pressures. The question remains how to value the results from previous studies with blood pressure threshold-based analyses. Heterogeneity in hypotension definitions, mechanisms, analysis methods, study populations and outcomes hamper comparison of results of various studies.

It seems essential to further consider hypotension mechanisms and analysis methods that are in line with the physiological situation before hypotension can be related to postoperative organ injury. This may be done by either studying well defined hypotension mechanisms in a homogeneous study population and type of surgery or with a complex blood pressure intervention study with individualised blood pressure targets based on a priori hypotension and organ injury risks. The results of these studies may help to understand the complex clinical context and effects of certain hypotension mechanisms on the perfusion of different organs. By designing such future studies, one should keep in mind that the interpretation of intraoperative hypotension and postoperative organ injury cannot take place without both thorough understanding of the dynamic intraoperative situation and methodological points of attention regarding hypotension research.

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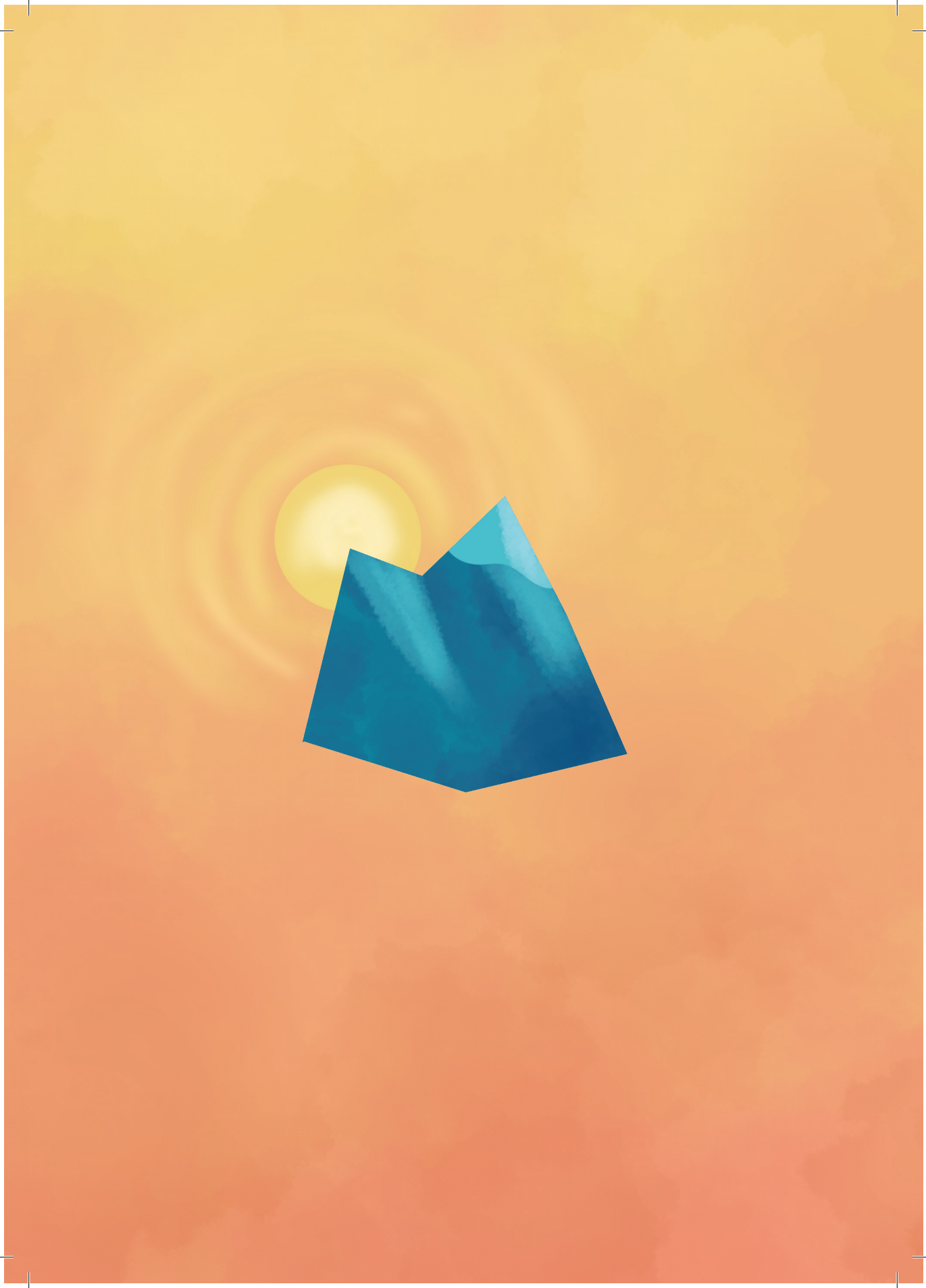


SUMMARY

SUMMARY

Haemodynamic disturbances are common during surgery. Adequate circulation and organ perfusion is important for transportation of oxygen and nutrients to the cells and removal of carbon dioxide and waste products. Blood pressure measurements are often used to get an impression of blood flow and organ perfusion. Blood pressure and blood flow are related but not the same. When a surgical patient has low blood pressure, thus is hypotensive, during surgery, the anaesthetist tries to determine the cause and tries to solve the problem. This seems an apparently simple, since common, perioperative problem. However, in daily practice, intraoperative hypotension can be a challenging problem due to various hypotension mechanisms that can be present and the dynamic and complex clinical context. In addition, despite extensive research it is not clear which intraoperative blood pressures are too low.

Chapter 2 provides an overview of the reported associations between intraoperative hypotension and postoperative organ dysfunction after noncardiac surgery. First, a systematic search of literature was performed and quality criteria were applied to the included studies. Second, studies were classified based on the reported strengths of associations for various blood pressure thresholds and occurrence of postoperative myocardial injury, acute kidney injury, mortality, stroke and delirium. Forty-two relevant studies were identified and analysed. Prolonged exposure to a mean blood pressures below 80 mmHg ≥ 10 minutes and shorter exposure to a mean blood pressure < 70 mmHg increased the risk of postoperative myocardial injury, acute kidney injury and mortality. These risks rapidly increase for short durations of exposure to mean blood pressure < 65 - 60 mmHg and any exposure < 55 – 50 mmHg. No clear relation was found between low intraoperative blood pressures and postoperative ischaemic stroke or delirium. It should be noted that the included articles also showed large variation in baseline characteristics of included patients, definition and analysis of intraoperative hypotension and definition and analysis of postoperative outcomes. We concluded that limited studies of good methodological quality were available to provide evidence for the relation between intraoperative hypotension and postoperative stroke or delirium. The lack of insight in the relation between hypotension and cerebral outcomes stimulated us to focus on the exploration of cerebral outcomes.

We conducted various studies to further explore the relation between intraoperative hypotension and perioperative cerebral organ dysfunction. **Chapter 3** is the first of three studies. Cerebral dysfunction is sometimes difficult to determine. Delirium is a common syndrome after surgery and might be a sign of inadequate cerebral perfusion. In this chapter, we studied the effects of intraoperative hypotension on occurrence

of postoperative delirium after cardiac surgery. In previously published studies often occurrence or duration of intraoperative hypotension was studied. However, the contribution of depth and duration of intraoperative hypotension to postoperative organ dysfunction were unclear. By using the area under the threshold, both depth and duration were taken into account to study the effects of intraoperative hypotension on postoperative delirium. For this study, data from patients included in the 'DExamethasone for Cardiac Surgery' randomised clinical trial in the University Medical Center Utrecht was analysed. Four definitions of intraoperative hypotension based on two absolute thresholds (mean blood pressure < 60 mmHg and < 50 mmHg) and two relative mean blood pressure thresholds (mean blood pressure – 40% and -30%) were applied to calculate area under the threshold. Deep and prolonged intraoperative hypotension seemed to increase the risk of postoperative delirium after cardiac surgery, but this was not statistically significant. So, independent of the applied definition, intraoperative hypotension was not associated with occurrence of postoperative delirium after cardiac surgery.

In many studies, intraoperative hypotension definitions were often based on low blood pressure thresholds. However, in **Chapter 2** it was suggested that also higher intraoperative blood pressure levels were associated with occurrence of postoperative organ dysfunction. Therefore, we studied the relation between 'normal' and lower mean blood pressure values with occurrence of postoperative delirium in a cohort of patients who underwent transcatheter aortic valve replacement in **Chapter 4**. Intraoperative hypotension was defined as the area's under various, predefined mean blood pressure thresholds varying from < 100 mmHg to < 60 mmHg. Delirium was common after transcatheter aortic valve replacement and patients who developed delirium had higher area under the threshold values compared to patients who did not develop postoperative delirium. In addition, patients who received general anaesthesia during the procedure had higher area under the threshold values compared to patients who received procedural sedation. Despite this difference, the results did not show an association between any of intraoperative hypotension definitions with occurrence of postoperative delirium. In both studies (**Chapter 3 and Chapter 4**), the contribution of other risk factors than intraoperative hypotension seemed more important in the relation with occurrence of postoperative delirium.

The next step in the exploration of postoperative cerebral outcomes was based on one specific (potentially modifiable) hypotension mechanism. β-blockers are popular class of β-adrenergic receptor antagonists. The next step in the exploration of postoperative cerebral outcomes was based on one specific (potentially modifiable) hypotension mechanism. β-blockers are popular class of β-adrenergic receptor antagonists. This

type of medication is widely used mainly for the regulation of heart rate and blood pressure. Although this class shares (cardiovascular) targets, β-blockers differ in their selectivity for different β-adrenergic receptor subtypes. There is growing evidence that the wanted cardiovascular effects are sometimes accompanied by unwanted effects on other organ systems. One hypothesis is β-blockers lead to an imbalance in the desirable and undesirable β-adrenergic effects. (i.e. β2-mediated attenuation of compensatory increases in blood flow during physiological stress). In **Chapter 5**, we studied the association between perioperative β-blocker selectivity and the need for a temporarily shunt during carotid endarterectomy in a cohort of participants of the 'AtheroExpress study'. β-blockers were categorised according to their selectivity for the β1- and β2-adrenergic receptors into four groups: no β-blocker use, metoprolol and β-blockers with a higher (bisoprolol, atenolol) or lower (propranolol, labetalol, sotalol) β1/β2 selectivity ratio than metoprolol. Intraoperative hypotension was considered as an intermediate variable and potential mechanisms through which β-blockers exert their effects on cerebral blood flow. Intraoperative hypotension was defined as duration and the area under six mean blood pressure thresholds varying from < 75 mmHg to < 55 mmHg. We could not demonstrate a relation of perioperative β-blocker use, independent of selectivity, on occurrence of intraoperative hypotension or the need for a temporarily shunt during carotid endarterectomy. We concluded that analysis of a predictable hypotension mechanism for reduced blood flow did not gain more insight in the relation between intraoperative blood pressures and cerebral hypoperfusion. Despite the mechanistic approach in a quite homogenous study population (one surgical procedure), we still could not unravel the relation between intraoperative hypotension and perioperative cerebral outcomes.

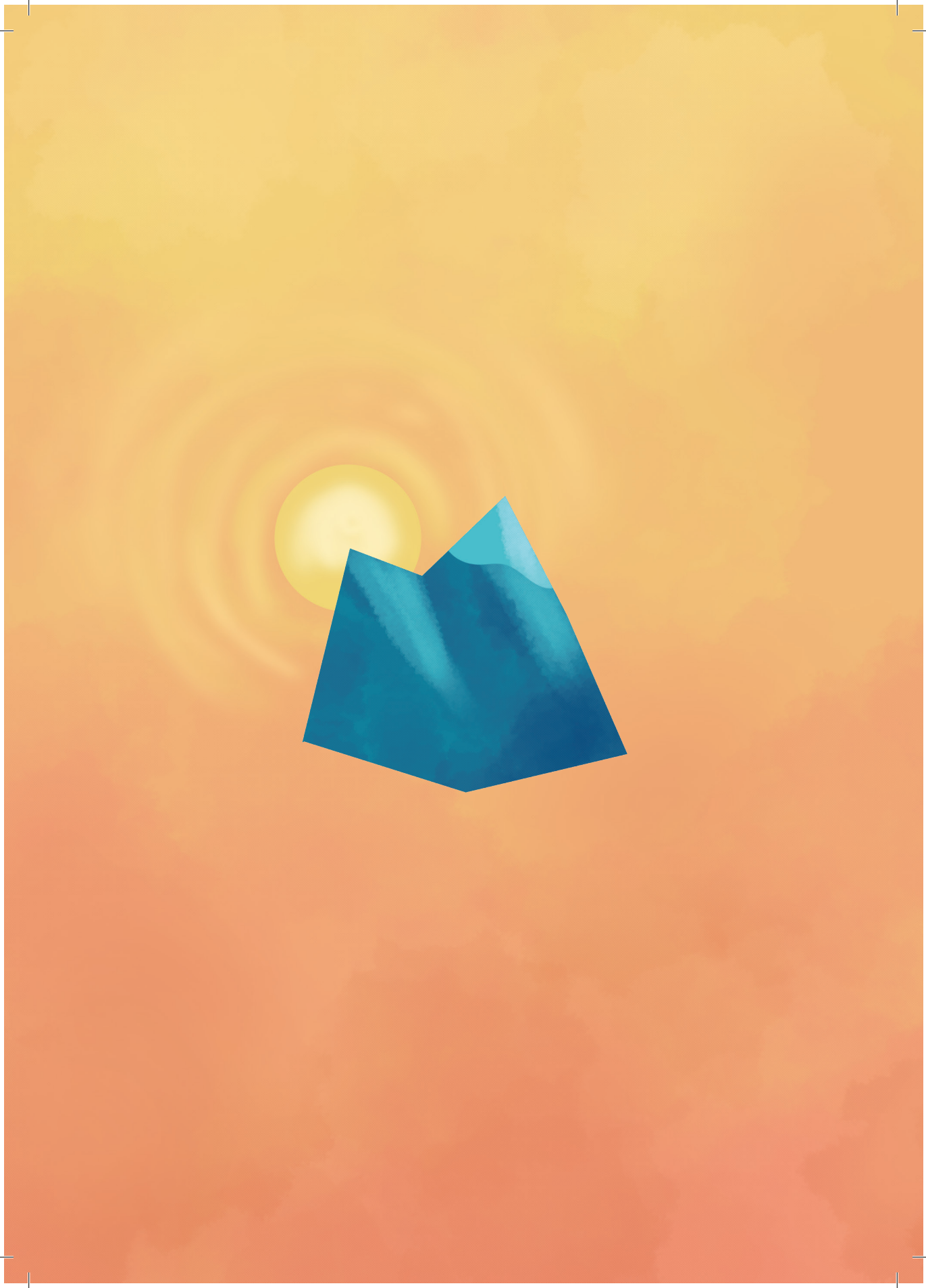
Along the way, we gained more insight in the pitfalls of the current intraoperative hypotension analyses methods based on blood pressure thresholds. In **Chapter 6** we reconsidered the traditional intraoperative hypotension analysis methods and focused on the contribution of depth and duration of hypotension and the relation with postoperative myocardial injury. Two analysis strategies were developed and analysed. The first analysis method comprises of determination of mean blood pressure percentiles based on all intraoperative blood pressures. The second analysis method consisted of depth- and duration-weighted areas under the normal mean blood pressure range (i.e. mean blood pressure < 100 mmHg). The advantages of these strategies are 1. The analysis methods are more in line with physiological principles and 2. Avoidance of an arbitrarily chosen cut-off point and 3. The complete intraoperative blood pressure course is analysed. Both analysis strategies were applied to a large cohort of patients who underwent intermediate to high risk (of a perioperative cardiac events) noncardiac surgery in the University Medical Center Utrecht. The outcomes under study were

postoperative myocardial injury and in-hospital mortality. Postoperative myocardial injury was defined as troponin I elevation above the clinical cut-off during the first three days after surgery. No mean blood pressure threshold was identified, but intraoperative blood pressures have a continuous relation with postoperative myocardial injury and in-hospital after noncardiac surgery. Short blood pressure dips, indicated by the 5th mean blood pressure percentile and depth-weighted area under the normal threshold, were strongly related to postoperative myocardial injury and in-hospital mortality. In contrast, the relation between a steady intraoperative blood pressure course, indicated by the 50th mean blood pressure percentile and duration-weighted area under the threshold, and both outcomes is unclear.

Chapter 7 describes the results of an exploratory study on arterial waveform parameters analysis and their relation with changes in mean blood pressure after a vasopressor bolus (phenylephrine or ephedrine) during noncardiac surgery. During this observational study, patients were observed during noncardiac surgery. The time of a vasopressor bolus was registered. The arterial waves were extracted and analysed ten minutes before and ten minutes after the vasopressor bolus administration. The following arterial waveform parameters were selected for analysis: heart rate, pulse pressure, dicrotic notch pressure, the standard deviation of the blood pressure points of the arterial pressure wave, duration of systolic phase corrected for heart rate, duration of diastolic phase corrected for heart rate, maximal slope during systolic upstroke corrected for heart rate and systolic upstroke time corrected for heart rate. The primary outcome was the absolute change in mean blood pressure after a bolus as compared with the absolute change in selected arterial waveform parameters. Twenty-four episodes with a phenylephrine bolus and seventeen episodes with an ephedrine bolus were analysed in twenty-six patients. Blood pressure is in varying degrees dependent on arterial waveform parameters, and the degree of this dependence can change when a bolus of phenylephrine or ephedrine is administered. The relation between arterial waveform parameters and the mean blood pressure seems to be different between patients and vasopressors. Standard deviation, pulse pressure, dicrotic notch pressure and dP/dt_{max} and their relation with mean blood pressure are probably dependent on the underlying mechanism of intraoperative hypotension.

In the **General discussion**, the researchers' insights regarding the relation between intraoperative hypotension and postoperative organ injury in the complex clinical context are summarised. Although various studies a relation between low intraoperative blood pressures and postoperative myocardial injury, acute kidney injury and mortality, the relation with cerebral outcomes remains unclear. Existence of one blood pressure threshold as a cut-off is unlikely from a clinical perspective. Therefore, development

of intraoperative hypotension methods that better resemble the clinical situation is important. In addition, more focus on hypotension mechanisms might provide more insight in the effects of low intraoperative blood pressures on organ hypoperfusion and dysfunction.



SAMENVATTING

SAMENVATTING IN HET NEDERLANDS

Hemodynamische verstoringen komen vaak voor tijdens operaties. Een adequate circulatie en perfusie van de organen is belangrijk voor transport van zuurstof, voedingsstoffen en verwijdering van afvalstoffen zoals koolstofdioxide. Om een indruk te krijgen van de bloedstroom naar en doorbloeding van de organen worden bloeddrukmetingen gebruikt. Bloeddruk en perfusie zijn aan elkaar gerelateerd, maar zijn niet hetzelfde. Als een patiënt tijdens de operatie een te lage bloeddruk heeft, oftewel als de patiënt hypotensief wordt, dan probeert de anesthesioloog de oorzaak te achterhalen en het probleem op te lossen. Een te lage bloeddruk is een veelvoorkomend probleem tijdens de operatie, dus het probleem oplossen lijkt simpel. Echter, in de dagelijkse praktijk is intraoperatieve hypotensie een uitdagend probleem doordat er verschillende oorzaken van hypotensie tegelijkertijd aanwezig kunnen zijn, want een operatie is een dynamische en complexe klinische situatie. Daarnaast is er, ondanks uitvoerig onderzoek, niet duidelijk welke bloeddrukken te laag zijn.

In **Hoofdstuk 2** wordt een overzicht gegeven van de gerapporteerde associaties tussen intraoperatieve hypotensie en postoperatieve orgaan dysfunctie na niet-cardiale chirurgie. Eerst werd een systematische zoekstrategie naar relevante onderzoeken opgezet, uitgevoerd en werden kwaliteitscriteria op de gevonden onderzoeken toegepast. Daarna werden de onderzoeken geclassificeerd op basis van de sterkte van het effect voor verschillende bloeddrukgrenzen. Tevens werd de relatie tussen een te lage bloeddruk en het optreden van postoperatieve mortaliteit, acute nierfunctiestoornissen, myocardschade, een beroerte, delier en verlengde opnameduur geëxtraheerd. Er werden tweeënveertig relevante onderzoeken gevonden en geanalyseerd. Langdurige blootstelling aan gemiddelde bloeddrukken < 80 mmHg voor ≥ 10 minuten en kortere blootstelling aan gemiddelde bloeddrukken < 70 mmHg lijken het risico op postoperatieve myocard schade, acute nierfunctiestoornissen en mortaliteit te verhogen. Deze risico's nemen snel toe bij kortdurende gemiddelde bloeddrukken < 65 – 60 mmHg en elke blootstelling aan gemiddelde bloeddrukken < 55 – 50 mmHg. Er werd geen duidelijke relatie gevonden tussen lage intraoperatieve bloeddrukken en postoperatieve beroerte of delier. Hierbij moet wel worden opgemerkt dat er tussen de geïncludeerde artikelen grote variatie is in patiëntkenmerken, definitie en analyse van intraoperatieve hypotensie, definitie en analyse van postoperatieve uitkomsten. We concludeerden dat er slechts een beperkt aantal onderzoeken van goede methodologische kwaliteit beschikbaar is met betrekking tot de relatie tussen intraoperatieve hypotensie en postoperatieve beroerte en delier. Het gebrek aan inzicht in de relatie tussen lage intraoperatieve bloeddrukken en cerebrale uitkomsten stimuleerde ons om de relatie tussen hypotensie en cerebrale uitkomsten verder te exploreren.

We hebben verschillende studies opgezet om de relatie tussen intraoperatieve hypotensie en perioperatieve cerebrale dysfunctie te onderzoeken. **Hoofdstuk 3** is de eerste van de drie onderzoeken. Het disfunctioneren van het brein is vaak moeilijk vast te stellen. Delier komt vaak na operaties voor en dit syndroom zou een uiting zou kunnen zijn van onvoldoende hersenperfusie. In dit hoofdstuk bestudeerden we de effecten van intraoperatieve hypotensie op het optreden van een postoperatief delier na hartchirurgie. In voorgaande onderzoeken werd vaak het optreden van hypotensie of de duur van hypotensie bestudeerd. Het is echter niet bekend wat de bijdrage is van de diepte en de duur van intraoperatieve hypotensie op postoperatieve orgaan dysfunctie. Door gebruik te maken van de oppervlakte onder de bloeddrukgrens, worden zowel diepte als duur meegenomen tijdens de analyse van de effecten van intraoperatieve hypotensie op het optreden van een postoperatief delier. Voor dit onderzoek werd data gebruikt van patiënten die deelnemen aan de gerandomiseerde klinische trial 'DExamethasone for Cardiac Surgery' in het Universitair Medisch Centrum Utrecht. Vier intraoperatieve hypotensie definities gebaseerd op gemiddelde bloeddruk grenzen werden toegepast; twee absolute grenzen (gemiddelde bloeddruk < 60 mmHg en < 50 mmHg) en twee relatieve grenzen (gemiddelde bloeddruk - 40% en - 30%). Op basis van deze hypotensie definities werden de oppervlaktes onder de bloeddrukgrenzen berekend. Diepe, langdurige intraoperatieve hypotensie leek het risico op een postoperatief delier te verhogen, maar deze effecten waren niet statistisch significant. Onafhankelijk van de definitie was intraoperatieve hypotensie dus niet geassocieerd met het optreden van postoperatief delier na cardiale chirurgie.

In veel onderzoeken waren de definities van intraoperatieve hypotensie gebaseerd op erg lage bloeddruk grenzen. In **Hoofdstuk 2** vonden we echter dat ook (langdurige) hogere bloeddrukken geassocieerd werden met het optreden van postoperatieve orgaan dysfunctie. Daarom hebben we in **Hoofdstuk 4** het verband tussen 'normale' en lage gemiddelde bloeddrukken geanalyseerd in relatie tot postoperatief delier in een cohort van patiënten die een percutane aortaklep vervanging hebben ondergaan. Intraoperatieve hypotensie werd gedefinieerd als de oppervlaktes onder gemiddelde bloeddrukgrenzen variërend van < 100 mmHg tot < 60 mmHg. Delier kwam vaak voor na percutane aortaklepvervanging en de patiënten die een delier kregen hadden grotere oppervlaktes onder de bloeddrukgrenzen dan patiënten die geen delier ontwikkelden. Daarnaast hadden patiënten die de procedure onder algehele anesthesie ondergingen, hogere oppervlaktes onder de bloeddrukgrenzen in vergelijking met patiënten die de procedure met procedurele sedatie ondergingen. Ondanks deze verschillen lieten de resultaten van de analyses geen verband zien tussen de intraoperatieve hypotensie en het optreden van postoperatief delier. In beide hoofdstukken (**Hoofdstuk 3 en Hoofdstuk 4**) leek de bijdrage van andere risicofactoren belangrijker dan intraoperatieve hypotensie met betrekking tot het optreden van een postoperatief delier.

De volgende stap in de exploratie van postoperatieve cerebrale uitkomsten was gebaseerd op een specifiek (en potentieel beïnvloedbaar) hypotensie mechanisme. β-blokkers vormen een populaire groep medicijnen die β-adrenerge receptoren antagoneren. Deze medicijnen worden veel gebruikt, vooral voor de regulatie van hartfrequentie en bloeddruk. Hoewel deze groep hetzelfde aangrijpingspunt heeft, verschillende de β-blokkers in hun selectiviteit voor de verschillende subtypes β-adrenerge receptoren. Er is steeds meer wetenschappelijk bewijs dat de gewenste cardiovasculaire effecten van β-blokkers soms gepaard gaan met ongewenste effecten op andere orgaansystemen. De hypothese bestaat dat β-blokkers voor een verstoring zorgen van gewenste en ongewenste β-adrenerge effecten (bijvoorbeeld door de verstoring van β2-gemedieerde compensatoire toename van de bloedstroom tijdens fysiologische stress). In **Hoofdstuk 5** bestudeerden we de associatie tussen β-blokker selectiviteit en de noodzaak voor een tijdelijke shunt tijdens carotis endarteriëctomie in een cohort bestaande uit patiënten die deelnemen aan het 'AtheroExpress' onderzoek. De β-blokkers werden ingedeeld in vier groepen aan de hand van hun selectiviteit voor de β1-receptor en voor de β2-receptor: geen β-blokker gebruik, metoprolol gebruik en gebruik van β-blokkers met een hogere (bisoprolol, atenolol) of een lagere (propranolol, labetalol, sotalol) β1/β2-selectiviteitsratio dan metoprolol. Eén van de mogelijke mechanismen waardoor β-blokkers effect zouden kunnen uitoefenen op de cerebrale perfusie, is door middel van intraoperatieve hypotensie. Intraoperatieve hypotensie werd gedefinieerd als de duur en oppervlakte onder zes gemiddelde bloeddrukgrenzen variërend van < 75 mmHg tot < 55 mmHg. Wederom konden we geen relatie aantonen tussen perioperatief β-blokker gebruik, onafhankelijk van de selectiviteit, op het optreden van hypotensie of de noodzaak voor een tijdelijk shunt tijdens carotis endarteriëctomie. We concludeerden dat analyse van een voorspelbaar hypotensie mechanisme ons niet meer inzicht gaf in de relatie tussen intraoperatieve bloeddrukken en cerebrale hypoperfusie. Ondanks de mechanistische benadering in een behoorlijk homogene studie populatie (één type chirurgie), waren we niet in staat om de relatie tussen intraoperatieve hypotensie en perioperatieve cerebrale uitkomsten op te helderen.

Tijdens het onderzoeksproces kregen we steeds meer inzicht in de tekortkomingen van de huidige hypotensie analysemethodes die gebaseerd waren op bloeddrukgrenzen. In **Hoofdstuk 6** hebben we de traditionele intraoperatieve hypotensie analysemethodes heroverwogen en hebben we onze aandacht gericht op de bijdrage van de diepte en duur van hypotensie en de relatie met postoperatieve myocard schade na niet-cardiale chirurgie. Twee analysemethodes werden ontwikkeld en geëvalueerd. De eerste strategie bestond uit het (achteraf) bepalen van bloeddrukpercentielen op basis van alle intraoperatieve bloeddrukken. De tweede analysemethode bestond uit diepte- en duur-gewogen oppervlaktes onder een normale gemiddelde bloeddruk (hiermee

wordt bedoeld een gemiddelde bloeddruk < 100 mmHg). De voordelen van beide analysemethodes zijn 1. De analysemethodes sluiten beter aan op de fysiologische situatie en 2. Arbitraire gekozen afkappunten worden vermeden en 3. Het gehele bloeddrukverloop tijdens de operatie wordt geanalyseerd. Beide analysemethodes werden toegepast op een groot cohort met patiënten die een gemiddeld tot hoog risico (op perioperatieve cardiale problemen), niet-cardiale operaties in het Universitair Medisch Centrum Utrecht ondergingen. De uitkomsten postoperatieve myocard schade en overlijden tijdens ziekenhuisopname werden bestudeerd. Myocard schade werd gedefinieerd als troponine I stijging boven de klinische grens gedurende de eerste drie dagen na de operatie. Er werd niet één omslagpunt voor een bloeddrukgrens gevonden, maar intraoperatieve bloeddrukken bleken juist een continue relatie met postoperatieve myocard schade en overlijden tijdens ziekenhuisopname na niet-cardiale chirurgie te hebben. Korte, diepe bloeddrukdalingen, gedefinieerd als het 5e gemiddelde bloeddrukpercentiel en de diepte-gewogen oppervlakte onder de normale gemiddelde bloeddruk, waren sterk gerelateerd aan postoperatieve myocard schade en overlijden tijdens ziekenhuisopname. Echter, de relatie tussen een stabiel intraoperatief bloeddrukverloop, gedefinieerd als het 50^{e} gemiddelde bloeddruk percentiel en de duur-gewogen oppervlakte onder de normale gemiddelde bloeddruk, met beide uitkomsten bleef onduidelijk.

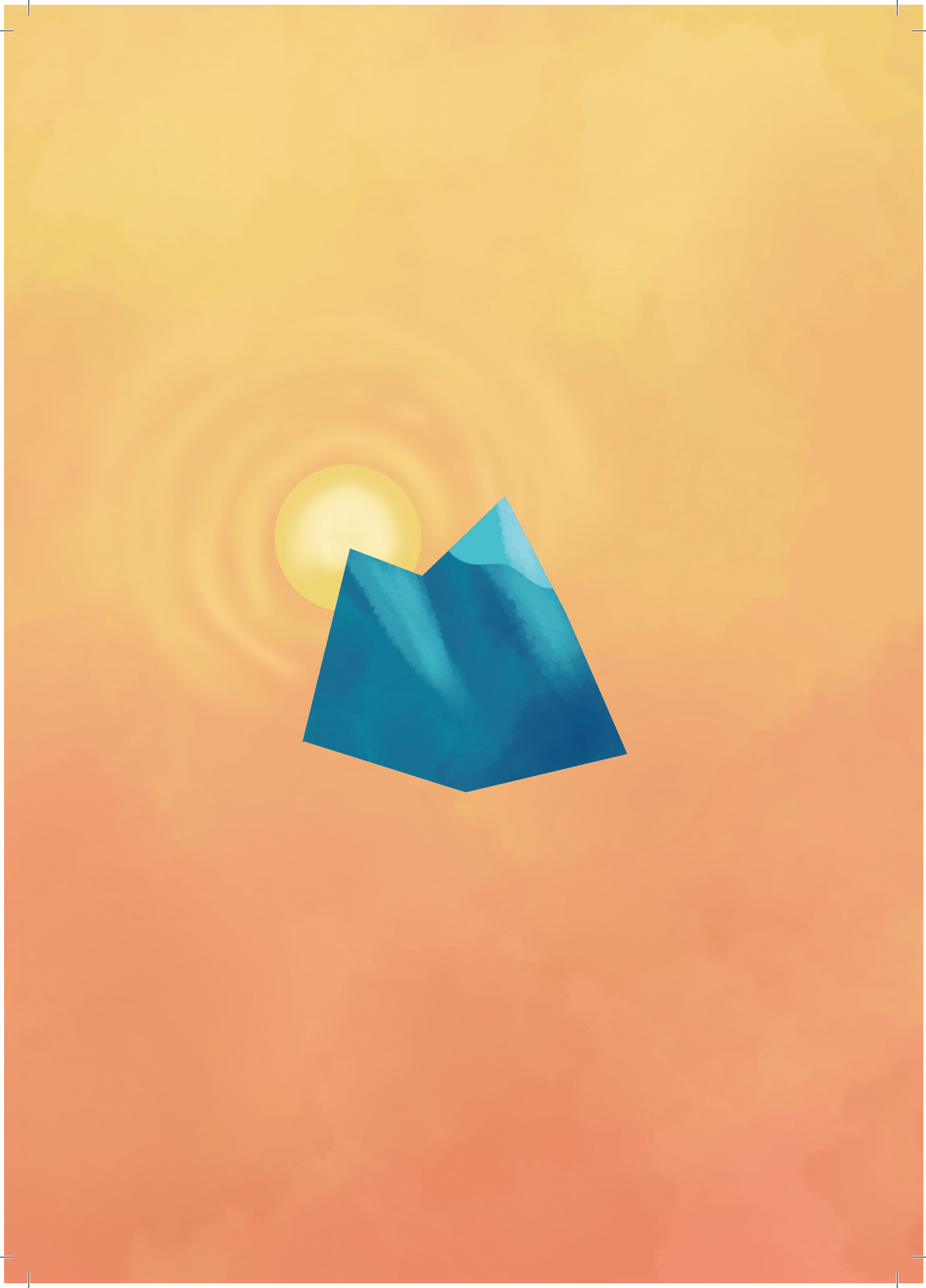
In **Hoofdstuk 7** worden de resultaten beschreven van een exploratie en analyse van arteriële bloeddrukgolf parameters en hun relatie met veranderingen van de gemiddelde bloeddruk na een bolus vasopressor (fenylefrine of efedrine) tijdens niet-cardiale chirurgie. Tijdens dit onderzoek werden patiënten geobserveerd tijdens niet-cardiale chirurgie. Het tijdstip van toediening van elke vasopressor gift werd nauwkeurig geregistreerd. De arteriële bloeddrukgolven werden geëxtraheerd en geanalyseerd gedurende een periode van 10 minuten voor en 10 minuten na de vasopressor toediening. De volgende arteriële golf parameters werden geselecteerd voor verdere analyse: hartfrequentie, polsdruk, 'dicrotic notch' druk, de standaarddeviatie van de bloeddrukpunten, duur van de systolische fase gecorrigeerd voor hartfrequentie, duur van de diastolische fase gecorrigeerd voor hartfrequentie, de maximale hellingshoek tijdens systolische drukstijging gecorrigeerd voor hartfrequentie en de duur van de systolische drukstijging gecorrigeerd voor hartfrequentie. Vierentwintig episodes rondom een fenylefrine bolus en zeventien episodes rondom een efedrine bolus werden geanalyseerd in zesentwintig patiënten. Bloeddruk is in verschillende mate afhankelijk van arteriële bloeddrukgolf parameters en de relatie kan variëren afhankelijk of er een bolus fenylefrine of efedrine is toegediend. De relatie tussen arteriële bloeddrukgolf parameters en de gemiddelde bloeddruk lijkt te verschillen tussen patiënten en tussen vasopressoren. Standaarddeviatie, polsdruk, 'dicrotic notch' druk en dP/dt_{max}

en hun relatie met de gemiddelde bloeddruk zijn waarschijnlijk afhankelijk van het onderliggende intraoperatieve hypotensie mechanisme.

In de **Algemene discussie** worden de inzichten van het onderzoeksteam met betrekking tot de relatie tussen intraoperatieve hypotensie en postoperatieve orgaan schade in de complexe, klinische situatie samengevat. Ondanks dat diverse onderzoeken een relatie laten zien tussen lage intraoperatieve bloeddrukken en postoperatieve myocard schade, acute nierfunctiestoornissen en mortaliteit, blijft de relatie met cerebrale uitkomsten onduidelijk. Vanuit een biologisch en klinisch perspectief lijkt het bestaan van een bloeddruk omslagpunt erg onwaarschijnlijk. Daarom is het belangrijk om intraoperatieve hypotensie analysemethodes te ontwikkelen die beter aansluiten bij de klinische situatie. Tevens kan meer aandacht voor hypotensie mechanismen helpen om meer inzicht te krijgen in de effecten van lage, intraoperatieve bloeddrukken op verminderde orgaanperfusie en -disfunctie.

PART 5

APPENDICES



APPENDIX 1

SUPPLEMENTARY TABLES OF CHAPTER 2

SUPPLEMENTARY TABLES OF CHAPTER 2

Supplementary table 1 Criteria list for assessing the methodological quality of studies on IOH and postoperative adverse outcomes

Item	Criteria	Category	Score
Study design			
A	Description of study design	IV	- / + / ?
B	IOH in research question or aims	B, IV	- / + / ?
Study population			
C	Description of study population	EV	- / + / ?
D	Description of in- and exclusion criteria	EV	- / + / ?
E	Sufficient numbers and sample size	P	- / + / ?
Follow-up (extent and length)			
F	Follow-up	IV	- / + / ? / NA
G	Loss-to-follow-up	B, IV	- / + / ? / NA
Anaesthetic procedures			
H	Type of anaesthesia	IV	- / + / ?
Hypotension and confounding factors			
I	Definition of IOH	B	- / + / ?
J	IOH variable and analysis	B	- / = / + / ?
Outcome assessment			
K	Reproducible assessment of relevant outcome criteria	B	- / + / ?
L	Blinding	B	- / + / ?

	Explanation of criteria
	Positive if prospective design was used (RCT with blood pressure related intervention, Prospective cohort study, prospective case-control study). Positive if IOH or intraoperative haemodynamic variables is included in primary or secondary objectives.
	Positive if patient recruitment is comparable in all groups. Positive if criteria were formulated for at least age, relevant comorbidity, type of surgery and type of anaesthesia. Positive if information is given about sample size calculation. If no sample size calculation is provided, sufficient numbers of patients should be studied. Negative if less than 20 outcomes were reported.
	Positive if in-hospital follow-up ≥ 2 days and if applicable, long-term follow-up ≥ 6 months. Not applicable for case-control studies. Positive if loss-to-follow-up < 25% on the last moment of follow-up compared to the number at baseline. Not applicable for case-control studies.
	Positive if anaesthetic procedures (type, intraoperative medication, interventions for IOH) are described.
	Positive if a clear, clinically relevant definition of IOH and information about intraoperative anaesthesia registration is provided. Positive if IOH was assessed as a continuous determinant (i.e., minutes, area-under-the-curve) in a way. = if IOH was assessed by categories. Negative if IOH was assessed as a dichotomous outcome. Not applicable for all RCTs.
	Positive if classification system or outcome criteria are described and if outcome assessment is reproducible. Positive if observers were blinded for IOH status.

Supplementary table 1 Criteria list for assessing the methodological quality of studies on IOH and postoperative adverse outcomes

Item	Criteria	Category	Score
Data presentation			
M	Frequencies of most important outcome measures	IV	- / + / ?
N	Frequencies of most important patient-related and surgery-related factors	B	- / + / ?
O	Appropriate analysis techniques	B	- / + /?

+ Positive (sufficient information and a positive assessment); - negative (sufficient information, but potential bias due to inadequate design of conduct; ? unclear (insufficient information).

Supplementary table 2 Summary of study characteristics of studies on intraoperative hypotension and postoperative adverse outcomes after noncardiac surgery, ranked according to study quality score (%)

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Hirsch et al. 2015	100	co	Major noncardiac surgery	594	SBP or MAP ↓ > 10 - 40% compared to baseline, MAP < 50 mmHg, BP variance	Duration, BP variance
Monk et al. 2015	93	co	Major surgical operations from the The Veterans Affairs Surgical Quality Improvement Program database	18,756	Population based thresholds for AUT, SBP < 90 mmHg, MAP < 60 mmHg, DBP < 50 mmHg, SBP ↓ > 30%, >40%, ≥ 50%	AUT, duration 2 - 4.9 min or ≥ 5 min
Willingham et al. 2015	93	co	Adults from the B-Unaware, BAG-RECALL and Michigan Awareness Control Study (mixed surgical population)	13,198	MAP < 75 mmHg	Cumulative duration and numbers of 5 minutes epochs spend in 'triple low' condition: MAP < 75 mmHg and BIS < 45 and MAC < 0.80
Bijker et al. 2012	92	CC	Noncardiac and non-neurologic surgery, matching (1:6) variables: age and type of surgery	48,421 (42/252)	SBP < 70 mmHg; < 80 mmHg; < 90 mmHg; < 100 mmHg; SBP↓ >10%; >20%; >30%; >40%; MAP < 40 mmHg; < 50 mmHg; < 60 mmHg; < 70 mmHg; MAP↓ >10%; >20%; >30%; >40%	Duration

	Explanation of criteria
	Positive if frequency (n, %) of the outcome(s) is/are reported. Positive if demographic/clinical information (patient and surgery characteristics) and potential confounders was presented. Positive if the results of a clear multivariable regression techniques with adjustment for confounding were provided for the association of IOH with the outcome(s).
	Abbreviations: B: bias; EV: external validity; IOH: intraoperative hypotension; IV: internal validity; NA: not applicable (criteria are not relevant for design or conduct of the study), P: precision; RCT: randomised clinical trial

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
	Delirium	Confusion Assessment Method	2 days	Day 1: 33%, day 2: 31%	MAP variance, mmHg² (per 10 units) 1.038 (1.010 - 1.067) duration MAP < 50 mmHg, p = 0.409
	Mortality	All cause	30 days	1.8%	AUT SBP = 3.3 (2.2 - 4.8) AUT MAP = 2.8 (1.9 - 4.3) AUT DBP = 2.4 (1.6 - 3.8) SBP < 70 mmHg ≥ 5min = 2.9 (1.7 - 4.9) MAP < 50 mmHg ≥ 5min = 2.4 (1.3 - 4.6) DBP < 30 mmHg ≥ 5min = 3.2 (1.8 - 5.5) MAP↓ > 50% ≥ 5 min = 2.7 (1.5 - 5.0)
	Mortality	All cause?	30 days, 90 days	0.8%, 1.9%	HR cumulative duration, 30 days, low/low/low = 1.09 (1.07 – 1.11 per 15 min) HR cumulative duration, 90 days, low/low/low = 1.09 (1.08 – 1.11 per 15 min)
	Stroke	Acute onset of new focal neurologic deficit of cerebral origin persisting more than 24 hours without haemorrhage on CT	10 days	0.09%	SBP ↓ > 30% 1.013 (99.9% CI 1.000 - 1.025). other thresholds n.s.

Supplementary table 2 Continued

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Mizota et al. 2017	87	co	Liver tranplantation	231	MAP < 50 mmHg, MAP < 40 mmHg, absolute or relative MAP decrease	Duration
Sun et al. 2015	87	co	Noncardiac surgery with invasive blood pressure measurements	5,127	Total number of minutes spend in each MAP category (0, 1-5, 6-10, 10-20, > 20 min), MAP < 55; < 60; < 65 mmHg	Duration
Schmid et al. 2016	86	RCT	Major abdominal surgery	180	MAP > 70 mmHg achievement rate during surgery (time MAP > 70 mmHg / total duration of surgery	Achievement rate
Roshanov et al. 2017	80	co	Sample from Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) study: ≥ 45 years, general or regional anaesthesia and overnight admission	14,687	SBP < 90 mmHg of any duration for which an intervention was initated	Dichotomous
Salmasi et al. 2017	80	co	In-patient surgery with pre- and postoperative creatinine measurement	57,315	MAP < 65 mmHg, MAP ↓ > 20%, time in lowest absolute and relative MAP categories	Duration, AUT
Babazade et al. 2016	80	co	Colorectal surgery, duration ≥ 1 hour	2,521	SBP < 80 mmHg, MAP < 55 mmHg	Categories based on median duration of hypotension: MAP 0 min or 0 - 2.73 min or ≥ 2.73 min; duration SBP 0 min or 0 - 3.69 min or ≥ 3.69 min

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
	AKI	↑ [Cr] x100% from baseline or urine production < 0.5mL·kg·h^{-1} for ≥ 12 hours (KDIGO)	7 days	30.7%	MAP 40 - 49 mmHg, 1 - 9min: 1.64 (0.49 - 2.53), MAP 40 - 49 mmHg, >10 min: 2.11 (0.61 - 7.22), MAP < 40mmHg, 1 - 9 min: 3.80 (1.17 - 12.30), MAP < 40 mmHg, > 10 min: 5.06 (1.26 - 20.40), absolute MAP decrease per 10 mmHg: 2.11 (1.32 - 3.47), relative MAP decrease per 10% decrease: 1.51 (1.11 - 2.09)
		MI: peak [Tn T] ≥ 0.03 ng·ml^{-1}	3 days	7.9%	1.04 (0.90 - 1.20)
		Stroke: new focal neurologic deficit thought to be vascular in origin with signs and symptoms lasting > 24 hours	30 days	0.6%	1.14 (0.85 - 1.54)
	MI	Postoperative [TnT] > 0.03ng·ml^{-1} or [CK-MB] > 8.8 ng·ml^{-1}	7 days	3.1%	MAP < 65 mmHg, 13 - 28min: 1.34 (98.75% CI 1.06 - 1.68), > 28 min: 1.60 (98.75% 1.28 - 2.01), AUT MAP < 65 mmHg (42 - 90 mmHg·min): 1.30 (98.75% CI 1.04 - 1.63), (> 91 mmHg·min): 1.62 (98.75% 1.30 - 2.02), other thresholds and duration n.s.
	AKI	[Cr] ↑ ≥ 50% or 0.3 mg·dl^{-1} (AKIN)	2 days	6.3%	MAP < 55 mmHg, 11 - 20 min: 2.34 (1.35 - 4.05), MAP < 55 mmHg, > 20 min: 3.53 (1.51 - 8.25), MAP < 60 mmHg, 11 - 20 min: 1.84 (1.11 - 3.06), MAP < 60 mmHg, > 20 min: 1.70 (0.93 - 3.10), MAP < 65 mmHg, 11 - 20 min: 1.57 (0.70 – 3.53), MAP < 65 mmHg, > 20 min: 2.25 (0.99 – 5.07)
	AKI	Maximum change in serum [Cr] and in Cr clearance	7 days	Change in Cr clearance: control (-12 ± 24 ml·min^{-1}·1.73 m^2) vs. goal directed therapy (-10 ± 24 ml·min^{-1}·1.73 m^2)	Regression coefficient change of Cr clearance 27.9 (5.9 – 49.8) = 0.28 ml· min $^{-1}$·1.73 m^2 higher Cr clearance per percent of the total surgery time with MAP > 70 mmHg
	MACCE (composite endpoint)	Mortality	30 days	MACCE: 9.6%, mortality: 2.1%	MACCE: 1.11 (0.98 - 1.25), mortality: 1.41 (1.07 - 1.86)
	AKI	↑ [Cr] more than 1.5-fold or more than 0.3 mg·dl-1 greater than the preoperative [Cr]	7 days	5.6%	MAP < 65mmHg, 13 - 28 min: 1.20 (98.75% CI 1.02 - 1.40), > 28 min: 1.35 (1.14 - 1.58), MAP ↓>20% > 90min: 1.27 (98.75% CI 1.01 - 1.61), AUT MAP < 65 mmHg (> 91 mmHg·min): 1.34 (98.75% CI 1.15 - 1.58), AUT MAP ↓ > 20% (728% * min): 1.35 (98.75% CI 1.07 - 1.70), other thresholds and durations n.s.
	LOS	Time to discharge alive		Weighted median [IQR]: 7 days [5 – 10]	HR (SBP): 0.97 (0.93 – 1.01) for 5 min increase of MAP, HR (MAP): 0.97 (0.91 – 1.04) for 5 min increase of MAP

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Supplementary table 2 Continued

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Hallqvist et al. 2016	80	co	Major elective noncardiac surgery who were scheduled for an overnight admission to the postoperative unit	300	SBP↓ > 50% compared to baseline > 5 min	Dichotomous
van Waes et al. 2016	80	co	Vascular surgery	890	MAP < 60 mmHg, MAP < 50 mmHg, MAP ↓ > 30%, > 40% compared to baseline	Duration
Mascha et al. 2015	80	co	Noncardiac surgery, > 60 min, ASA classification < 5	104,401	MAP < 55 – 80 mmHg (per 10 minutes), 10 minutes sustained MAP < 70 mmHg	Time-weighted average intraoperative MAP, cumulative duration
Pipanmekaporn et al. 2014	80	co	Thoracotomy or thoracoscopy for non-cancerous lesions	719	MAP < 60 mmHg or SBP < 80 mmHg > 15 min	Dichotomous
Walsh et al. 2013	80	co	Noncardiac surgery, > 1 night in hospital, pre-op and post-op Cr measurement	33,330	MAP < 75 - 55 mmHg	Duration
Bijker et al. 2009	80	co	General or vascular surgery	1,705	Minimal episode duration (1, 5 or 10 min) below: SBP < 70 mmHg; < 80 mmHg; < 90 mmHg; < 100 mmHg; SBP↓ > 10%; > 20%; > 30%; > 40%; MAP < 40 mmHg; < 50 mmHg; < 60 mmHg; < 70 mmHg; MAP↓ > 10%; > 20%; > 30%; > 40%	Duration
Kheterpal et al. 2009	80	co	General, vascular and urologic surgery operations requiring general, epidural, or spinal anaesthesia	7,740	SBP < 80 mmHg or 70 mmHg, MAP < 60 mmHg or 50 mmHg, MAP or SBP ↓ > 30% or 40% with duration > 10min	Dichotomous

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
	MI	Myocardial injury: Tn T post-op > 14 ng·l⁻¹ (99% cut-off point) on day 1 Myocardial infarction: according to joint European Society of Cardiology and American College of Cardiology Consensus.	30 days	Myocardial injury: 30%, infarction: 5%	Myocardial injury: 4.4 (1.8 – 11.1). Infarction: not reported
	MI	Myocardial injury: Tn T > 99th percentile with a 10% coefficient of variation Infarction: according to joint European Society of Cardiology and American College of Cardiology consensus.	3 days	Myocardial injury: 24%, infarction: 4.3%	Myocardial injury: RR (MAP < 60 mmHg, > 30 min) 1.7 (98.8% CI 1.1 – 2.6), RR (MAP < 50 mmHg, 6 – 10 min) 2.0 (98.8% CI 1.1 – 3.6), RR (MAP ↓ > 30%, > 30 min) 2.8 (98% CI 1.6 – 5.1) RR (MAP ↓ > 40%, > 30 min) 1.8 (98.8% CI 1.2 – 2.6)
	Mortality		30 days	1.3%	MAP < 70 mmHg > 10 min 0.76 (0.72-0.80 per 5 mmHg), MAP < 50 mmHg 1.12 (1.15-1.30 per 10min), MAP < 55 mmHg 1.13 (1.09-1.17), MAP < 60 mmHg 1.09 (1.07-1.11), MAP < 70 mmHg 1.04 (1.03-1.05), MAP < 80 mmHg 1.02 (1.01-1.03)
	MI	Relevant ECG changes and increased serum CK-MB or TnI level, confirmed by cardiologist	30 days	0.83%	RR 2.6 (1.6 - 4.3)
	Mortality		30 days	1.5%	MAP < 55mmHg 1-5 min: 1.16 (0.91 – 1.46), 6 – 10 min: 1.16 (0.84 – 1.60), 11 – 20 min: 1.26 (0.89 – 1.80), > 20 min: 1.79 (1.21 – 2.65)
	AKI	Highest postoperative [Cr] more than 1.5-fold or more than 0.3 mg·dl⁻¹ greater than the preoperative [Cr]	7 days	7.4%	MAP < 55mmHg 1 - 5 min: 1.18 (1.06-1.31), 6 - 10 min: 1.19 (1.03-1.39), 11 - 20 min: 1.32 (1.11-1.56), >20 min: 1.51 (1.24-1.84)
	MI	[Troponin T] > 0.04 µg·l⁻¹ or [CK-MB] > 8.8 ng·ml⁻¹	7 days	2.3%	MAP < 55 mmHg 1 - 5 min: 1.30 (1.06-1.5), 6 - 10 min: 1.47 (1.13-1.93), 11 - 20 min: 1.79 (1.33-2.39), > 20 min: 1.82 (1.31-2.55)
	Mortality	All cause	1 year	5.2%	Independent of IOH definition; HR episode duration ≥ 1 min: n.s., HR episode duration ≥ 5 min: n.s., HR episode duration ≥ 10 min: n.s.,
	MI	New Q-waves on ECG or [TnI] > 0.30 ng·dl⁻¹	30 days	0.3%	Multivariable results not reported

Supplementary table 2 Continued

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Monk et al. 2005	80	co	Noncardiac surgery, procedures not affecting postoperative cognitive function	1,064	SBP < 80 mmHg, MAP < 55 mmHg	Duration
White et al. 2016	73	co	Anaesthesia Sprint Audit of Practice included in the National Hip Fracture Database	11,085	MAP < 75 mmHg, SBP < 85 mmHg, lowest recorded SBP and MAP	Dichotomous?
Brinkman et al. 2015	73	co	Elective open abdominal aorta repair	40	MAP ≤ 65 mmHg	Duration, AUT
Petsiti et al. 2015	73	co	Elective, major abdominal surgery with BIS monitoring	248	MAP < 60 mmHg or MAP < 70 mmHg and with > 30% ↓ from baseline	Dichotomous
Marcantonio et al. 1998	73	co	Major elective noncardiac surgery	1,341	SBP ↓ to < 66% of preoperative baseline or < 90 mmHg requiring pressors or fluid resuscitation	Dichotomous
Tallgren et al. 2007	71	RCT	Elective abdominal aorta repair	69	MAP > 60 mmHg, > 15 minutes intraoperatively or > 60 minutes postoperatively	Dichotomous
House et al. 2016	67	co	Noncardiac, nonthoracic surgery	46,799	Duration of profound hypotension (MAP < 40mmHg) > 95th percentile (>2 min)	Dichotomous, Surgical Apgar Score
Sessler et al. 2012	67	co	Single volatile anaesthetic and BIS monitoring	24,120	Cumulative duration of 'triple low': MAP < 75 mmHg, BIS < 45, MAC < 0.80	Duration
Sabaté et al. 2011	67	co	Intermediate-to-high surgery-specific risk	3,519	MAP ↓ ≥ 20 mmHg or 20%, > 1 hour	Dichotomous

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
	Mortality	All cause	1 year	5.5%	1.044 (1.016 – 1.072)
	Mortality		5 days, 30 days	5 days: 1.5%, 30 days: 5.1%	5 day mortality: (lowest intraoperative MAP) 0.980 (0.967 – 0.993) for every mmHg increase of MAP, (lowest intraoperative SBP) 0.983 (0.973 – 0.994) for every 5 mmHg increase of SBP 30 day mortality: (lowest intraoperative MAP) 0.976 (0.964 – 0.988) for every mmHg increase of MAP, (lowest intraoperative SBP) 0.968 (0.951– 0.985) for every 5 mmHg increase of SBP
	AKI	Serum [Cr]↑ ≥ 50% or >26.4 µmol·l^{-1} (AKIN)	2 days	20%	Student t-tests: (duration) 42 ± 39 min (AKI) vs. 20 ± 22 min (no AKI), $p < 0.04$; (AUC) 280 ± 315 mmHg·min^{-1} (AKI) vs. 90 ± 115 mmHg·min^{-1} (no AKI), $p < 0.01$
	LOS	Cut-off: 9 days		Incidence not reported; mean LOS 10.8 (SD 7.3) days	4.269 (1.743 - 10.455)
	Delirium	Daily structured interviews by study personnel including Confusion Assessment Method and Chart/Nursing Intensity Index criteria	5 days	9%	0.8 (0.5 - 1.3)
	AKI	[Cr] ↑ > 50% or serum cystatin C from baseline or urine production of < 0.5 ml·kg^{-1}·h for 6 hours	1 day	21.7%	8.5 (1.8 - 39.4)
	MI	Tn leak: [TnI] 0.6 - 1.5 ng·ml^{-1} or [TnT] 0.1 - 0.3 ng·ml^{-1}, myocardial infarction: [Tn > 1.5 ng·ml^{-1} or [Tn T] > 0.3 ng·ml^{-1}	30 days	0.9%	Tn leak: 1.64 (1.37-1.97), myocardial infarction: 1.35 (1.12-1.63)
	Mortality	In-hospital and 30 days mortality	30 days	In hospital: 0.5%, 30 days: 0.8%	MAP/BIS/MAC: HR low/high/high = 0.729 (0.342 – 1.558), HR low/high/low = 2.534 (1.617 – 3.970), HR low/low/high = 1.492 (0.852 – 2.611), HR low/low/low = 3.957 (2.567 – 6.098)
	LOS	Excessive length of stay compared with the diagnostic related group-adjusted national average length of stay for the primary surgery as identified from the stay-based administrative record		Fraction: 0.24 (0 min triple low condition) - 0.37 (> 60 min triple low condition)	HR low/high/high = 0.969 (0.850 – 1.104), HR low/high/low = 1.139 (1.001 – 1.297), HR low/low/high = 1.078 (0.941 – 1.236), HR low/low/low = 1.470 (1.268 – 1.704)
	MACCE (composite endpoint)	Mortality: cardiovascular or cerebrovascular	In hospital	MACCE: 4.3% mortality: 1.0%	MACCE: 2.3 (1.5 – 3.7). After bootstrapping: 2.3 (80% CI of the OR 1.6 – 3.1)

Supplementary table 2 Continued

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Taffé et al. 2009	67	co	Anaesthesia Databank Switzerland	147,573	MAP ↓ > 30% of baseline MAP > 10min	Dichotomous
Sirivatanauksorn et al. 2014	60	co	Liver transplantation	81	MAP < 70 mmHg > 30min	Dichotomous
Tassoudis et al. 2011	60	co	Elective major abdominal surgery with an expected duration > 2 hours	100	MAP < 60 mmHg or MAP < 70 mmHg and MAP ↓> 30%. Duration IOH ≤ or > 10% total duration of surgery	Dichotomous
Stapelfeldt et al. 2017	53	co	Patients from Cleveland Clinic, Vanderbilt Medical Center and Saint Louis Univerity Medical Center databases	152,445 (subset: 35,904)	31 Thresholds with MAP < 75 - 45mmHg	Duration
Jiang et al. 2016	53	co	Spinal surgery	451	SBP < 80 mmHg	Dichotomous
Yang et al. 2016	47	co	≥ 75 years, elective surgery, total intravenous anaesthesia	480	MAP ↓ > 30% compared to baseline	Dichotomous
Yue et al. 2013	47	co	Abdominal aortic aneurysm repair	71	MAP < 65 mmHg or SBP ↓ > 30 mmHg	Dichotomous
Franck et al. 2011	47	co	Surgery under general anaesthesia	2,350	4 definitions: SBP < 100 mmHg or ↓ > 30%, SBP < 80 mmHg; SBP ↓ > 20% and SBP < 92 mmHg	Dichotomous
Patti et al. 2011	47	co	Elective nonlaparascopic colorectal surgery for carcinoma	100	MAP ≤ 60 mmHg	Dichotomous
Vasivej et al. 2016	46	CC	nonaortic surgery, matching (1:4) variables: surgeon and surgical procedure	55,648 (42/168)	MAP < 65 mmHg	Dichotomous
Thakar et al. 2007	40	co	Gastric bypass surgery	491	MAP < 60 mmHg	Dichotomous

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
		MI: ↑ [CK-MB] or [Tn] + ECG changes or coronary intervention	In hospital	0.3%	
		Stroke: embolic, thrombotic, or haemorrhagic event lasting ≥ 30 min with or without persistent residual motor, sensory, or cognitive dysfunction	In hospital	0.4%	
	Mortality	intraoperative or Immediate postoperative mortality		0.03%	5.80 (2.98 - 11.30)
	AKI	↑ Serum [Cr] x 1.5 times first week after surgery	7 days	71.6%	3.84 (1.11 - 13.30)
	LOS	Prolonged LOS: > 9 days.		IOH duration >10%: 26% IOH duration ≤ 10%: 11%	4.56 (1.85 – 10.96)
	Mortality		30 days	1.8%	Model without blood loss: % increase in odds per minute; MAP < 75 mmHg: 0.2% (0.0% - 0.4%); MAP < 45 mmHg: 11.0% (8.0% - 14.0%), model with blood loss: % increase in odds per minute; MAP < 75 mmHg: 0.1% (0.0% - 0.3%); MAP < 45 mmHg: 9.5% (6.5% - 12.7%)
	Delirium	Cognitive tests consisting of Clinical Dementia Rating and Global Deterioration Scale	30 days	9.3%	7.52 (0.181 – 17.938)
	Delirium	Confusion Assessment Method by neurologist if symptoms of delirium were present.	3 days	29%	Unadjusted OR 1.471 (0.583 – 2.354)
	AKI	RIFLE-criteria	In hospital	Risk: 56.3%, Injury: 18.8%, Failure: 25%	6.008 (1.176 – 30.683)
	LOS	Duration of hospital stay (days)	Hospital stay	-	Not reported
	Delirium	Confusion Assessment Method	Hospital stay	18%	9.74 (2.5 - 37.9)
	Stroke	Clinical evaluation by neurologist and conformation by CT or magnetic resonance imaging of the brain	30 days	0.075%	Fisher's exact test: p = 0.779
	AKI	[Cr] ↑ > 50% relative to baseline or dialysis requirement	3 days	8.6%	Not reported

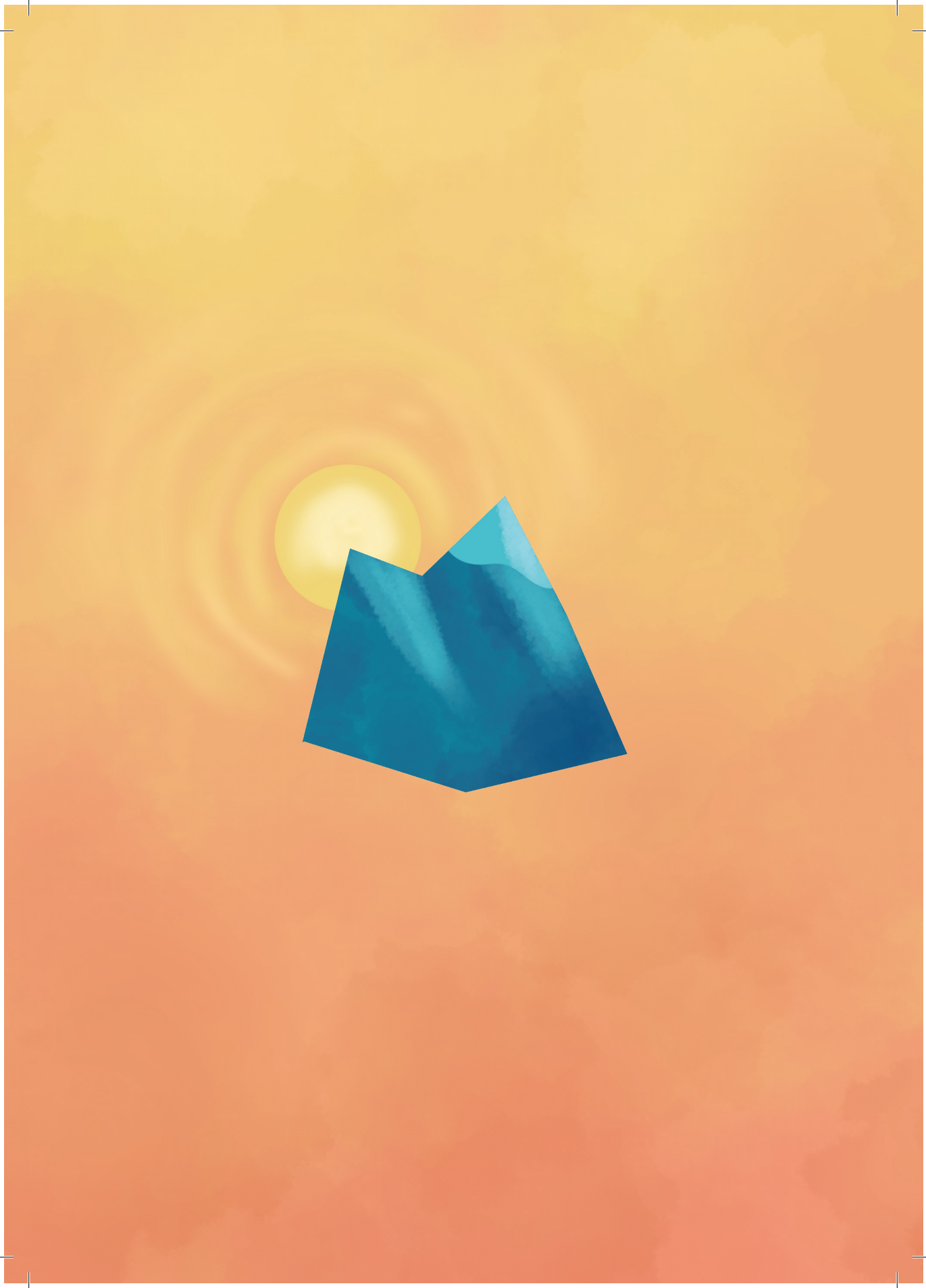
Supplementary table 2 Continued

First author (year)	QS (%)	Study design	Study population	Sample size	IOH definition	IOH analyses
Barone et al. 2002	38	CC	Low-risk patients undergoing noncardiac surgery	25,501	SBP < 100mmHg, > 10min	Dichotomous
Lima et al. 2003	33	co	Liver transplantation	92	MAP < 65mmHg	Dichotomous
Nakamura et al. 2009	31	CC	Repair thoracic aorta (open procedure versus stent graft)	72	SBP < 70 mmHg	Dichotomous
Davidovic et al. 2017	27	co	Elective open abdominal aneurysm repair	450	SBP? < 100 mmHg	Dichotomous
Sharma et al. 2006	23	CC	Laparoscopic gastric bypass for morbid obesity	1,800	SBP < 100mmHg, > 5 min	Dichotomous

Abbreviations: AKI: acute kidney injury; AKIN: Acute Kidney Injury Network definition; AUT: area under the threshold; BIS: bispectral index; BP: blood pressure; CC: case-control study; CK-MB: creatine kinase MB; co: cohort study; Cr: creatinine; DBP: diastolic blood pressure; ECG: electrocardiogram; IOH: intraoperative hypotension; HR: hazard ratio; KDIGO: Kidney Disease Improving Global Outcomes;

	Outcome type	Outcome assessment	Duration of follow-up	Incidence	Associations OR (95% CI)
	MI	ECG changes, CK-MB > 2.5% of the total CK and confirmation by internist or cardiologist	Hospital stay?	0.09%	6.15 (1.89-20.05)
	AKI	[Cr] > 2.0 mg·dl^{-1}	30 days	61%	3.85 (1.05 - 13.7)
	Mortality	In hospital	Hospital stay	5.6%	34 (1.52 - 761)
	Mortality		30 days	1.55%	6.61 (0.71 - 61.07)
	AKI	[Cr] > 1.4 mg·dl^{-1} at any time and [Cr] ↑ > 0.3 mg·dl^{-1} from the baseline value	7 days	2.8%	RR 5.6 (? - ?)

LOS: length of stay; MAC: mean alveolar concentration; MACCE: major adverse cardiac and cerebrovascular events; MAP: mean blood pressure; MI: myocardial injury; OR: odds ratio; QS: quality score; RCT: randomised controlled trial; RIFLE: Risk, Injury, Failure, Loss of kidney function and End-stage kidney disease; RR: relative risk; SBP: systolic blood pressure; Tn: troponin



APPENDIX 2

SUPPLEMENTARY TABLES OF CHAPTER 5

SUPPLEMENTARY TABLES OF CHAPTER 5

Supplementary table 1 Patient and baseline characteristics for the overall cohort and according the need for an intraluminal shunt

Age, years, median [IQR]
Sex, male, n (%)
Carotid stenosis characteristics
Stenosis type, n (%)
De novo, n (%)
Restenosis, n (%)
Ipsilateral carotid stenosis, n (%)
0 – 50%
50 – 70%
70 – 99%
Contralateral carotid stenosis, n (%)
0 – 50%
50 – 70%
70 – 99%
100%
Cardiovascular risk factors and comorbidities
History of
Hypertension, n (%)
Hypercholesterolaemia, n (%)
Coronary artery disease, n (%)
History of coronary intervention, n (%)
Diabetes mellitus, n (%)
Previous transient ischaemic attack or stroke, n (%)
Previous stroke, n (%)
Estimated glomerular filtration rate according to Cockcroft-Gault equation, ml·min·1,73 m^{-2}, median [IQR] median [IQR]
Haemoglobin level, mmol·l^{-1} median [IQR]
Low-density lipoprotein cholesterol, mmol·l·1, median [IQR]
Current smoker, n (%)
Preoperative systolic blood pressure, mmHg, median [IQR]
Preoperative diastolic blood pressure, mmHg, median [IQR]

	All patients (n = 1,120)	No shunt (n = 969)	Shunt (n = 15)	Missings n (%) ‡
	69 [63 – 76]	69 [62 – 76]	70 [65 – 76]	0 (0)
	777 (69)	662 (69)	105 (70)	0 (0)
				26 (2)
	1053 (96)	930 (96)	145 (96)	
	45 (4)	39 (4)	6 (4)	
				73 (7)
	10 (1)	7 (1)	3 (2)	
	87 (8)	73 (8)	14 (10)	
	950 (91)	827 (91)	123 (88)	
				158 (14)
	533 (55)	477 (57)	56 (44)	
	102 (11)	96 (12)	6 (5)	
	163 (17)	145 (17)	18 (14)	
	164 (17)	117 (14)	47 (37)	
	837 (76)	723 (76)	114 (78)	16 (1)
	729 (72)	632 (72)	97 (72)	110 (10)
	183 (18)	154 (17)	29 (21)	73 (7)
	258 (23)	225 (23)	33 (22)	9 (1)
	274 (25)	238 (25)	36 (24)	0 (0)
	902 (81)	775 (80)	127 (84)	0 (0)
	369 (33)	314 (32)	55 (36)	0 (0)
	68 [54 – 86]	70 [54 – 87]	63 [50 – 82]	117 (10)
	8.8 [8.1 – 9.3]	8.8 [8.1 – 9.3]	8.8 [8.1 – 9.2]	54 (5)
	2.5 [1.8 – 3.2]	2.5 [1.8 – 3.2]	2.4 [2.0 – 3.2]	662 (59)
	375 (34)	322 (34)	49 (33)	17 (2)
	150 [135 – 170]	150 [135 – 170]	150 [135 – 170]	178 (16)
	80 [71 – 90]	80 [70 – 90]	80 [72 – 90]	178 (16)

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Supplementary table 1 Continued

Preoperative medication use
β-blocker, n (%)
No β-blocker, n (%)
Metoprolol, n (%)
Bisoprolol, n (%)
Atenolol, n (%)
Sotalol, n (%)
Propranolol, n (%)
Labetalol, n (%)
Diuretics, n (%)
Calcium channel blocker, n (%)
Angiotensin converting enzyme inhibitor, n (%)
Angiotensin receptor blocker, n (%)
Antiplatelet drugs, n (%)
Intraoperative and surgical characteristics
Maintenance of anaesthesia ‡‡
Isoflurane, n (%)
Sevoflurane, n (%)
Propofol, n (%)
Intraoperative β-blocker bolus, n (%)
Metoprolol, n (%)
Esmolol, n (%)
Labetalol, n (%)
Intraoperative heart rate, beats per minute, median [IQR]
Intraoperative vasopressor pump use, n (%)
Phenylephrine, n (%)
Noradrenaline, n (%)
Intraoperative inotrope pump use, n (%)
Dobutamine, n (%)
Dopamine, n (%)
Milrinone, n (%)
Mean blood pressure before induction, mmHg, median [IQR]

	All patients (n = 1,120)	No shunt (n = 969)	Shunt (n = 15)	Missings n (%) ‡
	484 (43)	414 (43)	67 (44)	4 (0)
	636 (57)	552 (57)	84 (56)	
	301 (27)	268 (28)	33 (22)	
	77 (7)	65 (7)	12 (8)	
	48 (4)	38 (4)	10 (7)	
	41 (4)	30 (3)	11 (7)	
	9 (1)	9 (1)	0 (0)	
	8 (1)	7 (1)	1 (1)	
	387 (35)	330 (34)	57 (38)	4 (0)
	266 (24)	227 (24)	39 (26)	4 (0)
	336 (30)	292 (30)	44 (29)	4 (0)
	258 (23)	216 (23)	42 (28)	6 (1)
	964 (87)	832 (87)	132 (87)	7 (1)
				0 (0)
	557 (50)	484 (50)	73 (48)	
	552 (49)	478 (49)	74 (49)	
	41 (4)	32 (3)	9 (6)	
				0 (0)
	49 (4)	44 (5)	5 (3)	
	15 (1)	12 (1)	3 (2)	
	2 (0)	2 (0)	0 (0)	
	59 [53 – 66]	59 [53 – 66]	59 [54 – 68]	9 (1)
				0 (0)
	658 (59)	572 (59)	86 (57)	
	155 (14)	139 (14)	16 (11)	
				0 (0)
	8 (1)	6 (1)	2 (1)	
	7 (1)	4 (0)	3 (2)	
	1 (0)	1 (0)	0 (0)	
	116 [104 – 127]	115 [104 – 127]	117 [102 – 128]	273 (24)

Supplementary table 1 Continued

Duration of mean blood pressure under the threshold, minutes, median [IQR]
< 75 mmHg
< 70 mmHg
< 65 mmHg
< 60 mmHg
< 55 mmHg
< 50 mmHg
Area-under-the-threshold based on mean blood pressure, mmHg·min, median [IQR]
< 75 mmHg
< 70 mmHg
< 65 mmHg
< 60 mmHg
< 55 mmHg
< 50 mmHg
Intraoperative fraction of inspired oxygen, median [IQR]
Intraoperative end-tidal carbon dioxide, mmHg, median [IQR]
Duration of surgery, minutes, median [IQR]
Blood loss, milliliters, median [IQR]

‡ Number of missings before multiple imputation. ‡‡ Numbers do not add up to 1,120 as anaesthesia maintenance in 30 patients was established with a combination of propofol and/or isoflurane and/or sevoflurane.

All patients (n = 1,120)	No shunt (n = 969)	Shunt (n = 15)	Missings n (%) ‡
			9 (1)
16 [7 – 32]	16 [6 – 31]	21 [9 – 37]	
9 [3 – 19]	9 [3 – 19]	11 [4 – 24]	
4 [1 – 11]	4 [1 – 11]	6 [1 – 13]	
2 [0 – 6]	2 [0 – 6]	2 [0 – 6]	
0 [0 – 3]	0 [0 – 3]	1 [0 – 4]	
0 [0 – 1]	0 [0 – 1]	0 [0 – 2]	
			9 (1)
138 [41 – 298]	134 [39 – 287]	185 [60 – 343]	
65 [13 – 166]	63 [11 – 161]	91 [18 – 196]	
25 [1 – 86]	23 [1 – 81]	36 [4 – 112]	
7 [0 – 39]	6 [0 – 38]	11 [0 – 56]	
0 [0 – 15]	0 [0 – 14]	2 [0 – 24]	
0 [0 – 3]	0 [0 – 2]	0 [0 – 8]	
0.46 [0.42 – 0.51]	0.46 [0.43 – 0.51]	0.46 [0.42 – 0.51]	9 (1)
34 [32 – 35]	34 [32 – 35]	33 [32 – 35]	9 (1)
150 [133 – 171]	149 [132 -170]	160 [144 – 181]	9 (1)
250 [153 – 400]	250 [150 – 400]	400 [200 – 775]	998 (89)

Abbreviations: IQR: interquartile range

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Supplementary table 2 Baseline characteristics and balance achieved of patients without preoperative β-blockers compared to β-blocker users before and after propensity score matching

	Before matching
	Absolute standardised differences
Intraluminal shunt, n (%)	0.02
Age, years, median [IQR]	0.08
Sex, male, n (%)	0.02
Body Mass Index, $kg{\cdot}m^{-2}$, median [IQR]	0.34
Restenosis, n (%)	0.07
Ipsilateral carotid stenosis, 70 - 100%, n (%)	0.01
Contralateral carotid stenosis, 70 - 100%, n (%) †	0.16
Hypertension, n (%)	0.36
Hypercholesterolaemia, n (%)	0.10
Coronary artery disease, n (%)	0.43
History of coronary intervention, n (%)	0.49
Diabetes mellitus, n (%)	0.17
Previous transient ischaemic attack or stroke, n (%)	0.02
Previous stroke, n (%)	0.10
Current smoker, n (%)	0.06
Estimated glomerular filtration rate according to Cockcroft-Gault equation, $ml{\cdot}min{\cdot}1{,}73\ m^{-2}$, median [IQR]	0.10
Haemoglobin level, $mmol{\cdot}l^{-1}$, median [IQR]	0.04
Low-density lipoprotein cholesterol, $mmol{\cdot}l^{-1}$ median [IQR]	0.17
High-density lipoprotein cholesterol, $mmol{\cdot}l^{-1}$ median [IQR]	0.36
Total cholesterol, $mmol{\cdot}l^{-1}$, median [IQR]	0.21
Triglyceride, $mmol{\cdot}l^{-1}$ median [IQR]	0.09
Diuretics, n (%)	0.26
Calcium channel blocker, n (%)	0.33
Angiotensin converting enzyme inhibitor, n (%)	0.36
Angiotensin receptor blocker, n (%)	0.14
Antiplatelet drugs, n (%)	0.12
Absolute risk reduction (95% confidence interval) ‡	
Matched numbers of observations (weighted)	
Matched numbers of observations (unweighted)	

The c-statistic of the final propensity score model was 0.757. † Contralateral stenosis categories were combined to 0 – 70% and 70 - 100%. ‡ The estimated treatment effect and 95% confidence intervals were calculated using the Abadie-Imbens standard error for matched samples.

	Baseline table: Before matching		Baseline table: After matching		After matching
	No β-blocker users (n = 636)	**β-blocker users (n = 484)**	**No β-blocker users (n = 636)**	**β-blocker users (n = 484)**	**Absolute standardised differences**
	84 (13)	67 (14)	145 (13)	146 (14)	0.00
	70 [62 – 76]	70 [64 – 77]	70 [64 – 76]	69 [64 – 77]	0.00
	444 (70)	333 (69)	754 (70)	761 (70)	0.01
	26 [24 – 28]	27 [25 – 29]	26 [24 – 28]	26 [24 – 28]	0.04
	23 (4)	24 (5)	50 (5)	39 (4)	0.05
	578 (91)	439 (91)	975 (90)	965 (89)	0.03
	193 (30)	183 (38)	370 (34)	366 (34)	0.01
	438 (70)	407 (84)	846 (78)	848 (78)	0.01
	440 (69)	356 (74)	770 (71)	781 (72)	0.02
	68 (11)	131 (27)	183 (17)	202 (19)	0.05
	91 (14)	168 (35)	247 (23)	257 (24)	0.02
	136 (21)	138 (29)	265 (24)	258 (24)	0.02
	514 (81)	388 (80)	875 (81)	901 (83)	0.06
	222 (35)	147 (30)	365 (34)	351 (32)	0.03
	220 (35)	154 (32)	347 (32)	353 (33)	0.01
	69 [55 – 88]	68 [54 – 84]	68 [54 – 87]	70 [54 – 84]	0.01
	8.7 [8.1 – 9.3]	8.8 [8.1 – 9.3]	8.7 [7.9 – 9.2]	8.8 [8.0 – 9.3]	0.03
	2.6 [1.9 – 3.4]	2.5 [1.8 – 3.2]	2.5 [1.8 – 3.3]	2.5 [2.0 – 3.3]	0.01
	1.2 [(0.9 – 1.5]	1.1 [0.8 – 1.3]	1.1 [0.9 – 1.4]	1.2 [0.9 – 1.4]	0.07
	4.6 [3.7 – 5.6]	4.3 [3.6 – 5.2]	4.5 [3.6 – 5.5]	4.4 [3.7 – 5.5]	0.01
	1.3 [1.0 – 1.9]	1.5 [1.0 – 2.1]	1.4 [1.0 – 2.0]	1.4 [1.0 – 2.0]	0.04
	187 (29)	201 (42)	388 (36)	384 (35)	0.01
	112 (18)	154 (32)	250 (23)	266 (25)	0.03
	147 (23)	191 (40)	329 (30)	344 (32)	0.03
	132 (21)	129 (27)	257 (24)	263 (24)	0.01
	562 (88)	408 (84)	933 (86)	934 (86)	0.00
	0.1% (-4.7% - 4.9%)				
	1,083				
	3,470				

Abbreviations: IQR: interquartile range

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Supplementary table 3 Baseline characteristics and balance achieved of patients with a preoperative β-blocker with a lower β1/β2 selectivity ratio compared to other β-blocker exposure groups before and after propensity score matching

	Before matching
	Absolute standardised differences
Intraluminal shunt, n (%)	0.20
Age, years, median [IQR]	0.18
Seks, male, n (%)	0.05
Body Mass Index, kg·m^{2}, median [IQR]	0.35
Restenosis, n (%)	0.19
Ipsilateral carotid stenosis, 70 - 100%, n (%)	0.02
Contralateral carotid stenosis, 70 - 100%, n (%) †	0.39
Hypertension, n (%)	0.40
Hypercholesterolaemia, n (%)	0.11
Coronary artery disease, n (%)	0.49
History of coronary intervention, n (%)	0.38
Diabetes mellitus, n (%)	0.19
Previous transient ischaemic attack or stroke, n (%)	0.11
Previous stroke, n (%)	0.08
Current smoker, n (%)	0.13
Estimated glomerular filtration rate according to Cockcroft-Gault equation, ml·min·1,73 m^{-2}, median [IQR]	0.13
Haemoglobin level, mmol·l^{-1} median [IQR]	0.07
Low-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.24
High-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.33
Total cholesterol, mmol·l^{-1}, median [IQR]	0.27
Triglyceride, mmol·l^{-1} median [IQR]	0.03
Diuretics, n (%)	0.48
Calcium channel blocker, n (%)	0.17
Angiotensin converting enzyme inhibitor, n (%)	0.44
Angiotensin receptor blocker, n (%)	0.02
Antiplatelet drugs, n (%)	0.66
Absolute risk reduction (95% confidence interval) ‡	
Matched numbers of observations (weighted)	
Matched numbers of observations (unweighted)	

The c-statistic of the final propensity score model was 0.822. ◊ Other group consists of patients without preoperative β-blockers, metoprolol users and patients on ß-blockers with a higher β1/β2 selectivity ratio compared to metoprolol. † Contralateral stenosis categories were combined to 0 – 70% and 70 - 100%. ‡

	Baseline table: Before matching		Baseline table: After matching		After matching
	Lower β1/β2 selectivity ratio than metoprolol (n = 58)	**Other ◊ (n = 1,062)**	**Lower β1/β2 selectivity ratio than metoprolol (n = 58)**	**Other ◊ (n = 1,062)**	**Absolute standardised differences**
	12 (21)	139 (13)	210 (24)	116 (13)	0.25
	73 [63 – 79]	70 [63 – 77]	68 [63 – 76]	70 [64 – 77]	0.06
	39 (67)	738 (70)	597 (68)	605 (69)	0.02
	27 [25 – 29]	26 [24 – 28]	27 [25 – 28]	26 [24 – 29]	0.03
	5 (9)	42 (4)	21 (2)	37 (4)	0.12
	53 (91)	964 (91)	824 (94)	798 (91)	0.13
	30 (52)	346 (33)	247 (28)	352 (40)	0.27
	52 (90)	793 (75)	750 (86)	718 (82)	0.11
	44 (76)	752 (71)	741 (85)	633 (72)	0.34
	22 (38)	177 (17)	263 (30)	184 (21)	0.20
	23 (40)	236 (22)	312 (36)	238 (27)	0.18
	19 (33)	255 (24)	279 (32)	229 (26)	0.12
	49 (85)	853 (80)	700 (80)	711 (81)	0.03
	17 (29)	352 (33)	259 (30)	283 (32)	0.06
	16 (28)	358 (34)	271 (31)	265 (30)	0.01
	68 [54 – 79]	69 [54 – 87]	69 [54 – 78]	67 [54 – 85]	0.05
	8.8 [8.0 – 9.6]	8.8 [8.1 – 9.3]	8.6 [8.0 – 9.1]	8.8 [8.1 – 9.3]	0.25
	2.2 [1.8 – 2.8]	2.5 [1.9 – 3.4]	2.7 [2.0 – 3.7]	2.5 [1.8 – 3.3]	0.29
	1.0 [0.8 – 1.3]	1.1 [0.9 – 1.4]	1.2 [0.9 – 1.4]	1.1 [0.9 – 1.3]	0.07
	4.0 [3.4 – 5.2]	4.3 [3.6 – 5.5]	4.5 [3.7 – 5.7]	4.3 [3.6 – 5.3]	0.22
	1.4 [1.0 – 2.0]	1.4 [1.0 – 2.0]	1.4 [1.1 – 1.9]	1.4 [1.0 – 2.0]	0.03
	33 (57)	355 (33)	375 (43)	364 (42)	0.03
	18 (31)	248 (23)	351 (40)	229 (27)	0.28
	29 (50)	309 (29)	407 (47)	300 (34)	0.25
	13 (22)	248 (23)	230 (26)	204 (23)	0.07
	35 (60)	935 (88)	721 (82)	728 (83)	0.02
	10.7% (- 0.9% - 22.3%)				
	875				
	2,653				

The estimated treatment effect and 95% confidence intervals were calculated using the Abadie-Imbens standard error for matched samples.

Abbreviations: IQR: interquartile range

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Supplementary table 4 Baseline characteristics and balance achieved of patients with metoprolol compared to other β-blocker exposure groups before and after propensity score matching

	Before matching
	Absolute standardised differences
Intraluminal shunt, n (%)	0.10
Age, years, median [IQR]	0.04
Sex, male, n (%)	0.09
Body Mass Index, kg·m^2, median [IQR]	0.28
Restenosis, n (%)	0.04
Ipsilateral carotid stenosis, 70 - 100%, n (%)	0.00
Contralateral carotid stenosis, 70 - 100%, n (%) †	0.04
Hypertension, n (%)	0.37
Hypercholesterolaemia, n (%)	0.16
Coronary artery disease, n (%)	0.33
History of coronary intervention, n (%)	0.44
Diabetes mellitus, n (%)	0.10
Previous transient ischaemic attack or stroke, n (%)	0.06
Previous stroke, n (%)	0.09
Current smoker, n (%)	0.08
Estimated glomerular filtration rate according to Cockcroft-Gault equation, ml·min·1,73 m^{-2}, median [IQR]	0.02
Haemoglobin level, mmol·l^{-1} median [IQR]	0.04
Low-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.14
High-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.15
Total cholesterol, mmol·l^{-1}, median [IQR]	0.13
Triglyceride, mmol·l^{-1} median [IQR]	0.09
Diuretics, n (%)	0.14
Calcium channel blocker, n (%)	0.23
Angiotensin converting enzyme inhibitor, n (%)	0.24
Angiotensin receptor blocker, n (%)	0.16
Antiplatelet drugs, n (%)	0.04
Absolute risk reduction (95% confidence interval) ‡	
Matched numbers of observations (weighted)	
Matched numbers of observations (unweighted)	

The c-statistic of the final propensity score model was 0.709. ◊ Other group consists of patients without preoperative β-blockers and patients on ß-blockers with a lower or higher β1/β2 selectivity ratio compared to metoprolol. † Contralateral stenosis categories were combined to 0 – 70% and 70 - 100%.

	Baseline table: Before matching		Baseline table: After matching		After matching
	Metoprolol (n = 301)	**Other ◊ (n = 819)**	**Metoprolol (n = 301)**	**Other ◊ (n = 819)**	**Absolute standardised differences**
	33 (11)	118 (14)	136 (13)	158 (15)	0.06
	69 [64 – 77]	70 [63 – 77]	69 [63 – 77]	70 [63 – 76]	0.00
	200 (66)	577 (71)	776 (72)	758 (70)	0.04
	27 [25 – 29]	26 [24 – 28]	26 [4 – 28]	26 [24 – 28]	0.01
	11 (4)	36 (4)	32 (3)	51 (5)	0.10
	273 (91)	744 (91)	983 (91)	978 (90)	0.02
	105 (35)	271 (33)	395 (37)	360 (33)	0.07
	260 (86)	585 (71)	832 (77)	845 (78)	0.03
	230 (76)	566 (69)	771 (71)	780 (72)	0.02
	83 (28)	116 (14)	216 (20)	191 (18)	0.06
	112 (37)	147 (18)	281 (26)	254 (24)	0.06
	83 (28)	191 (23)	261 (24)	267 (25)	0.01
	248 (82)	654 (80)	876 (81)	875 (81)	0.00
	90 (30)	279 (34)	335 (31)	345 (32)	0.02
	92 (31)	282 (34)	341 (32)	352 (33)	0.02
	71 [55 – 87]	69 [54 – 87]	67 [53 – 86]	69 [54 – 87]	0.06
	8.8 [8.0 – 9.3]	8.7 [8.1 – 9.3]	8.8 [8.0 – 9.2]	8.7 [8.0 – 9.4]	0.12
	2.5 [1.9 – 3.2]	2.6 [1.8 – 3.4]	2.5 [1.9 – 3.4]	2.5 [1.8 – 3.3]	0.03
	1.1 [0.9 – 1.4]	1.1 [0.9 – 1.4]	1.1 [0.9 – 1.4]	1.1 [0.9 – 1.4]	0.08
	4.3 [3.6 – 5.2]	4.5 [3.6 – 5.6]	4.4 [3.6 – 5.4]	4.4 [3.6 – 5.5]	0.04
	1.5 [1.1 – 2.1]	1.3 [1.0 – 2.0]	1.4 [1.0 – 2.1]	1.4 [1.0 – 2.0]	0.02
	119 (40)	269 (33)	394 (36)	397 (36)	0.01
	94 (31)	172 (21)	241 (22)	259 (24)	0.04
	115 (38)	223 (27)	333 (31)	339 (31)	0.01
	85 (28)	176 (22)	270 (25)	266 (25)	0.01
	264 (88)	706 (86)	911 (84)	935 (86)	0.06
	-2.1% (-7.3% - 3.1%)				
	1,082				
	3,452				

‡ The estimated treatment effect and 95% confidence intervals were calculated using the Abadie-Imbens standard error for matched samples.

Abbreviations: IQR: interquartile range

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Supplementary Table 5 Baseline characteristics and balance achieved of patients with a preoperative β-blocker with a higher β1/β2 selectivity ratio compared to other β-blocker exposure groups before and after propensity score matching

	Before matching
	Absolute standardised differences
Intraluminal shunt, n (%)	0.13
Age, years, median [IQR]	0.02
Sex, male, n (%)	0.11
Body Mass Index, kg·m^{2}, median [IQR]	0.10
Restenosis, n (%)	0.11
Ipsilateral carotid stenosis, 70 - 100%, n (%)	0.02
Contralateral carotid stenosis, 70 - 100%, n (%) †	0.11
Hypertension, n (%)	0.01
Hypercholesterolaemia, n (%)	0.13
Coronary artery disease, n (%)	0.09
History of coronary intervention, n (%)	0.09
Diabetes mellitus, n (%)	0.11
Previous transient ischaemic attack or stroke, n (%)	0.21
Previous stroke, n (%)	0.02
Current smoker, n (%)	0.08
Estimated glomerular filtration rate according to Cockcroft-Gault equation, ml·min·1,73 m^{-2}, median [IQR]	0.14
Haemoglobin level, mmol·l^{-1}, median [IQR]	0.00
Low-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.04
High-density lipoprotein cholesterol, mmol·l^{-1} median [IQR]	0.49
Total cholesterol, mmol·l^{-1}, median [IQR]	0.15
Triglyceride, mmol·l^{-1} median [IQR]	0.07
Diuretics, n (%)	0.11
Calcium channel blocker, n (%)	0.25
Angiotensin converting enzyme inhibitor, n (%)	0.18
Angiotensin receptor blocker, n (%)	0.04
Antiplatelet drugs, n (%)	0.02
Absolute risk reduction (95% confidence interval) ‡	
Matched numbers of observations (weighted)	
Matched numbers of observations (unweighted)	

The c-statistic of the final propensity score model was 0.724. ◊ Other group consists of patients without preoperative β-blockers, metoprolol users and patients on ß-blockers with a lower β1/β2 selectivity ratio compared to metoprolol. † Contralateral stenosis categories were combined to 0 – 70% and 70 - 100%.

	Baseline table: Before matching		Baseline table: After matching		After matching
	Higher β1/β2 selectivity ratio than metoprolol (n = 125)	**Other ◊ (n = 995)**	**Higher β1/β2 selectivity ratio than metoprolol (n = 125)**	**Other ◊ (n = 995)**	**Absolute standardised differences**
	22 (18)	129 (13)	161 (16)	144 (14)	0.05
	70 [65 – 76]	70 [63 – 77]	70 [61 – 76]	69 [63 – 76]	0.07
	8 (6)	39 (4)	108 (11)	40 (4)	0.01
	26 [24 – 29]	26 [24 – 28]	26 [24 – 29]	26 [24 – 28]	0.10
	8 (6)	39 (4)	108 (11)	40 (4)	0.22
	113 (90)	904 (91)	933 (93)	919 (91)	0.05
	48 (38)	328 (33)	314 (31)	358 (36)	0.10
	95 (76)	750 (75)	798 (79)	759 (75)	0.10
	82 (66)	714 (72)	715 (71)	705 (70)	0.02
	26 (21)	173 (17)	235 (23)	193 (19)	0.10
	33 (26)	226 (23)	302 (30)	246 (24)	0.12
	36 (29)	238 (24)	279 (28)	255 (25)	0.05
	91 (73)	811 (82)	789 (78)	798 (79)	0.02
	40 (32)	329 (33)	284 (28)	333 (33)	0.11
	46 (37)	328 (33)	279 (28)	338 (34)	0.13
	66 [51 – 82]	70 [54 – 88]	71 [56 – 89]	69 [54 – 86]	0.10
	8.8 [8.2 – 9.4]	8.7 [8.1 – 9.3]	8.8 [8.2 – 9.4]	8.7 [8.1 – 9.3]	0.06
	2.5 [1.9 – 3.3]	2.5 [1.9 – 3.3]	2.8 [1.8 – 3.4]	2.5 [1.8 – 3.3]	0.03
	1.0 [0.8 – 1.2]	1.2 [0.9 – 1.4]	1.1 [0.9 – 1.4]	1.1 [0.9 – 1.3]	0.07
	4.4 [3.6 – 5.3]	4.4 [3.6 – 5.5]	4.5 [3.6 – 5.5]	4.4 [3.6 – 5.4]	0.01
	1.5 [1.0 – 2.2]	1.4 [1.0 – 2.0]	1.3 [1.0 – 1.9]	1.4 [1.0 – 2.0]	0.09
	49 (39)	339 (34)	378 (38)	347 (35)	0.06
	42 (34)	224 (23)	242 (24)	250 (25)	0.02
	47 (38)	291 (29)	310 (31)	312 (31)	0.00
	31 (25)	230 (23)	244 (24)	237 (24)	0.02
	109 (87)	861 (87)	897 (89)	875 (87)	0.07
	1,7% (-6.1% - 9.5%)				
	1,007				
	3,099				

‡ The estimated treatment effect and 95% confidence intervals were calculated using the Abadie-Imbens standard error for matched samples.

Abbreviations: IQR: interquartile range

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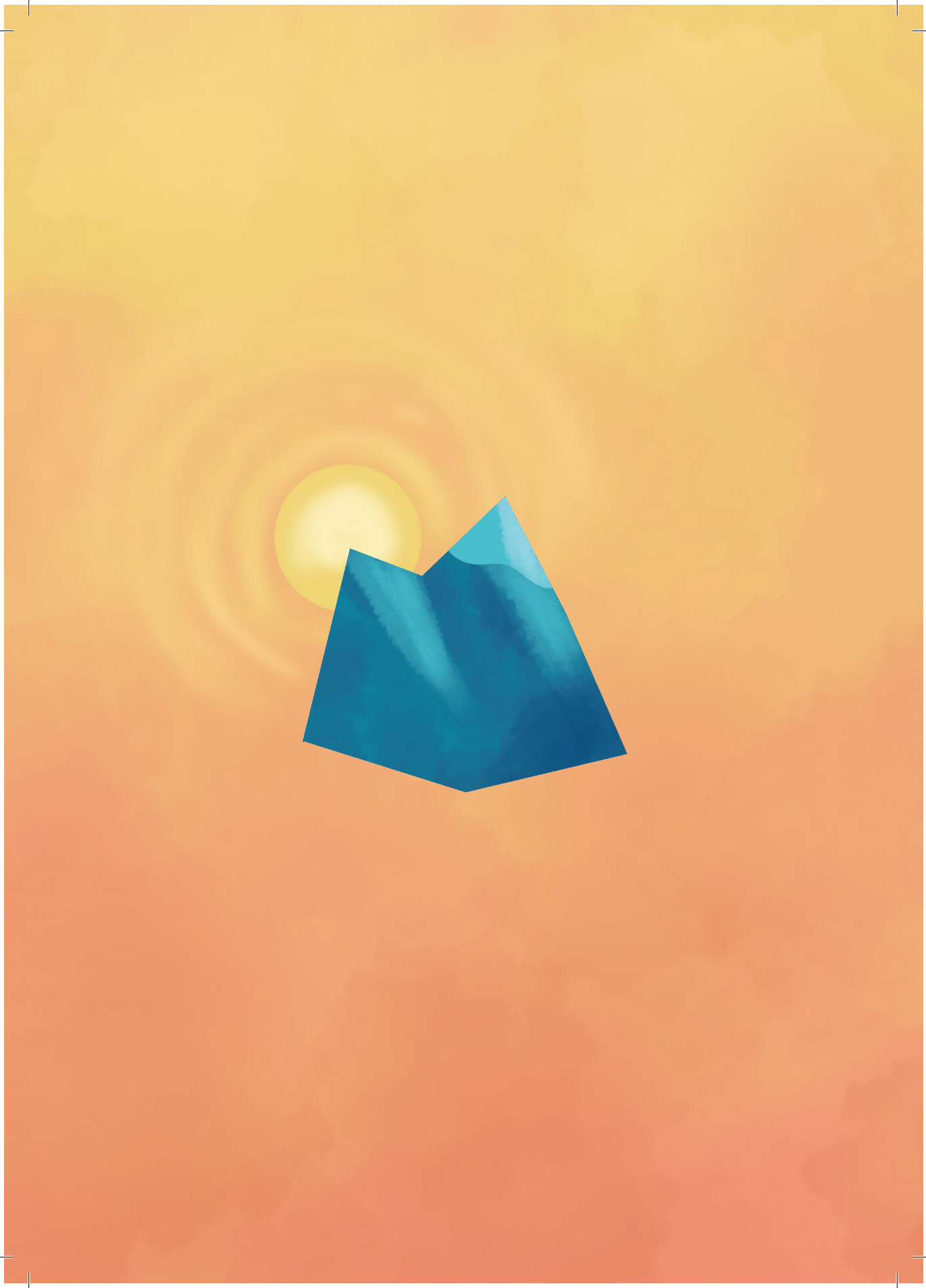
PART 6

EPILOGUE



DANKWOORD

DANKWOORD

Na een korte warming-up sta je klaar aan de start met je ploeggenoten. Je kijkt nog even om je heen naar de rest van het peloton voordat het startschot klinkt. De eerste paar kilometers starten nerveus; iedereen wil vooraan zitten. Daarna rij je de bewoonde wereld uit en begint het zware middenstuk. Onderweg is er veel tegenwind en zijn er diverse valpartijen. Tijdens elke beklimming voel je je benen verder verzuren. De finish lijkt dan nog eindeloos ver weg. Na urenlang overleven komt de finish dan toch in zicht! Nog een laatste eindspint en dan is het klaar.

Promoveren is net als wielrennen een teamprestatie: zonder anderen bereik je de finish niet. Hierbij wil ik alle mensen bedanken die hebben bijgedragen aan de totstandkoming van dit proefschrift en me hebben aangemoedigd toen de benen verzuurden.

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De trainingsmaatjes, mecaniciens en soigneurs

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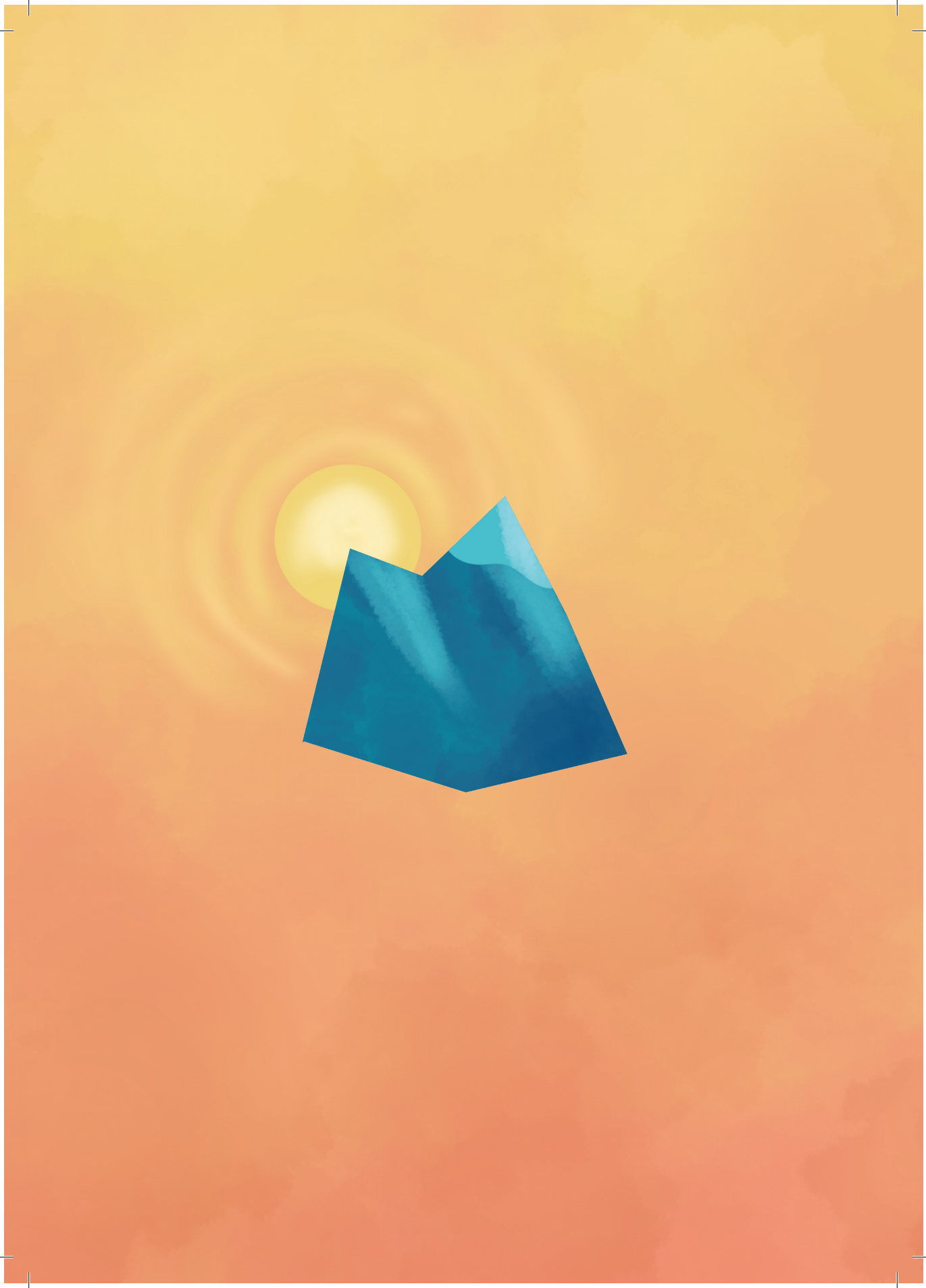

LIST OF PUBLICATIONS

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This thesis

E.M. Wesselink, T.H. Kappen, W.A. van Klei, J.M. Dieleman, D. van Dijk, A.J.C. Slooter. Intraoperative hypotension and delirium after on-pump cardiac surgery. *Br J Anaesth* 2015; 115: 427-33. PMID: 26209856

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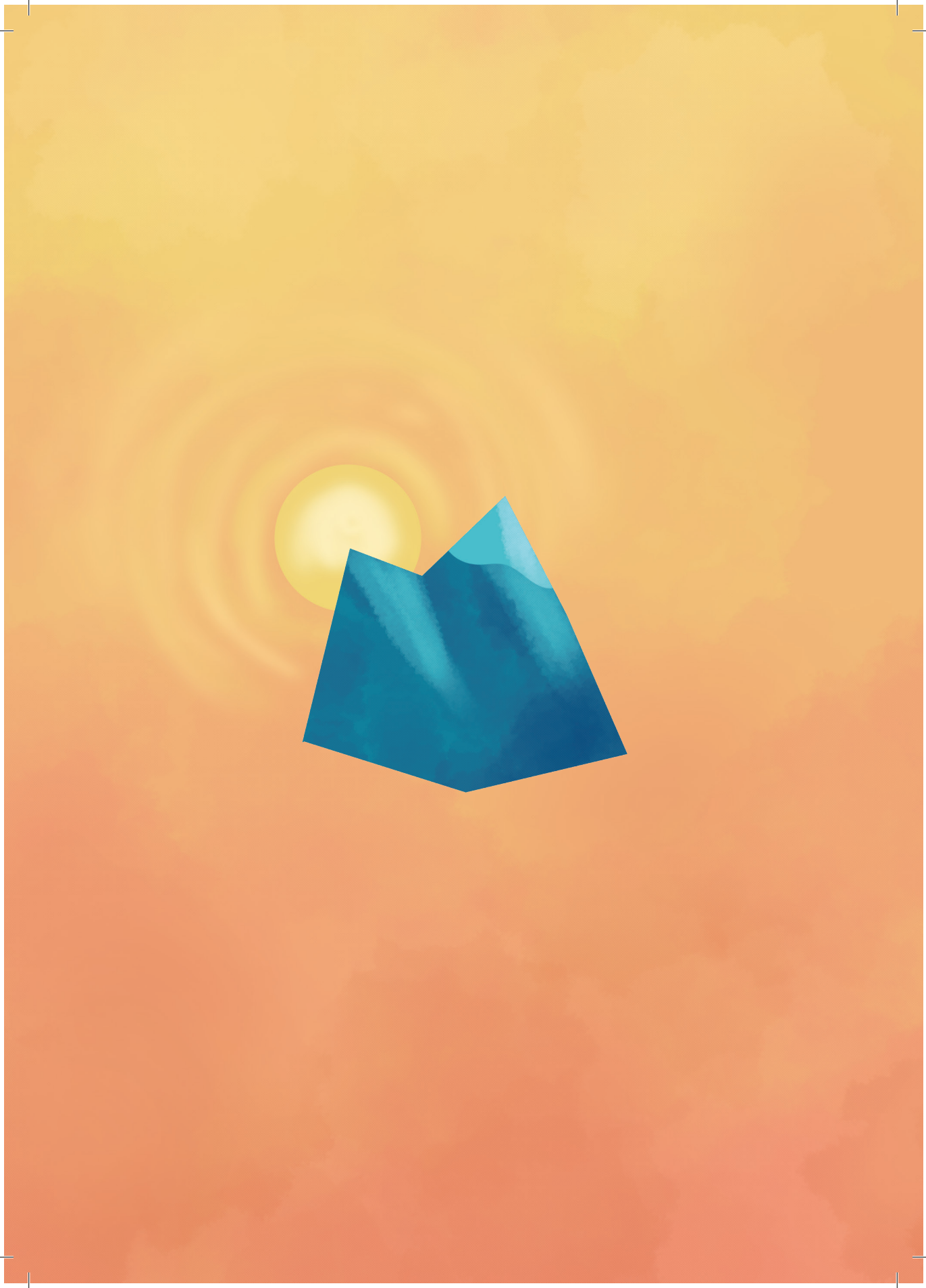

ABOUT THE AUTHOR

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Esther Wesselink was born on 21 September 1987 in Oldenzaal, the Netherlands. She grew up in Weerselo, a small village in Twente and graduated from high school at the Twents Carmel College 'de Thij', in Oldenzaal in 2005. She entered the Pharmacy programme at Utrecht University in the same year. In 2008, she obtained her bachelor diploma. She continued with the Selective Utrecht Medical Master (SUMMA) masters' programme at Utrecht University. During her medical study, she went to Gelre Hospitals in Apeldoorn and Zutphen and for the clinical rotations. She did electives at the anaesthesia department of the University Medical Center Utrecht (UMC Utrecht) and at the paediatric intensive care of the Wilhelmina's Children's Hospital both in Utrecht. Furthermore, she joined the International Federation of Medical Students' Association exchange programme for a clinical rotation in paediatrics in the PKU Muhammadiyah hospital in Yogyakarta, Indonesia in 2011.

In 2011 and 2012 she did a research project on the role of the inhibitory receptors LAIR-1 and SIRL-1 in allergic rhinitis under supervision of prof. dr. L. Bont and prof. dr. L. Meyaard at the departments of paediatrics and translational immunology at the Wilhelmina Children's Hospital Utrecht.

After her graduation from SUMMA in 2012, she began her residency in anaesthesia at the anaesthesia department of the UMC Utrecht under supervision of prof. dr. J.T.A. Knape and prof. dr. R.G. Hoff. Simultaneously, she started her Ph.D. training and research projects as described in this thesis (promotores: prof. dr. W.A. van Klei, prof. dr. A.J.C. Slooter; co-promotor: dr. T.H. Kappen). She obtained her MSc degree in Clinical Epidemiology at Utrecht University in 2016. As from 1 March 2020 she is registered as an anaesthetist and she has worked as an attending anaesthetist between March and October 2020 at the UMC Utrecht. She started a fellowship in intensive care medicine at the UMC Utrecht in October 2020 under supervision of prof. dr. D. van Dijk and dr. M.C. Kerckhoffs.