Intraoperative Hypotension

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Ph.D. thesis, with a summary in Dutch

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Intraoperative Hypotension

Intraoperatieve Hypotensie

(met een samenvatting in het Nederlands)

Proefschrift

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Co-promotor:	dr. W.A. van Klei

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Chapter 1

Introduction

Worldwide, approximately 234 million surgical procedures are performed every year.[1] For most of these operations, some form of anesthesia is necessary. In the majority of these cases, noninvasive blood pressure measurement is part of the minimal intraoperative monitoring standards.[2] The interpretation of blood pressure measurements is however not standardized. A uniform definition on what exactly constitutes a 'too low' blood pressure does not exist, although most would agree that a threshold for intraoperative hypotension (IOH) is dependent on age and comorbid conditions such as hypertension. Furthermore, much controversy exists on the consequences of intraoperative hypotension, in particular the extent to which it may influence adverse outcomes such as stroke, myocardial ischemia or renal failure. In this thesis several studies are described that aimed to refine the definition of intraoperative hypotension and gain more insight in its potential consequences.

Brief historical overview

In 1901, while on a trip through Europe, the young surgeon Harvey Williams Cushing (1869–1939) visited the Ospedale di San Matteo in Pavia (Italy) where he found a simple homemade blood pressure device in routine daily use by the bedside of every patient.[3] This 'sfigmomanometro' was built by Scipione Riva-Rocci (1863–1937) who developed it in 1896 using an inkwell, some copper piping, his bicycle's inner tubing and mercury. Cushing quickly sketched a diagram of the apparatus in his diary and finally even received a model as a gift.

Cushing brought Riva-Rocci's device with him to John Hopkins hospital in Baltimore and introduced it into the operating room.[4] In 1905, the Russian military surgeon Nikolai S. Korotkov (1874–1920) improved the method by adding a stethoscope to the design.[5] At first it was met with much skepticism but due to early adopters like Theodore C. Janeway (1872–1917) in New York City and George W. Crile (1864–1943) in Cleveland, the use of the sphygmomanometer in the operating room gradually spread around the world.[6] Cushing was however not the first to introduce the measurement of blood pressure into the operating room. In 1897, independent of Riva-Rocci, the British Leonard E. Hill (1866–1952) and Harold L. Barnard (1868–1908) published their 'simple and accurate form of sphygmometer' and described the use of their method under the influence of anesthetics and reported the first cases of rapid fall in blood pressure during chloroform anesthesia.[7]

In 1917, Cushing (who meanwhile was concentrating on neurosurgery) proposed the intentional lowering of blood pressure to reduce blood loss and improve surgical

field conditions.[8] However, it took until 1946 for this 'controlled hypotension' to be introduced into clinical practice by W. James Gardner (1898–1987), who lowered blood pressure for intracranial surgery by means of bloodletting and intra-arterially transfusing the autologous blood after the procedure.[9] In 1948, a high spinal anesthesia was used with postural adjustment to induce hypotension and to create a dry field[10] whilst in 1951 the high epidural block was introduced.[11] These methods were however never exercised extensively. Controlled hypotension became more common practice when George Edward Hale Enderby (1915–2003) performed pioneering studies using ganglionic blocking drugs and with the introduction of sodium nitroprusside as a hypotensive agent in 1962.[12]

Simultaneously, the potential harmful effects of lowering the blood pressure (*e.g.*, reactionary hemorrhage, delayed recovery, vision difficulties, anuria)—either deliberately or as an unintended side effect of anesthesia—started to be investigated. In the 1950's several remarkable studies were undertaken to investigate the possible deleterious effects of hypotension by deliberately lowering the blood pressure of volunteers to the point where they showed signs of cerebral circulatory insufficiency (sighing, yawning, staring, confusion or fainting).[13,14] With evidence starting to appear of harmful effects and in the absence of data supporting the usefulness to surgeons, the technique was criticized and interest waned.[15] Eventually, the definition of 'controlled hypotension' was adjusted from an initial systolic threshold of 60 mmHg *[sic]* or less into the least deviation from normal that would produce conditions that minimize bleeding.[16] The safe limits of these deviations for both controlled and unintended lowering of blood pressure have however never been established.

Background of the thesis

In 2005, Monk *et al.* published a study on the effect of anesthetic management on one-year mortality after noncardiac surgery. This study suggested that both intraoperative hypotension and 'deep anesthesia' as measured with an electroencephalographic monitor (BIS) were independently associated with one-year mortality.[17] The next year, Lienhart *et al.* published a survey of anesthesia-related mortality in France, revealing IOH and anemia to be the most important concerns associated with the occurrence of postoperative myocardial ischemia and infarction.[18] Furthermore, based on a posthoc analysis, the POISE trial (2008) suggested that hypotension could be a possible explaining mechanism for the increase in stroke risk found in patients treated with high-dose metoprolol as compared to the placebo treated patients.[19] These landmark

studies triggered a renewed interest in the topic of IOH but also extensive debate regarding the strength of the evidence of the proposed mechanisms by which IOH causes delayed adverse outcomes. The studies presented in this thesis were triggered by this—still ongoing—debate on the definition and adverse effects of hypotension on perioperative outcomes.

Goal of the thesis

With renewed interest in hypotension, it is becoming increasingly evident that much about IOH remains unclear and that the mechanisms by which it can potentially cause adverse outcomes have not been fully unraveled. The goal of this thesis is therefore to refine the understanding of IOH. To this aim, a series of studies were conducted to gain insight in its definitions, occurrence, etiology and outcome.

Outline of the thesis

This thesis consists of three parts. The first part covers the subject on how to define intraoperative hypotension (**chapter 2**) and on how to define the most appropriate baseline blood pressure for use in relative measures of hypotension (**chapter 3**). In addition, the difference between theoretical definitions and their use in daily clinical practice by anesthesia care providers is discussed (**chapter 4**). In the second part of this thesis, focus lies on the relation between intraoperative hypotension and adverse perioperative outcome, such as a postoperative stroke (**chapter 5**) or the risk of dying within one year after surgery (**chapter 6**). In the third part, all studies presented in this thesis are put into a larger perspective in the general discussion (**chapter 7**) and the results are discussed in the light of the current literature. Subsequently, the thesis is summarized (**chapter 8**), including a Dutch translation of the summary in **chapter 9**.

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Part I

Defining Intraoperative Hypotension

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Chapter 2

The incidence of intraoperative hypotension

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Abstract

Background: Intraoperative hypotension (IOH) is a common side effect of general anesthesia and has been reported to be associated with adverse perioperative outcomes. These associations were found using different definitions of IOH. It is unknown whether the incidences of IOH found with those different definitions are comparable. The authors aimed to describe the relation between the chosen definition and incidence of IOH.

Methods: First, a systematic literature search was performed to identify recent definitions of IOH that have been used in the anesthesia literature. Subsequently, these definitions were applied to a cohort of 15,509 consecutive adult patients undergoing noncardiac surgery during general anesthesia. The incidence of IOH according to the different threshold values was calculated, and the effect of a defined minimal duration of a hypotensive episode was studied.

Results: Many different definitions of IOH were found. When applied to a cohort of patients, these different definitions resulted in different IOH incidences. Any episode of systolic blood pressure below 80 mmHg was found in 41% of the patients, whereas 93% of the patients had at least one episode of systolic blood pressure more than 20% below baseline. Both definitions are frequently used in the literature. The relation between threshold values from the literature and IOH incidence shows an S-shaped cumulative incidence curve, with occurrence frequencies of IOH varying from 5% to 99%.

Conclusions: There is no widely accepted definition of IOH. With varying definitions, many different incidences can be reproduced. This might have implications for previously described associations between IOH and adverse outcomes.

Intraoperative hypotension (IOH) is a common and frequent side effect of anesthesia.[1,2] Previously, IOH was reported to be independently associated with adverse perioperative outcomes in several clinical settings, and even an association between IOH and long-term (one-year) mortality was reported.[3-7] These findings have important clinical and medicolegal consequences. Perioperative stroke, for example, has often been attributed to IOH,[8-11] although Limburg *et al*.[12] were unable to find an association between IOH and postoperative stroke. Furthermore, IOH was recently reported to be one of the most important concerns associated with the occurrence of postoperative myocardial ischemia and infarction.[13]

Studies that reported an association between IOH and adverse outcomes have used very different definitions of IOH. Some authors defined IOH as a decrease in systolic or mean blood pressure below a certain absolute threshold,[4] whereas others have used a decrease in blood pressure relative to the patients' baseline blood pressure.[14] Combinations of definitions including the duration of a decreased blood pressure have been used as well.[3] Even particular therapeutic actions of the attending anesthesiologist have been included in IOH definitions, such as administering fluids or a vasopressor.[1,2,15,16] Finally, and probably more confusing, is the use of different definitions of IOH by the same authors in subsequent publications, or the use of a different definition of IOH depending on the type of surgery.[17-19]

It seems evident that the incidence of IOH will depend on the chosen definition, although this has not been formally studied. We therefore hypothesized that different definitions of IOH will result in different incidences of IOH. We first performed a systematic literature search to identify the range of definitions of IOH that are used in the anesthesiology literature. Subsequently, these definitions were applied to a large cohort of patients to study the differences in observed frequencies of IOH across these definitions.

Materials and Methods

Study design

This study included a systematic literature search, followed by an observational, retrospective cohort study. This cohort analysis included adult patients who had undergone noncardiac surgery at the University Medical Center Utrecht (the Netherlands). The study protocol was approved by the hospital ethics committee. Because patients were not submitted to investigational actions but treated with usual care and the current study only documented the routinely gathered patient data, there was no need for written informed consent.

Part 1: Systematic Literature Search

A systematic PubMed/MEDLINE search over the period January 2000 to April 2006 was performed using only the term *'hypotension'*. Because we were mainly interested in the definition of IOH as used by anesthesiologists, the search was restricted to the four anesthesiology journals with the highest impact factor (IF) in 2004 (Institute for Scientific Information, Journal Citation Reports, 2004) and excluding pain journals. The selected journals were *Anesthesiology* (IF = 4.1), *British Journal of Anaesthesia* (IF = 2.5), *Anesthesia & Analgesia* (IF = 2.2) and *Anaesthesia* (IF = 2.2). Pediatric and animal studies, case reports, comments and letters to the editor were excluded because they seldom contained a definition of IOH. Articles studying hypotension exclusively in the postoperative period were excluded as well.

The selected articles were screened for the presence of a definition of IOH (J.B.B.). Criteria on which rescue treatment was given for low blood pressure were interpreted as a definition of IOH. When decreases in blood pressures were observed in a well-defined study period (*e.g.*, maximal decrease in systolic blood pressure > 20% from the baseline value within 80 minutes after induction of epidural anesthesia[20]), this time period was not interpreted as part of the definition of IOH. A second independent reviewer (T.H.K.) also screened the selected articles on the definition of IOH. When there was any inconsistency among the two reviewers, consensus was achieved using a third independent reviewer (W.A.v.K.). The found definitions of IOH were used for further analysis in part 2 of the current study.

Part 2: Cohort Study

Patients. The study included all consecutive adult patients (aged 18 years or older) undergoing noncardiac surgery during general anesthesia at the University Medical Center Utrecht between January 1, 2004, and January 1, 2006. Procedures performed during local or regional anesthesia (including peripheral blockades) and nonsurgical procedures performed in the operating room (*e.g.*, electroconvulsive therapy or cardioversion) were excluded. Patients for whom no baseline blood pressure could be calculated were also excluded.

Data collection and extraction. Data were obtained from an electronic anesthesia record-keeping (ARK) system. This ARK system stores data from the anesthesia ventilator and monitor (such as ventilator settings, blood pressure, heart rate, and oxygen saturation) every 60 seconds as well as data that are entered manually during anesthesia (such as administration of medications, time of intubation, and infusions).

In general, noninvasive blood pressure was measured at least every 5 minutes, and the most recent values from the anesthesia monitor from both noninvasive and invasive blood pressure were stored every minute where available.

When both noninvasive and invasive blood pressures were measured, invasive blood pressure measurements were used instead of noninvasive measurements.

The found definitions of IOH in part 1 used both absolute thresholds and thresholds relative to a baseline blood pressure. For IOH definitions using a blood pressure threshold relative to a baseline, the baseline was defined as the mean of all available blood pressure measurements before induction of anesthesia. This implies, of course, that at least one blood pressure measurement is available before induction of anesthesia. This in turn, obviously requires the availability of the exact time of induction. In our ARK system, however, induction is entered manually, often after all induction and intubation actions are completed. Therefore, we considered it to be a less reliable estimate of the exact time of induction. To give a more precise estimate of the time of induction, we developed an algorithm using LabView software (version 8; National Instruments Corporation, Austin, TX). The algorithm defined the time of induction as either the moment of administration of induction agents or 3 minutes before the first appearance of continuous expired carbon dioxide registration, whichever came first. In this, it was assumed that the expired carbon dioxide detection was a proxy for (manually) ventilating the patient, and that the induction medication was administered. Although it is routine practice that at least one blood pressure measurement is taken before induction of anesthesia, it is possible that using the aforementioned algorithm, no blood pressure measurement could be found before the estimated time of induction (*e.g.*, when intravenous induction was performed immediately after the first blood pressure measurement). These cases were excluded from the analysis.

Analysis. The analysis was performed using the aforementioned LabView program. For each patient, this program retrieved patient characteristics and a data array containing all blood pressure data from the ARK system. We calculated per patient the estimated time of induction and the baseline blood pressure. For each threshold from the used IOH definitions, absolute (mmHg) or relative to the calculated baseline (%), we calculated per patient the number and duration of IOH episodes. All analyses were repeated using time variables of 5 and 10 minutes for the minimal episode of IOH duration, according to the definitions used in the literature. Finally, for every IOH definition, the overall incidence of IOH (in the total cohort) was calculated using SPSS (release 12.0.1; SPSS Inc., Chicago, IL).

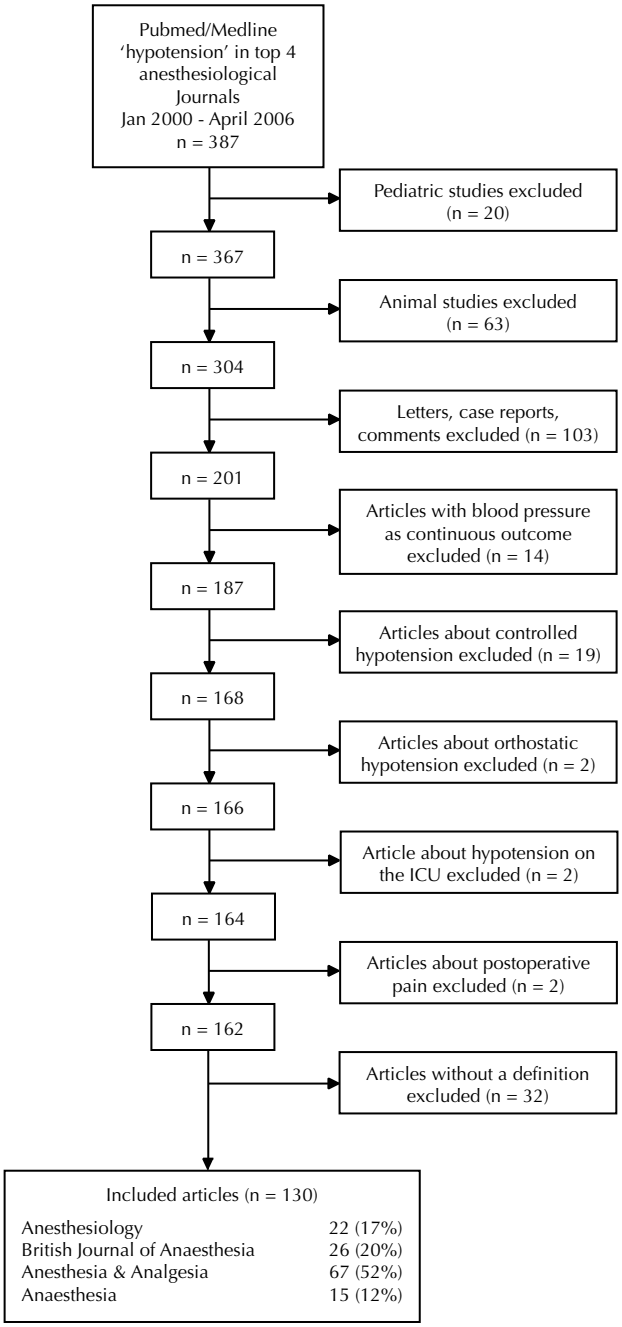

Figure 2.1 Schematic representation of the literature search.

Results

Part 1: Literature Search

The literature search resulted in 387 articles in the four selected anesthesiology journals. After application of the inclusion and exclusion criteria, 130 articles providing 140 definitions of IOH remained (figure 2.1). The reviewers agreed on 111 articles, and on 19 articles the third reviewer achieved consensus. The results of the systematic literature search are presented in Web table 1, which is available on the Anesthesiology Web site at http://www.anesthesiology.org. All definitions of IOH (table 2.1) were based on either systolic or mean blood pressure (or a combination of both), combined with an absolute threshold (mmHg) or a threshold relative to a baseline (%). Diastolic blood pressure was never included in a definition. Other components of the definitions were the minimal duration of the episode that the blood pressure was below the threshold in order to be qualified as IOH (the minimal episode duration), the interval at which the blood pressure was measured (such as every 1, 3, or 5 minutes), and the measuring method (noninvasive or invasive). There were 6 articles that also included the requirement of a therapeutic action of the attending anesthesiologist, such as administering fluids or a vasopressor, in the definition of IOH.[1,2,15,16,21,22]

A wide variety of threshold pressure values to determine IOH was found, both absolute and relative to a baseline (table 2.1). The most frequently used definitions were a systolic blood pressure below 80 mmHg (n = 10), a decrease in systolic blood pressure more than 20% below baseline (n = 18), and the 'combination definition' of an absolute and relative threshold described as a decrease in systolic blood pressure below 100 mmHg and/or 30% below baseline (n = 11). Definitions relative to a baseline require an unambiguous definition of this baseline. Of the 111 definitions that used a relative threshold, 55 (50%) actually presented the definition of this baseline. The baseline was most frequently based on blood pressure measurements taken immediately before induction of anesthesia. The minimal episode duration was less frequently mentioned than the baseline. In 14 of the 140 definitions (10%), a minimum duration was specified. For all other articles, it was not clear. If the minimal episode duration was mentioned, 1, 2, and 5 minutes were the most frequently used.

The measuring interval was not described in 29 of the 130 articles (22%). The most frequently used recording intervals for intraoperative blood pressures were 1 and 5 minutes (n = 36 and n = 38 articles, respectively). Both noninvasive and invasive measuring methods were described, depending on the clinical setting of the study. The

Table 2.1 Thresholds of intraoperative hypotension as found with the literature search

Definition	Articles (%)
Absolute systolic blood pressure thresholds	
SBP < 100 mmHg	2 (1.4)
SBP < 90 mmHg	5 (3.6)
SBP < 85 mmHg	1 (0.7)
SBP < 80 mmHg	10 (7.1)
Moderate: SBP < 100 mmHg, severe: SBP < 80 mmHg	2 (1.4)
Moderate: SBP < 85 mmHg, severe: SBP < 65 mmHg	1 (0.7)
SBP < 70 mmHg, later during surgery SBP < 100 mmHg	1 (0.7)
Relative systolic blood pressure thresholds	
Decrease in SBP > 10% from baseline	3 (2.1)
Decrease in SBP > 20% from baseline	18 (12.9)
Decrease in SBP > 25% from baseline	3 (2.1)
Decrease in SBP > 30% from baseline	7 (5.0)
Decrease in SBP > 40% from baseline	1 (0.7)
Decrease in SBP > 10 mmHg from baseline, moderate: < 90 mmHg	1 (0.7)
Decrease in SBP > 30 mmHg from baseline	1 (0.7)
Mild: decrease > 20%, moderate: 20–30%, severe: > 30% from baseline	1 (0.7)
Combinations of absolute and relative systolic blood pressure thresholds	
SBP < 100 mmHg or > 30% decrease from baseline	11 (7.9)
SBP < 100 mmHg or > 25% decrease from baseline	3 (2.1)
SBP < 100 mmHg or > 20% decrease from baseline	8 (5.7)
SBP < 100 mmHg and > 10% decrease from baseline	1 (0.7)
SBP < 95 mmHg or > 25% decrease from baseline	1 (0.7)
SBP < 90 mmHg or > 30% decrease from baseline	8 (5.7)
SBP < 90 mmHg or > 20% decrease from baseline	3 (2.1)
SBP < 80 mmHg or > 30% decrease from baseline	4 (2.9)
SBP < 80 mmHg or > 20% decrease from baseline	1 (0.7)
SBP < 75 mmHg or > 40% decrease from baseline	1 (0.7)
SBP < 100 mmHg, severe: decrease SBP > 30 mmHg from baseline	1 (0.7)
SBP < 90 mmHg or decrease > 30 mmHg from baseline	1 (0.7)
SBP < 90 mmHg or decrease > 20 mmHg from baseline	1 (0.7)
Absolute mean blood pressure thresholds	
MAP < 70 mmHg	1 (0.7)
MAP < 60 mmHg	2 (1.4)
MAP < 55 mmHg	2 (1.4)
MAP < 50 mmHg	1 (0.7)
Relative mean blood pressure thresholds	
Decrease in MAP > 10% from baseline, severe: 15% decrease	1 (0.7)
Decrease in MAP > 15% from baseline	1 (0.7)
Decrease in MAP > 20% from baseline	7 (5.0)
Decrease in MAP > 25% from baseline	5 (3.6)
Decrease in MAP > 30% from baseline	5 (3.6)

Table 2.1 (continued)

Definition	Articles (%)
Combinations of absolute and relative mean blood pressure thresholds	
MAP < 60 mmHg or decrease > 30% from baseline	1 (0.7)
MAP < 65 mmHg or decrease > 30% from baseline	1 (0.7)
MAP < 70 mmHg and decrease > 40% from baseline or MAP < 60 mmHg	1 (0.7)
Combinations of systolic and mean blood pressure measurements	
SBP < 100 mmHg or decrease in MAP > 30% from baseline	1 (0.7)
SBP < 100 mmHg or decrease in SBP or MAP > 20% from baseline	1 (0.7)
SBP < 90 mmHg or decrease in MAP > 25% from baseline	2 (1.4)
SBP < 80 mmHg or MAP < 55 mmHg	1 (0.7)
No blood pressure measurement specification	
Decrease in BP > 20% from baseline	3 (2.1)
Decrease in BP > 25% from baseline	1 (0.7)
Decrease in BP > 30% from baseline	1 (0.7)
Decrease in BP > 20 mmHg from baseline	1 0(0.7)

Total number of articles is greater than 130 because several articles contained more than one definition.
BP = blood pressure; MAP = mean arterial pressure; SBP = systolic blood pressure.

method of measurement was not described in 37 articles (28%). The remaining articles used noninvasive methods (n = 63), invasive methods (n = 20), or both (n = 10).

In summary, 10 of the 140 found IOH definitions (7%) included descriptions of all the aforementioned components (measurement method, blood pressure type, threshold value, baseline, minimal episode duration and measurement interval).[19,22-30]

Part 2: Cohort analysis

A reliable baseline blood pressure could be calculated for 15,509 (76%) of the 20,503 patients who underwent noncardiac surgery during general anesthesia in the selected time period. In the remaining patients, there was no preoperative blood pressure measurement more than 3 minutes before the estimated time of induction of anesthesia. These patients were excluded from the analysis. Baseline characteristics of the cohort for which a baseline blood pressure could be calculated are presented in table 2.2. The incidence of IOH and the mean number of episodes of IOH according to the most frequently used definitions in the literature are presented in table 2.3. When using the definitions from the literature, the lowest incidence of IOH was found with a systolic blood pressure below 70 mmHg for at least 5 minutes (5%), whereas the highest incidence was observed with a decrease in systolic blood pressure more than 10% from the baseline blood pressure without

Table 2.2 Characteristics of the cohort (n = 15,509)

Variable	n (%)
Mean age (SD)	50.7 (17.2)
Males	7,212 (46.5)
Mean duration of surgery in minutes (SD)	1:40 (1:33)
Median duration of surgery in minutes (25^{th}, 75^{th} percentiles)	1:12 (0:44,2:02)
Type of surgery	
Elective surgery	12,644 (81.5)
Emergency surgery	2,865 (18.5)
General surgery	3,492 (22.5)
Plastic surgery	1,128 (7.3)
Gynecology/obstetrics	1,658 (10.7)
ENT and dental surgery	2,782 (17.9)
Neurosurgery	1,706 (11.0)
Eye surgery	1,677 (10.8)
Orthopedic surgery	1,244 (8.0)
Urology	756 (4.9)
Vascular surgery	1,066 (6.9)
Blood pressure measurement	
Noninvasive	13,180 (85.0)
Invasive	2,329 (15.0)

* Values are number (%) unless indicated otherwise.

ENT = ear, nose & throat.

time criteria (99%). The curve showing the relation between blood pressure threshold and incidence of IOH using the information from table 2.3 showed a sigmoidal form. To construct the complete shape of the cumulative frequency distribution curve, threshold values higher and lower than the values found in the literature were also applied to the data set. This allowed us to calculate the incidence of IOH that would be found using these fictional thresholds (figure 2.2).

Discussion

We conducted a systematic review to summarize the definitions of intraoperative hypotension that are used in the anesthesia literature, and found a large variation. These definitions were applied to intraoperative data from a large cohort of patients, resulting in an apparent occurrence of IOH varying between 5% and 99%. The relation between thresholds used in the definitions and the frequency of IOH is sigmoidal.

Some methodologic issues must be addressed. First, because we derived our data from daily clinical practice, there may have been some artifacts in the blood pressure data (*e.g.*, the surgeon leaning against the blood pressure cuff or movement artifacts). These artifacts may give both falsely low and falsely high blood pressures, resulting in an overestimation or underestimation of the incidence of IOH. However, because most artifactual readings are single readings, the eventual effects of artifactual measurements are minimized in the analyses where intraoperative hypotension was defined with a minimal duration of 5 or 10 minutes. Second, definitions using a threshold relative to a baseline blood pressure obviously require a value for this baseline. In the current study, we used the mean of all available blood pressure measurements before the time of induction of anesthesia. This definition of the baseline blood pressure is critically dependent on an exact recording of the time of induction of anesthesia. The induction time in our cohort data were manually entered by the anesthesiologist in the ARK system, generally after all activities around the induction and intubation have been completed. This may have resulted in errors. To minimize this error, the time of induction was defined as the time of administration of induction medication only if this event was before the first appearance of expired carbon dioxide registration. Otherwise, we assumed that the medication was given 3 minutes before carbon dioxide registration. These measures were taken to prevent that an initial decrease in blood pressure after induction was included in the calculation of the baseline blood pressure, which would have resulted in an inappropriately low baseline blood pressure and thus in an underestimation of the occurrence frequency of IOH. However, with this strict definition of induction, we found no blood pressure recordings before induction time in 24% of the cases, which restricted the cohort to 15,509 patients. This does not mean that in these cases there was no blood pressure measurement before induction of anesthesia, but that anesthesia was induced within the 3 minutes preceding first registration of expired carbon dioxide registration. Nevertheless, we excluded these cases rather than including a falsely low blood pressure baseline in 24% of the patients, resulting in falsely low incidences. Because this exclusion was random across the cohort, it is unlikely that it introduced bias. Still, this cohort is large enough to estimate the incidence of IOH as a function of relative blood pressure thresholds. It is unlikely that the aforementioned limitations have influenced the shape of the S-curve, although falsely low baseline blood pressures might cause a shift to the right. Finally, to reduce the amount of data presented in this article, we studied only the effects of varying the threshold values and minimal episode durations on the frequency of IOH. The other IOH criteria, such as blood pressure type, measurement

Table 2.3 Incidence of intraoperative hypotension in 15,509 adult noncardiac surgery patients

	Incidence of IOH, % (mean number of episodes)		
	MED = 1min	MED = 5 min	MED = 10 min
Absolute thresholds, mmHg			
Systolic			
< 100	81.5 (3.1)	71.6 (1.8)	56.4 (1.1)
< 95	74.5 (2.7)	62.4 (1.5)	45.1 (0.8)
< 90	64.3 (2.2)	49.3 (1.1)	30.9 (0.5)
< 85	53.2 (1.6)	35.0 (0.7)	17.4 (0.3)
< 80	41.2 (1.1)	20.1 (0.3)	7.4 (0.1)
< 75	30.7 (0.6)	10.5 (0.2)	3.1 (0.04)
< 70	21.2 (0.4)	4.6 (0.1)	1.3 (0.01)
< 65	14.0 (0.2)	2.4 (0.03)	0.7 (0.01)
Mean			
< 70	77.7 (3.0)	65.9 (1.7)	48.6 (1.0)
< 65	65.2 (2.4)	49.4 (1.2)	31.3 (0.6)
< 60	50.7 (1.6)	31.1 (0.7)	16.1 (0.3)
< 55	36.3 (0.9)	15.8 (0.3)	6.6 (0.1)
< 50	24.0 (0.5)	7.1 (0.1)	2.3 (0.03)
Relative thresholds, % from baseline			
Systolic			
> 10%	98.6 (2.7)	96.9 (2.0)	92.4 (1.5)
> 15%	96.9 (3.0)	93.7 (2.1)	86.9 (1.5)
> 20%	93.3 (3.2)	88.0 (2.1)	78.3 (1.5)
> 25%	86.7 (3.1)	78.6 (2.0)	66.5 (1.3)
> 30%	76.5 (2.8)	65.6 (1.7)	52.4 (1.0)
> 40%	52.2 (1.7)	37.1 (0.8)	24.0 (0.4)
Mean			
> 10%	98.5 (2.6)	96.7 (2.0)	91.7 (1.5)
> 15%	97.0 (2.9)	93.9 (2.1)	86.6 (1.5)
> 20%	94.1 (3.1)	89.0 (2.1)	79.4 (1.5)
> 25%	88.6 (3.1)	80.7 (2.0)	68.6 (1.3)
> 30%	80.1 (2.9)	68.9 (1.8)	54.9 (1.1)
> 40%	56.1 (1.9)	40.6 (1.0)	26.6 (0.5)

IOH = intraoperative hypotension; MED = minimal episode duration.

method, or measurement interval, can be varied as well and are also likely to cause a similar left or right shift of the S-curve.

Many different definitions of IOH were found in the literature. These definitions were not only inconsistent in threshold values, but also in threshold type (absolute versus relative), baseline (if required), blood pressure type (systolic versus mean blood

pressure), measurement method (noninvasive versus invasive), measurement interval, and minimal episode duration. In our view, all of these components should be used in a proper definition of IOH. Nevertheless, only 10 (7%) of the 140 definitions analyzed contained descriptions of all of these criteria. The requirement of a therapeutic action by the attending anesthesiologist included in the definition of IOH raises a fundamental problem, because it implies that if a low blood pressure remains untreated, it would not qualify as IOH. Still, threshold value and type, baseline, blood pressure type, measurement method and interval, and minimal episode duration should be described unambiguously in a workable definition of IOH. For example, it is obviously not sensible to use a minimal episode duration for IOH of 1 minute when the measuring interval is 5 minutes.[31]

In recent years, there has been renewed interest in the effect of IOH on short- and long-term outcomes.[3-7] Lienhart *et al.*[13] recently reported IOH to be one of the most important concerns associated with the occurrence of postoperative myocardial ischemia and infarction. However, many of the reported associations between IOH and adverse outcomes have been obtained using widely different, arbitrarily chosen blood pressure thresholds, in most cases without applying a restriction with respect to the duration of a hypotensive episode. For that reason, the results of the studies reporting such associations are difficult to compare, and associations between hypotension and outcome observed with one definition of IOH might not be observed when using even a slightly different definition. This is supported by our finding that small changes in threshold values may result in very different incidences of IOH, especially in the commonly used definitions covering the steep area of the cumulative frequency distribution curve (figure 2.2). Moreover, it is remarkable to find definitions of IOH that include combinations of absolute and relative thresholds from different areas of the cumulative frequency distribution curve.[31,32] Still, basic physiology teaches that if blood pressure becomes 'low enough for a period that is long enough', organ perfusion will be compromised, which in turn might have detrimental effects to end organs. However, what is 'too low' and what is 'too long'? A clinically more relevant question would be at what threshold and episode duration the IOH will affect clinically relevant patient outcomes. These different patient outcomes (*e.g.*, myocardial ischemia, ischemic stroke, 'watershed' infarction) will probably have different threshold levels, both for the minimum blood pressure threshold value and for the minimal episode duration, at which significant associations can be found. Furthermore, these thresholds are also likely to depend on patient characteristics, such as age and comorbidity. There is some evidence for this assertion from studies on critical spinal cord perfusion. For

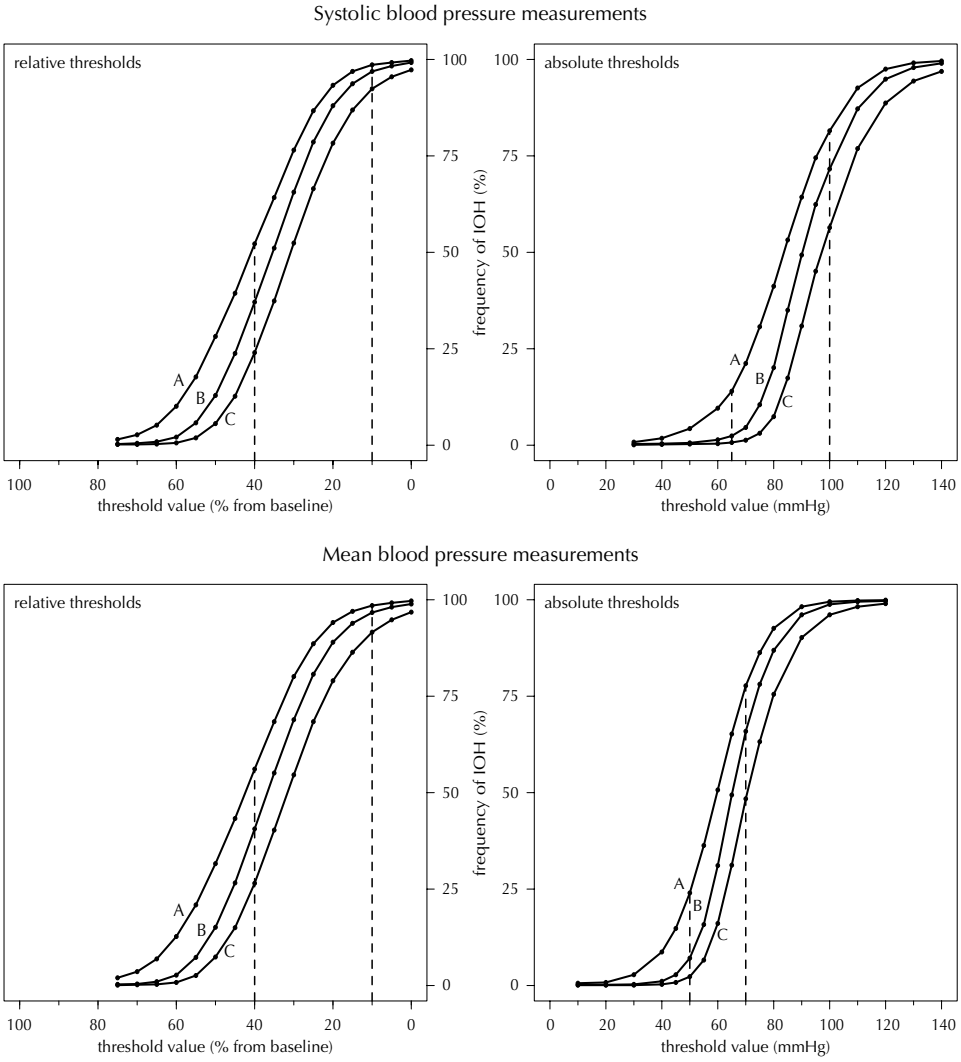

Figure 2.2 Incidence of intraoperative hypotension (IOH) as a function of the chosen definition threshold. Each figure shows the relation between the various blood pressure thresholds and the incidence of intraoperative hypotension for both systolic (*upper two figures*) and mean blood pressure (*lower two figures*). The figures on the *left* show the blood pressure thresholds relative to a baseline (%), whereas the figures on the *right* show the absolute blood pressure thresholds (mmHg). In each figure, the sigmoidal curves shift to the right with increasing duration of the minimal episode length for IOH (A, B and C). A = a minimal episode duration of 1 minute below the designated threshold; B = a minimal episode duration of 5 minutes below the designated threshold; C = a minimal episode duration of 10 minutes below the designated threshold. The *vertical* lines represent the range of blood pressure thresholds as found in the literature.

example, de Haan *et al.*[33] reported a decreased ischemic tolerance of the spinal cord to a lowering of perfusion pressure after clamping of noncritical segmental arteries in pigs. Similarly, one can hypothesize that a patient with peripheral vascular disease undergoing surgery will have a different tolerance for low blood pressures as compared with a healthy patient undergoing the same procedure. One can also imagine that a patient undergoing surgery with significant blood loss has a different tolerance for low blood pressures as compared with the same patient undergoing minor surgery. IOH thus becomes a dynamic phenomenon depending on patient characteristics and surgical factors rather than a static phenomenon based on fixed, arbitrarily chosen thresholds.

There is no accepted single definition for intraoperative hypotension. When published intraoperative hypotension criteria from the recent anesthesia literature are applied to actual patient data, the incidence of intraoperative hypotension varies between 5% and 99%. It is likely that this variation in intraoperative hypotension incidence has implications for the reported association between intraoperative hypotension and adverse perioperative outcomes, because associations observed with one definition might not be found using even a slightly different definition. We suggest that the problem of intraoperative hypotension should be approached as a dynamic phenomenon depending on various factors, rather than dichotomizing blood pressures based on arbitrarily chosen thresholds.

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180
160
140
120
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SPHYGMOMANOMETER
mmHg

Chapter 3

The baseline blood pressure

Submitted as: Bijker JB, Kappen TH, van Klei WA, Kalkman CJ. Blood pressure at the outpatient anesthesia clinic versus blood pressure immediately before induction of anesthesia: An observational cohort study to explore the baseline blood pressure.

Abstract

Background: Intraoperative hemodynamic changes are often related to a patient's baseline blood pressure. However, the most appropriate way to determine this baseline is unknown. Commonly, blood pressures measured in the operating room are considered stress related and thought to be higher compared to measurements obtained at the outpatient clinic.

Methods: We used data from a previously conducted literature review on intraoperative hypotension to provide an overview of the descriptions of baseline blood pressure. Subsequently, a retrospective cohort study among 14,044 consecutive adult patients who underwent noncardiac surgery was performed. From these patients, the blood pressures measured at the outpatient preoperative evaluation clinic were compared to the preinduction blood pressure measurements in the operating room using Bland-Altman plots.

Results: On average, the blood pressures in the operating room were 7–9 mmHg higher than those at the outpatient evaluation clinic. Furthermore, the differences showed large spread and increased at higher blood pressure levels. Mean blood pressure measurements showed much less dispersion as compared to systolic measurements. Premedication, age, history hypertension and ASA physical status did not appear to influence the difference between outpatient and operating room blood pressure.

Conclusions: Blood pressures in the operating room were slightly higher than outpatient measurements, but the difference was not considered clinically relevant. Based on these results and when the principle of regression to the mean are taken into account, one could hypothesize that for daily clinical practice, the baseline blood pressure is best based on averaging all available mean blood pressure measurements.

Induction and maintenance of anesthesia is frequently accompanied by changes in blood pressure and both intraoperative hypo- and hypertension have been associated with adverse perioperative outcome.[1–7] Often, changes in blood pressure are interpreted in relation to a baseline blood pressure. For example, the most frequently used definition of intraoperative hypotension is a 20% decrease in systolic blood pressure from baseline.[8]

However, a uniform and appropriate definition of a preoperative baseline blood pressure does not exist.[9] In a previous study we found that only 50% of the definitions that required a baseline blood pressure actually provided one.[8] If a definition was provided, the most frequently used baseline blood pressure was based on the measurement(s) immediately preceding the induction of anesthesia. Still, there is a widespread clinical belief that preinduction blood pressure readings in the operating room (OR) are influenced by anxiety-induced stress and may overestimate true baseline blood pressure. Blood pressure measurements taken during outpatient preoperative evaluation (OPE) or on hospital admission are often considered more appropriate, although large differences between blood pressures taken at the OPE clinic, the ward, the holding area and inside the OR have been demonstrated.[9] Furthermore, there is substantial physiological fluctuation in blood pressure over time.[10–13]

In the present study we tested the hypothesis that blood pressures measured in the OR immediately before induction of anesthesia are higher than those measured at the OPE clinic. To this aim, we conducted a retrospective cohort study to investigate the differences between blood pressures measured at the OPE clinic and in the OR.

Materials and Methods

Study design

The study was designed as an observational retrospective cohort study in which blood pressure measurements obtained from the OPE clinic and the OR were compared. In addition, data from a previously conducted systematic literature search[8] were used to give an overview of the definitions of the baseline blood pressure. Since patients were not subjected to investigational actions, the local hospital ethics committee waved the need for written informed consent.

Part 1: Literature Search

To explore the diversity of definitions of the baseline blood pressure, we used data from a previously conducted study on the definitions of intraoperative hypotension.[8] In this previous study we conducted a systematic literature search for definitions of intraoperative hypotension in four of the main peer-reviewed anesthesia journals (*Anesthesiology, Anesthesia & Analgesia, British Journal of Anaesthesia and Anaesthesia*) from January 2000 to April 2006. For further details of the literature search we refer to the previous publication.[8] From all definitions of intraoperative hypotension that used a threshold relative to a baseline blood pressure, the description of this baseline blood pressure was extracted.

Part 2: Cohort Study

Patients. All consecutive adult patients (aged 18 years or older) undergoing elective noncardiac surgery at the University Medical Center Utrecht, the Netherlands, in the period from January 1, 2005 to March 1, 2007, were selected. Patients for whom no baseline blood pressure could be calculated were excluded.

Data collection. Preoperative data were collected at the OPE clinic and included biometrical data, planned type of surgery, medical history, American Society of

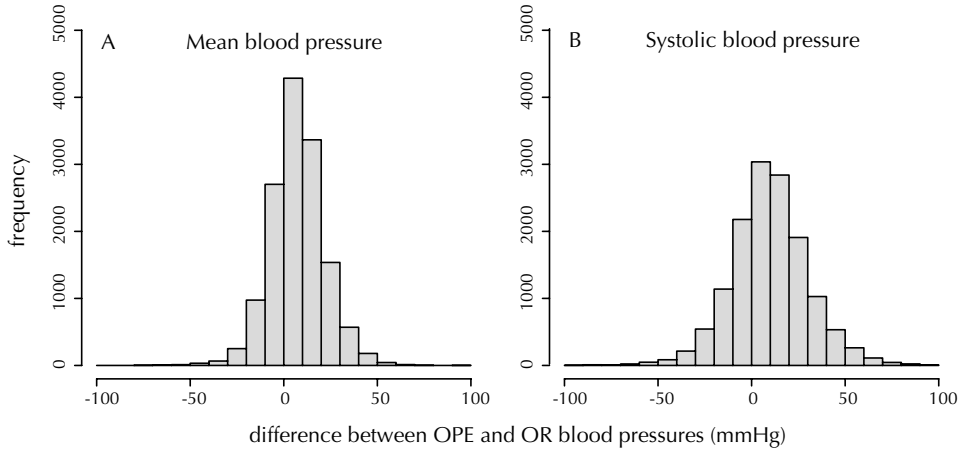

Figure 3.1 Histograms of the difference between outpatient preoperative evaluation and operating room blood pressure measurements for the *mean* (A) and *systolic* (B) blood pressures.

Table 3.1 Definitions of the baseline blood pressure as found in the literature (n = 110)

Variable	n (%)
Not defined	56 (51)
Baseline measured in the operating room	
One single measurement before administration of anaesthesia	12 (11)
Lowest MAP record in 10 minutes before surgery	1 (1)
Lowest of 3 pre-induction measurements	1 (1)
Lowest of 2 pre-induction measurements	1 (1)
Second of 2 pre-induction measurements	2 (2)
Average of 2 pre-induction measurements	4 (4)
Average of 3 pre-induction measurements	11 (10)
Average of 5 pre-induction measurements	1 (1)
Average/median of all pre-induction measurements	2 (2)
Baseline measured before day of surgery	
Measured on day before surgery	1 (1)
Average of 2 measurements obtained 24 hours before surgery	1 (1)
Average of 4 measurements obtained 24 hours before surgery	1 (1)
Average of 3 measurements on admission / at the ward	7 (6)
Average of 3 measurements during pre-anaesthetic visit	1 (1)
Measured during pre-anaesthesia consultation	2 (2)
Not clearly defined	
Three minute period of baseline measurement	1 (1)
Median / average of a 5 minutes baseline measurement	3 (3)
Ten minute period of baseline measurement	1 (1)
Average of preoperative visit, pre-anaesthesia consultation and pre-induction value	1 (1)

Anesthesiologists physical status and the blood pressure measured at the OPE clinic. This blood pressure was a single measurement in the sitting position, on either arm, using a Welch Allyn 52000 Series Vital Signs Monitor (Welch Allyn, Skaneateles Falls, NY).

Intraoperative data were obtained from an electronic anesthesia record keeping system. The preinduction OR blood pressure was defined as the mean of all available noninvasive blood pressure measurements before induction of anesthesia. In general, noninvasive blood pressures were measured at least every 5 minutes using the NIBP module of a Datex-Ohmeda S/5 (GE Healthcare, Waukesha, WI) anesthesia monitor. To obtain the blood pressure measurements before induction of anesthesia, an exact time of induction is obviously required. Since this time is entered manually in the anesthesia record keeping system, this time stamp was considered a less reliable estimate of the exact time of induction. To give a more precise estimate of the time

Table 3.2 Characteristics of the cohort (n = 14,044)

Variable	n (%)
Median age in years (interquartile range)	53 (39 – 65)
Male gender	6,374 (45)
American Society of Anesthesiologists physical status	
I	4,816 (34)
II	6,690 (48)
IIIor IV	1,354 (10)
Unknown	1,184 (8)
History of hypertension	
Yes	2,767 (20)
No	9,866 (70)
Unknown	1,411 (10)
Type of surgery	
General surgery	3,025 (22)
Plastic surgery	1,022 (7)
Gynaecology	1,531 (11)
Ear nose & throat	1,762 (13)
Oral & maxillofacial surgery	712 (5)
Neurosurgery	1,273 (9)
Eye surgery	1,500 (11)
Orthopaedic surgery	1,458 (10)
Urology	927 (7)
Vascular surgery	834 (6)
Benzodiazepine premedication*	4,329 (31)

Values are number (%) unless indicated otherwise.

* Midazolam (68%), Oxazepam (25%), Other (7%).

of induction, we used a previously published algorithm implemented with LabView software (version 8; National Instruments Corporation, Austin, TX).[8] The algorithm defined the time of induction as either the moment of administration of induction medication or 3 minutes before the first appearance of continuous expired carbon dioxide registration, whichever came first. In case of spinal or epidural anesthesia, the time of puncture was taken as the time of induction.

Statistical analysis. Bland-Altman analysis was used to compare both systolic and mean blood pressure measurements from the OPE clinic and the OR.[14] A difference between OPE and OR blood pressure of more than 10 mmHg was considered clinically relevant. The mean difference and 95% limits of agreement were calculated according to the regression method.[15,16] Subsequently, stratified series of Bland-Altman plots were made to

explore the influence of the administration of premedication, a history of hypertension, age and ASA physical status on the difference in OPE and OR blood pressure.

All analyses were performed using R (release 2.13.1; R Foundation for Statistical Computing, Vienna, Austria)

Results

Part 1: Literature Search

The previously conducted literature study yielded a total of 140 definitions of intraoperative hypotension. Of these definitions, 79% (n = 110) required a baseline blood pressure since a threshold relative to a baseline blood pressure was used. In 51% (n = 56) of the definitions where a baseline blood pressure was necessary, this baseline was not reported. An overview of the remaining 54 baseline definitions, resulting in 19 unique descriptions, is shown in table 3.1. Most often, a single measurement before induction of anesthesia was used as a baseline.

Part 2: Cohort analysis

In total, 17,149 patients met the inclusion criteria. In 3,105 cases (18%) there was no OPE blood pressure available (n = 1,521), no noninvasive OR baseline blood pressure available before the time of induction (n = 994) or neither of these two was available (n = 590), which left 14,044 patients to be included. The median duration between OPE visit and day of surgery was 20 days. The characteristics of the cohort are presented in table 3.2. In total 2,767 (20%) of the patients had a history of hypertension (either based on the use of antihypertensive medications or as indicated in the patient charts) and 4,329 (31%) had received premedication with benzodiazepines.

Histograms of the difference between the OPE and OR blood pressure measurements are presented in figure 3.1. The Bland-Altman plots for the total cohort, split by systolic and mean blood pressure measurements are presented in figure 3.2. This demonstrates a wide spread around the line of no difference. The difference in OPE and OR blood pressure increases towards higher mean blood pressures (figure 3.2). This figure also demonstrates that the mean blood pressure measurements (panel A) show much less spread around the regression line and the 95% limits of agreement (the dotted lines) are narrower than those around the systolic blood pressure measurements (panel B). Premedication appeared to lower the difference between systolic OPE and OR blood pressures but this effect was less apparent for mean blood pressure measurements

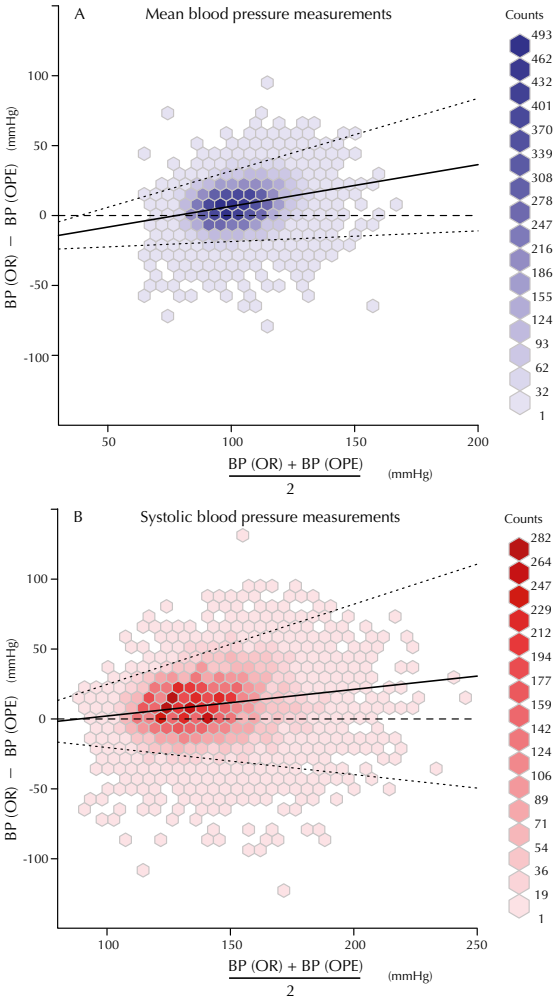

Figure 3.2 Bland-Altman plots for the total cohort (n = 14,044) of the differences in mean (A) and systolic (B) blood pressure measurements obtained on the outpatient preoperative evaluation clinic and in the operating room. The *solid* lines are the regression lines of the mean difference; the *dotted* lines are the upper and lower 95% limits of agreement. The *dashed* line is the line of no difference. Under each plot is the color legend for the number of observations per hexagonal bin.
OPE = outpatient preoperative evaluation; OR = operating room; BP = blood pressure.

(figure 3.3). There was no clear effect of a history of hypertension, of age < 50 years and of ASA physical status 3 and 4 on the difference between OPE and OR blood pressures (figure 3.3).

At the median of the average OPE and OR mean blood pressure (102 mmHg, figure 3.2, panel A, x-axis), the OR mean blood pressure was 7 mmHg (95% CI, -21 – 35) higher than the OPE mean blood pressure. This effect was more pronounced in patients who did not receive premedication. In these patients the OR mean blood pressure was 9 mmHg (95% CI, -19 – 36) higher than the OPE mean blood pressure, while for premedicated patients this difference was reduced to 5 mmHg (95% CI, -24 – 33). For the median of the systolic blood pressure measurements (138 mmHg, figure 3.2, panel B, x-axis) these differences were 9 mmHg (95% CI, -31 – 50) for the total

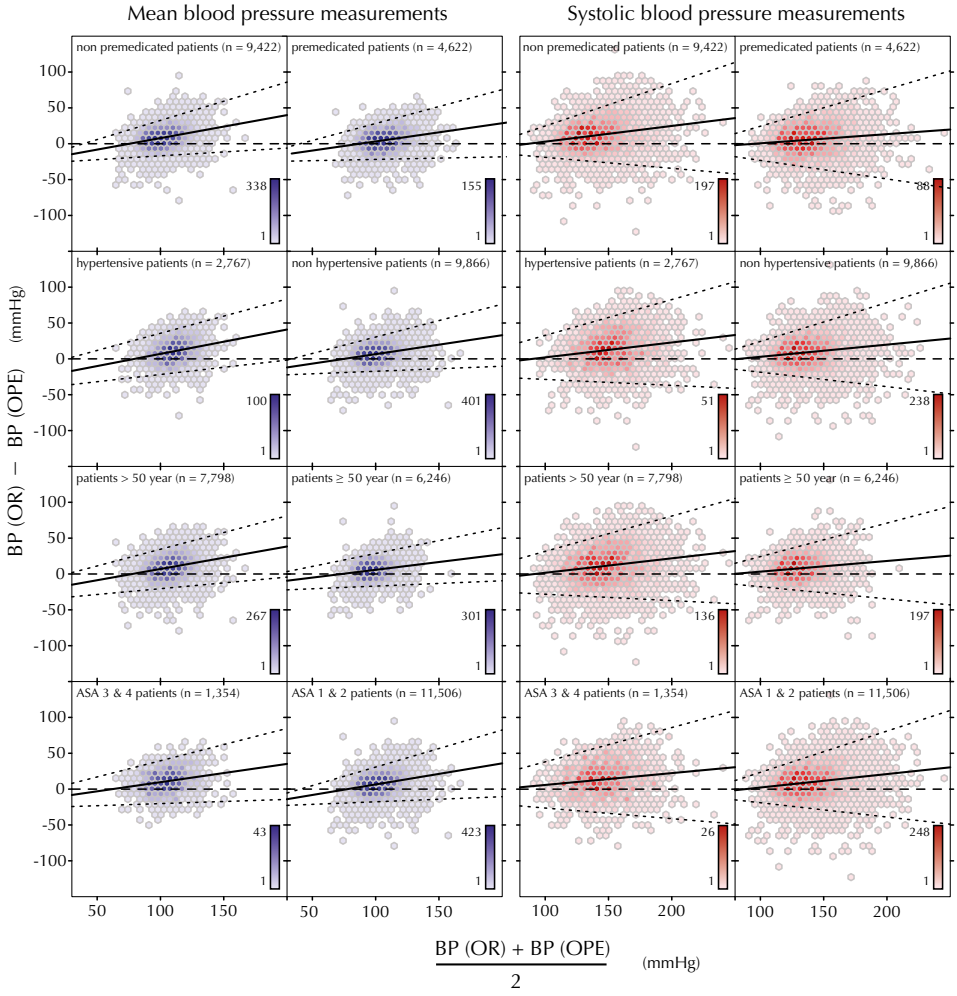

Figure 3.3 Bland-Altman plots for possible interactions between the difference in OPE and OR blood pressure measurements and patient characteristics. The *blue* figures are the mean blood pressure measurements, and the *red* figures are the systolic blood pressure measurements. The panel rows show from top to bottom the stratified effects of premedication, hypertension, age (> or ≤ 50 years) and ASA physical status on the difference in OPE and OR mean and systolic blood pressure measurements. The *solid* and *dotted* lines are the regression lines of the mean difference with their corresponding upper and lower 95% limits of agreement. The *dashed* lines are the lines of no difference. At the side of each panel is the color legend for the number of observations per hexagonal bin.

ASA = American Society of Anesthesiologists; OPE = outpatient preoperative evaluation; OR = operating room; BP = blood pressure.

cohort, 11 mmHg (-28 – 51) for those patients who did not receive premedication and 5 mmHg (-36 – 47) for the premedicated patients. However, as indicated by the confidence intervals, none of the aforementioned differences were statistically significant at the $P < 0.05$ level.

Discussion

In the present study we compared blood pressures measured at the OPE clinic and the mean of the preinduction blood pressure measurements in the OR. Although on average the OR blood pressures were slightly higher than those measured at the OPE clinic (difference 7–9 mmHg), the large variation in measurements caused approximately half of the patients to have a lower blood pressure in the OR than at the OPE clinic. Thus, the widespread clinical thinking that the admission or OPE blood pressure is lower and a better baseline than the allegedly stress-related OR blood pressure is refuted by the data presented in this study, which revealed a large variability in blood pressure measurements. Furthermore, the difference between OPE and OR blood pressure was not constant. In the higher blood pressure range, the OR blood pressure became increasingly higher than the OPE blood pressure. In contrast, in the lower blood pressure range, this difference decreased or even changed direction, with OR blood pressures becoming predominantly lower than the OPE blood pressure measurements (figure 3.2).

Literature on how to define a preoperative baseline blood pressure is sparse and the available studies on how to define a general hemodynamic baseline mainly describe methods of baseline measurement under research conditions. Definitions vary from the last reading of a series of five measurements taken at 90-second intervals[17] to continuous long-term (24–36 hours) invasive measurements.[13,18] However, in daily clinical practice these methods are not feasible since only a limited set of blood pressure measurements is available in the OR. Furthermore, preoperative anxiety and stress have been reported to elevate blood pressure significantly, even though benzodiazepine premedication has unpredictable and variable effects on both blood pressure and anxiety.[9,10,19] In addition, the normal physiological diurnal rhythm in blood pressure alone can already be responsible for fluctuations in blood pressure of up to 20%.[10–13]

Patient age and comorbidity did not appear to have an influence on the difference between OPE and OR blood pressures. Nevertheless, benzodiazepine premedication

had a small blood pressure lowering effect, but we considered none of the observed effects to be clinically relevant (a difference of 4 mmHg for the mean blood pressure and 6 mmHg if the systolic blood pressure was used), especially since the distribution of the measurements was so wide. However, the spread in the distribution of the differences in mean blood pressures was much less as compared to the distribution of the systolic measurements, resulting in narrower 95% limits of agreement. This suggests that the use of mean blood pressure values might result in a more consistent baseline blood pressure. In this, it is important to bear in mind that an oscillometric blood pressure device measures the mean blood pressure where the amplitude of the oscillations in the cuff is maximal, and that the mean blood pressure does not refer to a calculated value from systolic and diastolic values.[20] Furthermore, when the diurnal rhythms, physiological activity, stress and anxiety are taken into account it could be hypothesized that according to the principles of regression towards the mean, the most appropriate baseline blood pressure should be based on an 'averaging' (using either the mean or median) of all clinically available measurements.[21] However, even though no 'gold standard' of baseline blood pressure determination exists, firm conclusions can only be drawn when this hypothesis is tested properly using outcome data.

Some limitations need to be discussed. First, in 18% of the patients, no baseline blood pressure could be calculated or a blood pressure from the OPE clinic was not available. This was the result of the strict definition of the time of induction. Nevertheless, we rather excluded too many patients than risking including the initial drop in blood pressure after induction of anesthesia in the OR baseline blood pressure series, as this would introduce bias by falsely lowering the value of the OR baseline blood pressure. Furthermore, due to the retrospective nature of the study design, missing blood pressures from the OPE clinic could not be retrieved and those patients had to be excluded as well. Secondly, in our hospital blood pressure is not measured routinely on admission to the surgical ward (*e.g.,* in day-case surgery) or at the holding area. Therefore, the blood pressure measured at the OPE clinic was the blood pressure which was most often available before the patient's arrival in the OR and therefore used in this study. However, the blood pressure on admission can be expected to be similar to the OPE blood pressure if a patient is admitted several days before surgery, and similar to the OR blood pressure if a patient is admitted for same day surgery. Furthermore, the OPE blood pressure measurement was taken in the sitting position, whereas the OR measurements were in supine position. However, the sitting position affects mainly the diastolic blood pressure and does not result in difference in systolic pressure.[22,23] If an effect was to be anticipated it would be an overestimation of the

OPE blood pressure, making the difference between OPE and OR blood pressure only smaller.

In conclusion, a wide variety of definitions of a preoperative baseline blood pressure are in use in the literature and no consensus on a uniform definition does exist. Many of the available definitions were used for research purposes and are not applicable in daily clinical practice. When outpatient and operating room blood pressure measurements are compared, the widespread clinical belief that the—potentially stress-related—blood pressures measured in the operating room are higher than the blood pressures measured at the outpatient preoperative evaluation clinic could not be confirmed in the present study.

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180
160
140
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SPHYGMOMANOMETER
mmHg

Chapter 4

Intraoperative hypotension in daily clinical practice

Submitted as: Bijker JB, Houweling PL, Siccama I, van Klei WA, Kalkman CJ. Differences between self-reported definitions of intraoperative hypotension and actual treatment thresholds.

Abstract

Background: In the literature, many different definitions of intraoperative hypotension are used. It is however unknown whether these literature definitions also represent the definitions used by anesthesia team members in clinical practice. In the present study we investigated whether these theoretical definitions correspond with actual treatment thresholds for low blood pressure.

Methods: A questionnaire was used to elicit definitions of hypotension from anesthesia team members. Subsequently, a retrospective cohort study was used to study treatment thresholds for low blood pressure in patients undergoing knee arthroscopy under general or spinal anesthesia.

Results: The questionnaire yielded 33 definitions from 169 individuals. The most frequently reported definitions were a mean blood pressure below 60 mmHg, a systole below 80 mmHg or a decrease in either blood pressure more than 20–30%. Treatment thresholds in patients under general anesthesia agreed with self-reported absolute thresholds, but were allowed to decrease 37–40% from baseline. Treatment thresholds in patients under spinal anesthesia agreed with relative thresholds but this corresponded with a mean blood pressure of 75 mmHg or a systole of 100 mmHg.

Conclusions: Widely varying definitions of hypotension were elicited from anesthesia personnel. Nevertheless, in clinical practice, compliance with treatment strategies based on these theoretical definitions varied. In patients under general anesthesia, contrary to self-reporting, anesthesia team members preferably treated absolute thresholds, often allowing blood pressures to decrease up to 40% from baseline. In contrast, in patients under spinal anesthesia low blood pressures were treated at higher levels, with relative thresholds that better match self-reported definitions.

Many different definitions of intraoperative hypotension (IOH) can be found in the anesthesia literature.[1,2] Adverse outcomes reported to be possibly associated with IOH (*e.g.,* postoperative stroke, myocardial infarction or renal insufficiency) depend on the occurrence frequency of IOH, which in turn depends on the definition chosen from the literature.[1] However, it is unknown whether these literature definitions also represent the definitions as used by members of the anesthesia team in daily clinical practice. Obviously, the definition selected for use in daily practice not only has clinical relevance, but also medicolegal importance.[3]

As yet, no studies investigated whether the theoretical definitions of IOH correspond with actual treatment thresholds for intraoperative low blood pressure. In the present study we therefore investigated whether self-reported definitions of IOH from anesthesia personnel correspond with actual treatment thresholds for low blood pressure extracted from electronic anesthesia records. Furthermore, we hypothesized that low blood pressures would be treated differently in patients under general anesthesia than in patients under spinal anesthesia who are awake and can indicate low blood pressure by symptoms such as sweating, yawning or nausea. To these aims, we used a questionnaire to elicit the definitions of IOH that are used by anesthesia personnel. Subsequently, to determine treatment thresholds for low blood pressure in daily care, we conducted an observational cohort study among patients undergoing an arthroscopy of the knee under general or spinal anesthesia.

Materials and Methods

Study design

The present study included a questionnaire amongst anesthesia personnel to investigate the definitions of IOH as used in daily clinical practice. Subsequently, an observational retrospective cohort study was performed to compare the self-reported definitions to actual treatment thresholds for low blood pressure. The study protocol was approved by the hospital ethics committees of the two participating hospitals (the University Medical Center Utrecht and the Diakonessenhuis Utrecht). Since patients were not submitted to investigational actions and only routinely gathered data was used, the ethics committees waved the need for written informed consent.

Part 1: Questionnaire

A questionnaire was distributed amongst all anesthesiologists, anesthesia residents and anesthesia nurses from the University Medical Center Utrecht (UMCU), a 1,042 beds academic hospital, and the Diakonessenhuis Utrecht, a 559 beds general teaching hospital, both located in the city of Utrecht, the Netherlands. In the questionnaire, the respondents were asked to write down their definition of intraoperative hypotension. We also presented two hypothetical cases. The first case was a healthy patient, ASA physical status 1, undergoing an arthroscopy of the knee, and the second an older patient, ASA physical status 2, treated for hypertension, undergoing a laparoscopic cholecystectomy. For both, the treatment threshold for low blood pressure was asked. The translated questionnaire is presented in the Appendix.

Part 2: Cohort Study

Patients. All consecutive adult patients (aged 18 years or older) who underwent arthroscopy of the knee in either participating hospital in the period from January 1, 2000 to December 31, 2007 were included. Patients were included if a bolus of ephedrine (the first choice inotropic agent to treat intraoperative hypotension in both hospitals) was given. Exclusion criteria were the administration of any inotropic agent other than ephedrine.

Data collection. In both hospitals, preoperative data were collected from the outpatient preoperative evaluation clinics and intraoperative data were collected from the electronic anesthesia record-keeping systems. These systems recorded data from the anesthesia ventilator and monitor, such as ventilator settings, blood pressure, heart rate and oxygen saturation every minute (when available), as well as data that were entered manually during anesthesia, such as the administration of medications, time of intubation, and infusions. In general, noninvasive blood pressure was measured at least every 5 minutes. The blood pressure data were extracted from the record-keeping system using a dedicated program written in LabView (version 8; National Instruments Corporation, Austin, TX). For each patient this program retrieved a data array containing all blood pressure data from the record-keeping system. The baseline blood pressure was defined as the mean of the blood pressure reading at the outpatient preoperative evaluation clinic and all blood pressure readings in the operating room before induction of anesthesia. The time of induction of anesthesia was defined according to a previously described algorithm[1] as the moment of administration of induction medication or 3 minutes before the first appearance of continuous expired

carbon dioxide registration, whichever came first. In case of spinal anesthesia, the time of puncture was taken as the induction time.

Statistical analysis. For all patients from the cohort study who received a bolus of ephedrine to treat low blood pressure, the moment of first ephedrine administration was determined. Subsequently, the two blood pressure measurements preceding the moment of first administration of ephedrine were retrieved. The first was interpreted as the 'accepted' blood pressure, and the second reading was interpreted as the blood pressure that triggered administration of ephedrine. The treatment threshold was assumed to have been crossed between these two blood pressure measurements and was calculated as the mean of these two measurements. The distributions of the blood pressure data were tested on normality using the Lilliefors adaptation of the Kolmogorov-Smirnov test. The differences between the distributions of the treatment thresholds of the general and spinal anesthesia patients for absolute and relative, and systolic and mean blood pressure measurements were tested using Student's t-tests for normally distributed data or Mann-Whitney U tests for non-normally distributed data where appropriate.

All analyses were performed using R (release 2.13.1; R foundation for statistical computing, Vienna, Austria).

Results

Part 1: Questionnaire

In total, 186 questionnaires were handed out, of which 169 (91%) were returned. In the UMCU, 157 questionnaires were handed out amongst 46 anesthesiologists, 50 residents and 61 anesthetic nurses. The returns were 43 (93%), 47 (94%) and 54 (89%) respectively. In the Diakonessenhuis, 10 anesthesiologists returned 8 (80%) questionnaires and the 19 anesthesia nurses returned 17 (90%). The self-reported threshold values for intraoperative hypotension are presented in table 4.1.

The definitions most often reported were a mean arterial pressure (MAP) below 60 mmHg (38 times, 15%), a systolic blood pressure (SBP) below 80 mmHg (10 times, 4%) and a decrease in MAP or SBP of more than 20–30% from baseline (76 and 28 times, 30% and 11% respectively; table 4.1). The baseline blood pressure (when required) was based on the values measured at the outpatient preoperative evaluation clinic (n = 96, 57%), on measurements from the operating room before induction of anesthesia (n = 32, 19%), or both (n = 41, 24%). Most respondents did

Table 4.1 Self-reported definitions of intraoperative hypotension from the questionnaires

	Anesthesiologists		Anesthetic nurses		Residents	
Definition	UMCU (n = 71)	Diak (n = 17)	UMCU (n = 69)	Diak (n = 27)	UMCU (n = 71)	**Total** (n = 254)
SBP < 100 mmHg			3 (4)	3 (11)	1 (1)	7 (3)
SBP < 90 mmHg	3 (4)				1 (1)	4 (2)
SBP < 85 mmHg	1 (1)			1 (4)		2 (1)
SBP < 80 mmHg	4 (6)	2 (12)	2 (3)	2 (7)		10 (4)
SBP < 75 mmHg	2 (3)	1 (6)				3 (1)
SBP decrease > 20% from baseline	2 (3)	3 (18)		1 (4)	2 (3)	8 (3)
SBP decrease > 25% from baseline		1 (6)	1 (1)		6 (9)	8 (3)
SBP decrease > 30% from baseline	6 (9)		4 (6)		2 (3)	12 (5)
SBP decrease > 40% from baseline			1 (1)			1 (0)
SBP decrease > 30 mmHg from baseline	1 (1)		1 (1)		1 (1)	3 (1)
SBP decrease below the baseline DBP	1 (1)	1 (6)	3 (4)		4 (6)	9 (4)
MAP < 90 mmHg	1 (1)					1 (0)
MAP < 80 mmHg	1 (1)		1 (1)		1 (1)	3 (1)
MAP < 70 mmHg	1 (1)	1 (6)	2 (3)		2 (3)	6 (2)
MAP < 65 mmHg	1 (1)		1 (1)	1 (4)	3 (4)	6 (2)
MAP < 60 mmHg	9 (13)	3 (18)	11 (16)	5 (19)	10 (14)	38 (15)
MAP < 55 mmHg					1 (1)	1 (0)
MAP < 50 mmHg	3 (4)	2 (12)	2 (3)			7 (3)
MAP < 45 mmHg					1 (1)	1 (0)
MAP decrease > 10% from baseline			1 (1)		1 (1)	2 (1)
MAP decrease > 15% from baseline			1 (1)		1 (1)	2 (1)
MAP decrease > 20% from baseline	7 (10)	1 (6)	8 (12)	1 (4)	11 (16)	28 (11)
MAP decrease > 25% from baseline	6 (9)		3 (4)	1 (4)	11 (16)	21 (8)
MAP decrease > 30% from baseline	9 (13)		9 (13)	1 (4)	8 (11)	27 (11)
MAP decrease > 40% from baseline			1 (1)		1 (1)	2 (1)
MAP decrease > 10 mmHg from baseline				1 (4)		1 (0)
MAP decrease > 20 mmHg from baseline	1 (1)		1 (1)			2 (1)
MAP decrease > 30 mmHg from baseline				1 (4)		1 (0)
DBP < 70 mmHg				1 (4)		1 (0)
DBP < 60 mmHg			1 (1)	1 (4)		2 (1)
DBP < 40 mmHg		1 (6)				1 (0)
DBP decrease > 20% from baseline	1 (1)	1 (6)			3 (4)	5 (2)
DBP decrease > 30% from baseline	3 (4)					3 (1)
No definition	8 (11)		12 (17)	6 (22)		26 (10)

Values are number (%).

DBP = diastolic blood pressure; Diak = Diakonessenhuis Utrecht; MAP = mean arterial pressure; SBP = systolic blood pressure; UMCU = University Medical Center Utrecht.

not use the same definition for every patient (n = 125, 74%) but let it depend on age (n = 43) and/or comorbidity, *i.e.* a history of hypertension (n = 21), vascular disease (n = 23), cardiac disease (n = 18) or American Society of Anesthesiologists physical status in general (n = 46). Furthermore, most respondents also did not use the same definition for every surgical procedure (n = 100, 60%), *e.g.,* neurosurgery (n = 17), cardiac surgery (n = 12), carotid endarterectomy (n = 12) or ear, nose & throat procedures (n = 10).

The median of the reported treatment thresholds for hypothetical case one was 85 mmHg for the SBP (n = 61) and 65 mmHg for the MAP (n = 122). On average, the respondent allowed the blood pressure to drop 5 mmHg more than his self-reported definition. This corresponded with a decrease of 35% from both the systolic and mean baseline blood pressure according to the respondents own reported definition. For hypothetical case two, the median reported treatment threshold was 120 mmHg for the systolic blood pressure (n = 67) and 90 mmHg for the mean blood pressure (n = 118). This corresponded with a decrease of 30% from both the systolic and mean baseline blood pressure according to the respondents own reported definition.

On average, IOH was reported to be acceptable for 5 minutes (median 5 minutes, interquartile range 3–5 minutes). For 106 respondents (63%) the threshold for IOH from their self-reported definition was not the same as their treatment threshold. Furthermore, 95% of the respondents (n = 160) reported not to enter the threshold value for IOH as an alarm limit in the anesthesia monitor. On average, the respondents estimated the incidence of IOH to be 46% (median 48%, interquartile range = 30–61) and 59% (n = 98) of the respondents did not consider it necessary to always treat IOH. The majority of respondents believed that IOH could lead to perioperative complications (sometimes, n = 152, 91%; often, n = 8, 5%). Most reported potential complications were cerebral infarction (n = 108), acute coronary syndrome (n = 85), acute tubular necrosis (n = 59), postoperative cognitive decline (n = 33), increased risk of re-bleed (n = 9) and postoperative nausea and vomiting (n = 8).

Part 2: Cohort study

In total 7,149 patients underwent an arthroscopy of the knee, of which 910 met the inclusion criteria. A larger proportion of patients who underwent surgery in the UMCU (n = 119) received general anesthesia, whereas patients who underwent surgery in the Diakonessenhuis (n = 791) more often received spinal anesthesia (table 4.2). Furthermore, the patients under general anesthesia were in general slightly older, more often female and had a higher ASA physical status. The length of surgery did not differ between general and spinal anesthesia (table 4.2).

Table 4.2 Characteristics of the cohort (n = 910)

Variable	General anesthesia (n = 113)	Spinal anesthesia (n = 797)	*P* value*
Median age (IQ range), yr	52 (42–60)	48 (35–58)	< 0.01[a]
Male gender	52 (46)	474 (59)	< 0.01[b]
Hospital			
UMCU	35 (31)	84 (11)	< 0.01[b]
Diakonessenhuis	78 (69)	713 (89)	
ASA physical status			
1	70 (62)	601 (75)	< 0.01[c]
2	39 (35)	162 (20)	
3 & 4	2 (2)	8 (1)	
Unknown	2 (2)	26 (3)	
Duration of surgery in min. (IQ range)	71 (54–96)	72 (60–86)	0.64[a]

Values are number (%) unless indicated otherwise.

* *P* values were derived with *a*: Mann-Whitney U test for non-normally distributed continuous variables; *b*: Chi-squared test for categorical variables; *c*: Fisher's Exact test for categorical variables with less than 10 observations per category.

ASA = American Society of Anesthesiologists; IQ = interquartile; UMCU = University Medical Center Utrecht.

Since blood pressure data were not normally distributed we compared median values. The median of the MAP values at which low blood pressure was treated for patients under general anesthesia was 61 mmHg (interquartile range: 51–71 mmHg). For awake patients under spinal anesthesia the actual treatment threshold was 74 mmHg (interquartile range: 65–85 mmHg). When blood pressures were interpreted relative to a baseline value, MAP decreased by 37% (interquartile range: 26–72%) before initiation of treatment in patients under general anesthesia, whereas for those under spinal anesthesia MAP decreased by 30% (interquartile range: 16–75%) until it was treated. For systolic blood pressures these values were: an absolute treatment threshold of 82 mmHg (interquartile range: 71–100 mmHg) for patients receiving general anesthesia and 103 mmHg (interquartile range: 91–117 mmHg) for patients receiving spinal anesthesia. The relative systolic blood pressure thresholds were a decrease of 40% (interquartile range: 26–49%) from baseline for the patients receiving general anesthesia, and a decrease of 27% (interquartile range: 15–38%) from baseline for the patients receiving spinal anesthesia. Histograms of the treatment thresholds for low mean and systolic blood pressures are presented in figures 4.1 and 4.2 respectively. Indicated in grey are the ranges of threshold values that were reported as definitions of IOH in the questionnaire. All differences between the above-mentioned thresholds for general and spinal anesthesia patients were statistically significant ($P < 0.05$).

Discussion

Anesthesiologists, anesthesia residents and anesthetic nurses report a wide variety of definitions of IOH. The most often reported definition of IOH was a decrease in MAP below 60 mmHg or a decrease in MAP of more than 20–30% from baseline values. Often, the reported definition of IOH also depended on patient comorbidity or the type of surgery. This was illustrated by the two hypothetical cases, which yielded different treatment thresholds depending on patient comorbidity (young ASA 1 patient versus older ASA 2 patient with chronic hypertension). Furthermore, the theoretical definitions differed from treatment thresholds in daily clinical practice. When actual patient data were observed, mean blood pressures in patients under general anesthesia were indeed treated at a threshold of 60 mmHg, but this corresponded to an average decrease of 37% from baseline blood pressure. In contrast, in patients undergoing the same procedure under spinal anesthesia, low blood pressure was treated at a mean arterial pressure of 74 mmHg, which is significantly higher than for patients under general anesthesia. This corresponded with a decrease of 30% from baseline, which better matched the self-reported definitions.

This may imply that under general anesthesia, when the decision to treat low blood pressure is solely at the discretion of the attending anesthesia team member, there is a tendency to treat low blood pressures according to an absolute threshold (corresponding accurately with the observed treatment MAP threshold of approximately 60 mmHg or 80 mmHg for systolic blood pressure), instead of the frequently self-reported relative thresholds. This seems to be supported by the finding that 95% of the respondents to the questionnaire reported not to enter the IOH threshold value into the anesthesia monitor as an alarm threshold. However, when patients under spinal anesthesia are observed, where the decision to treat low blood pressure is also prompted by the patient's possible hypotensive symptoms (*e.g.*, dizziness, nausea or vomiting, transpiration, pallor), blood pressures were treated in general at higher absolute thresholds. These higher treatment thresholds corresponded with the definitions of IOH that use a threshold relative to a baseline. Similar results could be found in some older studies where healthy awake volunteers were subjected to a controlled hypotension test up to the point where they showed signs of cerebral circulatory insufficiency (dizziness, nausea, yawning, involuntary body movements or fainting). Blood pressures could be reduced to up to 55% before signs of cerebral ischemia developed.[4,5] It is tempting to conclude that avoidance of hypotension as indicated by patient symptoms is a positive incentive to prevent hypotension when

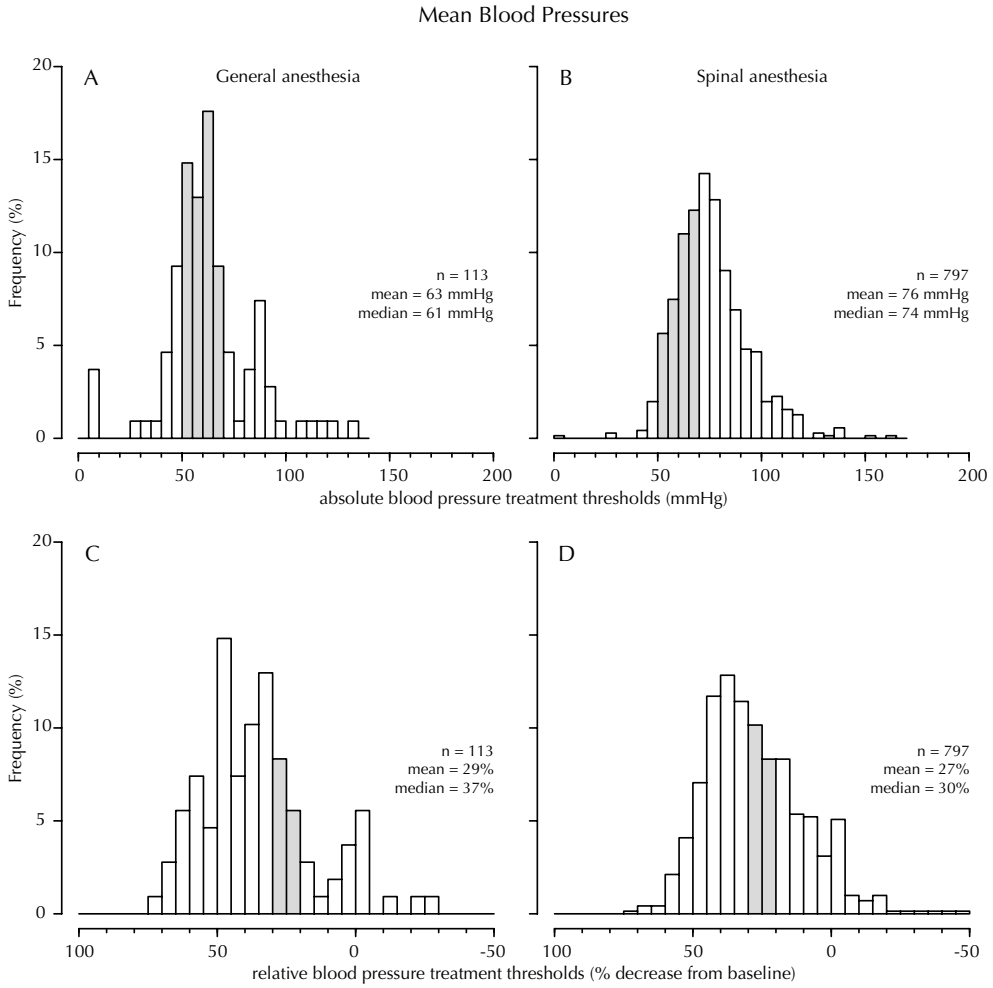

Figure 4.1 Histograms of the mean blood pressure treatment thresholds for both *absolute* thresholds (A and B) and thresholds *relative* to a baseline blood pressure (C and D), and for patients under *general* anesthesia (A and C) and patients under *spinal* anesthesia (B and D). In *grey* is the range of thresholds covering the most frequently reported definitions by the respondents of the questionnaire.

spinal anesthesia is used, whereas during general anesthesia there is no such feedback on the adequacy of the cerebral circulation. However, it seems reasonable to assume that reduced cerebral oxygen consumption under general anesthesia allows for the acceptance of lower blood pressures.

The wide variety of definitions of IOH was demonstrated earlier in searches of the

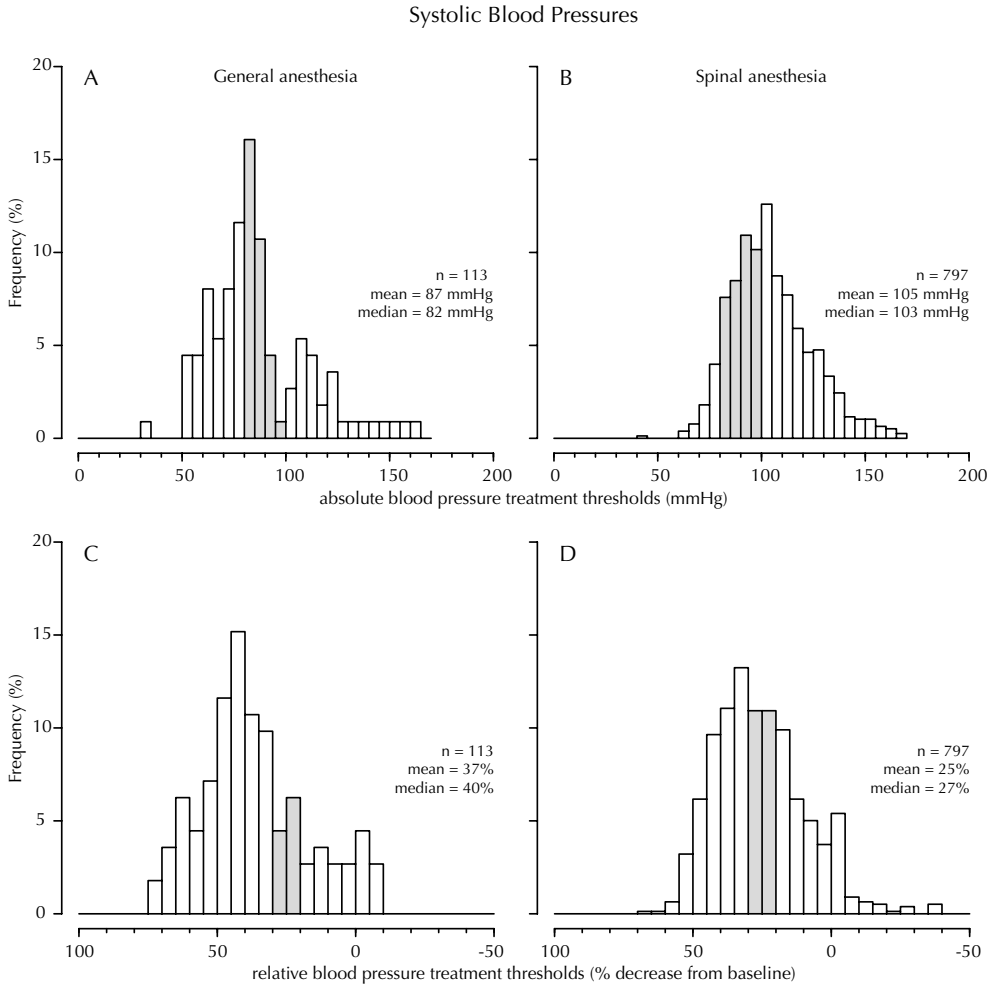

Figure 4.2 Histograms of the systolic blood pressure treatment thresholds for both *absolute* thresholds (A and B) and thresholds *relative* to a baseline blood pressure (C and D), and for patients under *general* anesthesia (A and C) and patients under *spinal* anesthesia (B and D). In *grey* is the range of thresholds covering the most frequently reported definitions by the respondents of the questionnaire.

anesthesia literature.[1,2] These revealed a systolic blood pressure below 80–100 mmHg and/or a decrease of more than 20–30% from baseline as the most frequently used definitions of IOH. Mean arterial pressure thresholds were less frequently mentioned but consisted mostly of a MAP below 60 mmHg and/or a decrease of more than 20–30% from baseline. These thresholds are consistent with the self-reported definitions

from the present study. However, the present study reveals that MAP thresholds are reported more frequently than systolic thresholds, contrary to earlier findings from the literature reviews where definitions containing systolic thresholds were more common.

The anesthesia literature on the discrepancy between theory and clinical practice of intraoperative blood pressure management is limited mainly to studies on voluntary reporting of critical incidents and the reliability of blood pressure automatically recorded into anesthesia information management systems versus manual recording.[6–9] These studies all conclude that self-reported information is less reliable than automatically generated data. Recently, Franck *et al.* reported that literature-definitions (*i.e.* the three most frequently reported definitions from a literature search performed earlier[1]) do not correlate well with the application of antihypotensive medication by anesthesiologists.[10] In this study the lowest systolic blood pressure measurement during surgery was compared with definitions of IOH. However, the lowest intraoperative blood pressure measurements may not necessarily reflect the actual trigger to treat low blood pressure. When hypotension does not readily respond to vasopressors and/or fluid administration, for example during sudden massive blood loss, the blood pressure will decrease further and no longer matches the used definition of IOH. Furthermore, Franck *et al.* used written anesthesia records, which are known to be less reliable for research purposes.[9] In another study that investigated anesthesia-related mortality, 39% of the mortality cases that were attributable to deviations from standard intraoperative care were due to inadequate management of hypotension.[11] A recent study among surgical teams revealed that units do not always follow their own recommendations.[12] They rightly ask whether this phenomenon can be universal to all medical literature. The present study suggests that this can also be observed in anesthesia teams not complying with their own definitions of IOH.

Some limitations of the study need to be addressed. First, the exact threshold that triggered an attending anesthesia team member to treat low blood pressure could obviously not be derived from the automated anesthesia record. We therefore observed the two blood pressure measurements preceding the first administration of ephedrine. We chose not only to use the blood pressure immediately preceding the ephedrine administration because this value triggering an action could be too low, but we also observed the measurement preceding the 'triggering' value, *i.e.* the last accepted value and took the average of those as a proxy for the blood pressure value that triggered initiation of treatment. We chose only to observe the blood pressures preceding the first ephedrine administration because repeated dosages could indicate

a nonresponse to the selected vasopressor drug by which the blood pressure could decrease further, thus falsely lowering the subsequently observed treatment threshold. Furthermore, we tried to rule out any other treatments of low blood pressure other than the administration of ephedrine, but nonpharmacological treatments such as rapid administration of fluids or decreasing the anesthetic concentration could not reliably be extracted from our retrospective database. This might have caused an underestimation of the treatment threshold when ephedrine would have been chosen after administration of fluids or lowering the anesthetic concentration. Nevertheless, the experience in both participating hospitals is that ephedrine administration is most often used as a first line treatment for IOH rather than a treatment of last resort. If necessary, ephedrine is combined with fluid administration or decreasing the anesthetic concentration. Another aspect to be taken into account is the difference between the characteristics of the patients undergoing general and spinal anesthesia. Patients who underwent an arthroscopy of the knee under general anesthesia were in general slightly older, more often female and had a higher ASA physical status than patients who underwent the same procedure under spinal anesthesia. However, based on the findings from the hypothetical cases from the questionnaire, it would be expected that in these patients the blood pressure was allowed to drop less than in the spinal anesthesia patients. It can therefore not explain the opposite finding that the blood pressures from the general anesthesia patients were treated at lower thresholds than the spinal anesthesia patients.

Even though this was an explorative study with an observational design, the results may have important clinical implications. They reveal that when the treatment of blood pressure is left at the discretion of the anesthesia team alone, the blood pressure will often decrease below the self-reported thresholds for treatment of hypotension. In contrast, when the decision to treat low blood pressure in awake patients under spinal anesthesia is possibly also prompted by patient symptoms, blood pressures are treated at higher thresholds that show better consistency with definitions of intraoperative hypotension using thresholds relative to a baseline blood pressure. This could indicate that based on patient symptoms it might be recommendable to adhere to these most frequently reported definitions and to prevent the blood pressure to decrease more than 20–30% from baseline.

Appendix

1. You are
   - ☐ Anesthesiologist
   - ☐ Resident in anesthesiology
   - ☐ Registered nurse anaesthetist

2. What is your definition of intraoperative hypotension (or the definition that you use the most)?

_____

3. Do you observe the systolic, diastolic or mean blood pressure?
   - ☐ Systolic
   - ☐ Diastolic
   - ☐ Mean

4. What baseline blood pressure do you use?
   - ☐ Blood pressure from the outpatient evaluation clinic
   - ☐ First blood pressure in the operating room
   - ☐ Different: _____

5. Do you use the same definition of intraoperative hypotension in all patients?
   - ☐ Yes
   - ☐ No, because: _____

6. Do you use the same definition of intraoperative hypotension in all types of surgery?
   - ☐ Yes
   - ☐ No, because: _____

7. How long do you accept intraoperative hypotension (according to your definition)?
   _____ minutes

8. Is the threshold from your definition also the threshold to initiate a treatment?
   - ☐ Yes
   - ☐ No, because: _____

9. Do you enter your threshold as an alarm setting on the anaesthesia machine?
   - ☐ Yes
   - ☐ No

10. How high do you think is the percentage of patients in daily anesthesiological practice that experience intraoperative hypotension?
   _____ %

11. Do you think that intraoperative hypotension should always be treated?

☐ Yes
☐ No, because: _____

12. Does intraoperative hypotension, in your opinion, lead to complications?

☐ No ☐ Often
☐ Sometimes ☐ Always

13. What complications?

14. Did you ever observe this?

☐ Yes, namely: _____
☐ No

15. Case 1: A 40 year old healthy patient, ASA physical status I, is presented for an arthroscopy of the knee. His first blood pressure in the OR is 165/90 (115) mmHg (blood pressure on the outpatient preoperative evaluation clinic is 125/80 (95 mmHg)

What is your threshold (mmHg) to diagnose intraoperative hypotension in this patient?

_____ mmHg or lower

What blood pressure would you observe?

☐ Systolic
☐ Diastolic
☐ Mean

Is this threshold the same as your treatment threshold?

☐ Yes
☐ No, because: _____

16. Case 2: A 65 year old patient, ASA physical status II, using a β blocker for hypertension, is presented for a laparoscopic cholecystectomy and has a first blood pressure in the operating room of 190/100 (130) mmHg (blood pressure on the outpatient preoperative evaluation clinic is 170/95 (120) mmHg)

What is your threshold (mmHg) to diagnose intraoperative hypotension in this patient?

_____ mmHg or lower

What blood pressure did you observe?

☐ Systolic
☐ Diastolic
☐ Mean

Is this threshold the same as your treatment threshold?

☐ Yes
☐ No, because: _____

Do you have any comments or questions?

_____

Thank you very much for your cooperation!

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Part II

The Effect of Intraoperative Hypotension on Postoperative Outcomes

180
160
140
120
100
80
60
40
20
HYGMOMANOMETER
mmHg

Chapter 5

Intraoperative hypotension and postoperative stroke

Submitted as: Bijker JB, Persoon S, Peelen LM, Moons KGM, Kalkman CJ, Kappelle LJ, van Klei WA. Intraoperative hypotension and postoperative ischemic stroke after general surgery: A nested case-control study.

Abstract

Background: Postoperative stroke is a rare but major complication after surgery. The most often proposed mechanism is an embolus originating from the heart or great vessels. The role of intraoperative hypotension in the occurrence and evolution of postoperative stroke is largely unknown.

Methods: A case-control study was conducted amongst 48,241 patients who underwent noncardiac and nonneurosurgical procedures in the period from January 2002 to June 2009. A total of 42 stroke cases (0.09%) were matched on age and type of surgery to 252 control patients. Conditional logistic regression analysis was used to estimate the effect of the duration of intraoperative hypotension (defined according to a range of blood pressure thresholds) on the occurrence of an ischemic stroke within 10 days after surgery, adjusted for potential confounding factors.

Results: After correction for potential confounders and multiple testing, the duration that the mean blood pressure was decreased > 30% from baseline remained statistically significantly associated with the occurrence of a postoperative stroke.

Conclusions: Intraoperative hypotension might play a role in the development of postoperative ischemic stroke. Especially for mean blood pressure values decreasing > 30% from baseline blood pressure, an association with postoperative ischemic stroke risks was observed.

Stroke is a rare but serious postoperative complication. Depending on the type and complexity of surgery, an ischemic stroke occurs in 0.1–3% of patients undergoing general surgery, and to even 10% after complex cardiac surgery.[1-3] Embolism is often considered the primary cause of a postoperative ischemic stroke. It may be related to postoperative atrial fibrillation or surgery induced hypercoagulability in combination with vulnerable plaques in carotid or major cerebral arteries.[1] Hypoperfusion, defined as any combination of extracranial stenosis and/or systemic hypotension, is reported to be responsible for only 9% of all postoperative strokes in cardiac surgery patients.[4] In other types of surgery, no association between intraoperative hypotension (IOH) and postoperative stroke has been found.[5-7] However, the recent results of the POISE-trial (which investigated the effect of metoprolol versus placebo on cardiovascular events in 8,351 noncardiac surgery patients) have renewed interest in hypotension as a possible cause for the increase in postoperative stroke.[8] Hypotension may result in low flow or so-called watershed infarcts, but this type of stroke occurs only sporadically during surgery.[9-11] Still, it is likely that the mechanism of a postoperative stroke is multifactorial and that even in embolic strokes IOH might aggravate the clinical course by increasing the size of the infarcted area.[12]

In the present study we therefore explore the hypothesis that the duration of IOH is associated with the occurrence of a postoperative ischemic stroke and that this association depends on the chosen definition of IOH. To this aim, we conducted a case-control study in a large cohort of patients using a range of frequently used definitions of IOH.

Materials and Methods

Study design

The present study was designed as a case-control study nested in a large retrospective cohort of patients undergoing anesthesia for noncardiac and nonneurosurgical procedures. The local hospital ethics committee approved the study protocol. Since patients were not subjected to investigational actions and all patients were treated with care as usual, no written informed consent was necessary.

Study population

All consecutive patients who underwent anesthesia for inpatient surgical procedures at the University Medical Center Utrecht (a 1,042 bed academic hospital) in the period

from January 1, 2002 to June 30, 2009 were included. Patients undergoing cardiac or neurosurgical procedures were excluded.

Data collection

Preoperative patient data were collected from preoperative evaluation clinic electronic patient records. These consisted of both biometric data (*e.g.*, age, gender, weight, preoperative blood pressure, etc.) and medical history. Intraoperative data from the patient monitor and anesthesia machine (*e.g.,* blood pressure, heart rate etc.) were stored every minute in an electronic anesthesia record-keeping system. Postoperative data were collected from the hospital information system and patient charts. An investigator blinded to the status of the patients (case or control) collected all patient data.

Intraoperative hypotension

IOH was defined according to a range of threshold values designated *a priori*. These blood pressure thresholds, both absolute (in mmHg) as well as relative to a baseline (in % decrease from baseline), were based on the most frequently used definitions from the anesthesia literature.[13] The selected range of blood pressure thresholds consisted of a systolic blood pressure below 100, 90, 80 and 70 mmHg, a mean blood pressure below 70, 60, 50 and 40 mmHg and a decrease in systolic or mean blood pressure of 10%, 20%, 30% and 40% from baseline. The continuous IOH variable was expressed as the number of minutes that the blood pressure was below the designated threshold.

The baseline blood pressure was defined as the mean of the blood pressures measured at the preoperative evaluation clinic (measured in the sitting position on either arm) and all available blood pressure measurements in the operating room before induction of anesthesia. The time of induction of anesthesia was estimated using a previously published algorithm implemented with LabView software (version 8; National Instruments Corporation, Austin, TX) and defined as either the moment of administration of induction medication or 3 minutes before the first appearance of continuous expired carbon dioxide registration, whichever came first.[13] In case of spinal or epidural anesthesia, the time of puncture was taken as the time of induction.

Cases

Cases were patients with an ischemic stroke, defined as the acute onset of new focal neurological deficit of cerebral origin persisting more than 24 hours without hemorrhage on CT, within 10 postoperative days. Potential stroke cases were therefore selected

Table 5.1 Characteristics of the stroke cases (n = 42)

	n (%)
Stroke characteristics	
Clinical diagnosis with normal CT findings	10 (23.8)
Symptomatic infarct on CT	32 (76.2)
Cortical infarct	
MCA	18 (42.9)
PCA	1 (2.4)
ACA	1 (2.4)
both MCA and PCA	1 (2.4)
Subcortical infarct	
MCA	4 (9.5)
Watershed infarct	
MCA/PCA	3 (7.1)
ACA/MCA	4 (9.5)
Outcomes	
Minor symptoms, no limitations	3 (7.1)
Some restrictions, no help needed	10 (23.8)
Help needed, still independent	9 (21.4)
Dependent, no constant attention required	5 (11.9)
Completely dependent	1 (2.4)
Dead	11 (26.2)
Unknown	3 (7.1)

Values are number of patients (%).

ACA = anterior cerebral artery; MCA = middle cerebral artery;

PCA = posterior cerebral artery.

as all patients in whom a CT scan of the brain was performed within 10 days after surgery. The diagnosis of ischemic stroke was made by chart review and all CT scans were re-observed by two neurologists (S.P. and L.J.K.), blinded for the intraoperative course. Diagnoses made on clinical grounds, *i.e.* without CT abnormalities, were also included as cases. The condition of the stroke patients at discharge from the hospital was scored on the modified Rankin Scale.[14]

Controls

For every patient with a postoperative stroke, six control patients were selected who underwent surgery in the same period (as close as possible to the date of surgery of

Table 5.2 Characteristics of the cases and controls (n = 294)

Variable	Stroke patients (n = 42)	Control patients (n = 252)	*P* value*
Median Age (IQ range)†	65.7 (57.2 – 75.5)	66.4 (57.5 – 75.7)	0.94[a]
Male gender	25 (59.5)	151 (59.9)	0.96[b]
ASA physical status			
1 & 2	19 (45.2)	180 (71.4)	< 0.01[b]
3 & 4	23 (54.8)	72 (28.6)	
History of			
Diabetes	11 (26.2)	41 (16.3)	0.12[b]
Atrial fibrillation	5 (11.9)	16 (6.3)	0.20[c]
Previous stroke	20 (47.6)	93 (36.9)	0.19[b]
Smoking	16 (38.1)	65 (25.8)	0.10[b]
Hypertension	33 (78.6)	171 (67.9)	0.21[c]
Antihypertensive medication‡			
Beta-blocker	18 (54.5)	87 (50.9)	0.70[b]
metoprolol	5 (27.8)**	48 (55.2)	
atenolol	5 (27.8)	16 (18.4)	
bisoprolol	1 (5.6)	18 (20.7)	
sotalol	4 (22.2)	0 (0)	
carvedilol	2 (11.1)	2 (2.3)	
labetalol	1 (5.6)	1 (1.1)	
propranolol	0 (0)	1 (1.1)	
pindolol	0 (0)	1 (1.1)	
ACE inhibitor	16 (48.5)	76 (44.4)	0.67[b]
Calcium antagonist	9 (27.3)	40 (23.4)	0.66[c]
Diuretics	10 (30.3)	67 (39.2)	0.34[b]
Type of surgery†			
General	13 (31.0)	78 (31.0)	NA§
Peripheral vascular	1 (2.4)	6 (2.4)	
Resection of head and neck tumors	6 (14.3)	36 (14.3)	
CEA	20 (47.6)	120 (47.6)	
Aortic repair	2 (4.8)	12 (4.8)	
Duration of surgery (IQ range)	168 (145 – 270)	162 (127 – 226)	0.21[a]
Type of anesthesia			
General or spinal	26 (61.9)	144 (57.1)	0.56[c]
Combined	16 (38.1)	108 (42.9)	

Values are number of patients (%) unless indicated otherwise.

* *P* values were derived with *a*: Mann-Whitney U test for non-normally distributed continuous variables; *b*: Pearson's Chi-squared test for categorical variables; c: Fisher's Exact test for categorical variables with less than 10 observations per category. † Cases and controls were matched on age and type of surgery. ‡ Percentages and *P* values are for the hypertensive patients. § Statistical testing was omitted since cases and controls were matched on this variable. ** Percentages for the beta-blocker types are relative to the beta-blocker group.

ASA = American Society of Anesthesiologists; CEA = carotid endarterectomy; IQ = interquartile; NA = not applicable.

the case) but who did not experience a postoperative stroke. A ratio of around 1:5 is known to yield the best results taking into account the effort to collect information of the controls.[15] Since most data was stored electronically and was relatively easy to collect, we chose a ratio of 1:6. Cases and controls were matched on age and type of surgery. For age we used frequency matching using age groups covering a decade (the control had to have the age of the case plus or minus 5 years). When no control with an identical type of surgery was available, a patient who underwent the most similar procedure was selected.

Potential confounders

Variables potentially confounding the association between the duration of IOH and postoperative stroke were predefined based on existing knowledge and the literature, and included: age, gender, comorbidity, antihypertensive medication, type and duration of surgery and type of anesthesia.[1-3,16,17] Comorbidity was included both as the ASA class and as a history of diabetes, atrial fibrillation, previous stroke or hypertension. Type of surgery was categorized into risk groups according to previous studies into: general surgery, peripheral vascular surgery, resection of head and neck tumors, carotid endarterectomy (CEA) and aortic repair.[1]

Statistical analysis

Differences in patient characteristics and potential confounders between the cases and controls were compared using the Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for continuous variables that were not normally distributed. Categorical variables were compared with the Pearson's Chi-squared test or the Fisher Exact test where appropriate.

Conditional logistic regression analysis was used to estimate univariate associations between the duration of IOH and postoperative stroke for the different definitions. Subsequently we adjusted for the above-defined potential confounders except for type of surgery since cases and controls were matched on this variable. Age was adjusted for since we used frequency matching using 10-year intervals.

Because a range of blood pressure thresholds was used for subsequent models, correction for multiple testing was deemed necessary. In the conditional logistic regression analyses we therefore tested against a P value of 0.001 and used 99.9% confidence intervals.[18]

All analyses were performed using R (release 2.13.1; R Foundation for Statistical Computing, Vienna, Austria).

Table 5.3 Adjusted odds ratios (per minute hypotension) for the association between the duration of intraoperative hypotension and postoperative stroke

IOH thresholds	Adjusted* OR† (99.9% CI)	*P* value
absolute systolic blood pressure thresholds in mmHg		
< 100	1.005 (0.993–1.016)	0.205
< 90	1.006 (0.991–1.022)	0.182
< 80	1.007 (0.981–1.034)	0.368
< 70	1.002 (0.952–1.051)	0.918
relative systolic blood pressure thresholds in % decrease from baseline		
> 10	1.010 (0.997–1.023)	0.010
> 20	1.010 (0.999–1.022)	0.003
> 30	1.010 (0.999–1.022)	0.003
> 40	1.011 (0.996–1.025)	0.020
absolute mean blood pressure thresholds in mmHg		
< 70	1.003 (0.993–1.014)	0.296
< 60	1.003 (0.988–1.019)	0.468
< 50	1.004 (0.962–1.046)	0.755
< 40	1.013 (0.939–1.088)	0.563
relative mean blood pressure thresholds in % decrease from baseline		
> 10	1.004 (0.991–1.016)	0.365
> 20	1.008 (0.996–1.021)	0.028
> 30	1.013 (1.000–1.025)	< 0.001‡
> 40	1.015 (0.999–1.031)	0.003

* Adjusted for ASA physical status, duration of surgery and history of diabetes, atrial fibrillation, previous stroke and smoking. † OR's are per minute intraoperative hypotension. ‡ Considered statistically significant when multiple testing is taken into account. ASA = American Society of Anesthesiologists; CI = confidence interval; MED = minimal episode duration; OR = odds ratio.

Results

During the study period, 48,241 patients underwent a noncardiac, nonneurosurgical procedure. The median duration between preoperative evaluation and surgery was 26 days. In 53 patients, the CT report was suspicious of a stroke. After reviewing the hospital charts and original CT scans, 42 patients (0.09%) were identified as definitive stroke cases. Of these, 32 were diagnosed based on CT abnormalities (26 on initial CT scan and 6 on delayed CT scan) and 10 were diagnosed based on clinical signs without CT abnormalities. The 11 excluded patients were diagnosed with hyperperfusion syndrome after CEA (n = 7), postanoxic encephalopathy secondary to a cardiac arrest

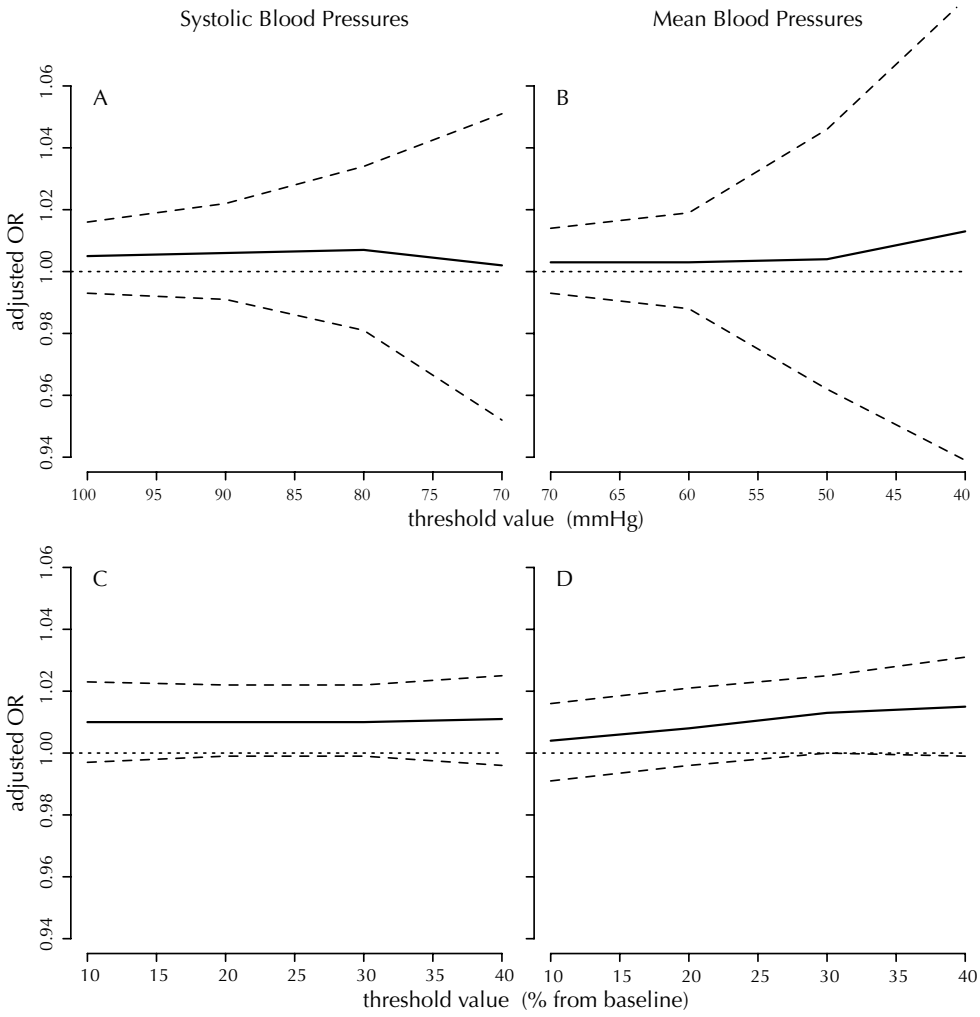

Figure 5.1 Adjusted odds ratios for the associations between duration of intraoperative hypotension, defined by *absolute* (A and B) and *relative* (C and D) thresholds for *systolic* (A and C) and *mean* (B and D) blood pressures, and postoperative stroke. The *dashed* lines represent the 99.9% confidence intervals. The horizontal *dotted* lines represent the level of no effect (odds ratio = 1).
OR = odds ratio.

1 day after CEA (n = 1), epileptic insult (n = 1) and an anterior spinal cord syndrome after aortic surgery (n = 1). During the study period, a temporal trend in the occurrence of postoperative strokes could not be observed. The characteristics of the cases with postoperative ischemic stroke are presented in table 5.1.

Subsequently, 252 control patients were selected. One stroke case underwent surgery of the brachiocephalic artery. This patient could be matched to only one patient with an identical procedure. The other five controls were matched using CEA patients. Similarly, two stroke cases that underwent surgery of the subclavian artery could not be matched to patients who underwent identical procedures. Again, CEA patients were used for matching. All these cases and their matched controls were analyzed as CEA patients. The median difference between the surgery date of the case and control was 20 months (interquartile range 9–36 months).

The characteristics of the stroke and control patients are presented in table 5.2. None of the crude associations between duration of IOH and postoperative stroke reached statistical significance (data not shown). After accounting for confounding and multiple testing, the duration that the mean blood pressure was decreased more than 30% from baseline was associated with the occurrence of a postoperative stroke (odds ratio = 1.013/minute hypotension, 99.9% confidence interval = 1.000–1.025; table 5.3). None of the associations for the other IOH threshold values reached statistical significance at the 0.001 level. The adjusted odds ratios are illustrated in figure 5.1, where the 99.9% confidence intervals for the thresholds relative to a baseline blood pressure (panels C and D) are much narrower than those for the absolute blood pressure thresholds (panels A and B).

Posthoc sensitivity analyses revealed no effect from type of surgery (data not shown), but the odds ratios for decreasing mean blood pressures relative to a baseline appeared larger (not statistically significant) in the 22 patients (52%) whose stroke occurred within 24 hours after surgery (figure 5.2). This effect could not be observed for other thresholds.

Discussion

In this explorative case-control study we investigated the possible association of intraoperative hypotension and the occurrence of a postoperative ischemic stroke within 10 days after general surgery. The observed stroke rate was 0.09%. After correction for potential confounding and multiple testing, the duration that the mean blood pressure was decreased > 30% from baseline blood pressure remained statistically significantly associated with the occurrence of an ischemic stroke.

Some limitations of the study need to be discussed. First, in the CEA patients, no routine preoperative ultrasound examination of the cerebropetal arteries was

performed. Occlusion of the contralateral internal carotid artery is associated with an increased risk of postoperative stroke.[19] However, as it is unlikely that preoperative contralateral carotid occlusion is associated with IOH, we do not believe this has significantly influenced the relation between IOH and postoperative stroke.

Furthermore, the period in which a stroke is considered a perioperative stroke varies between 3 and 30 postoperative days.[3] We chose a period of 10 postoperative days to find a compromise between finding too few cases when using a very short

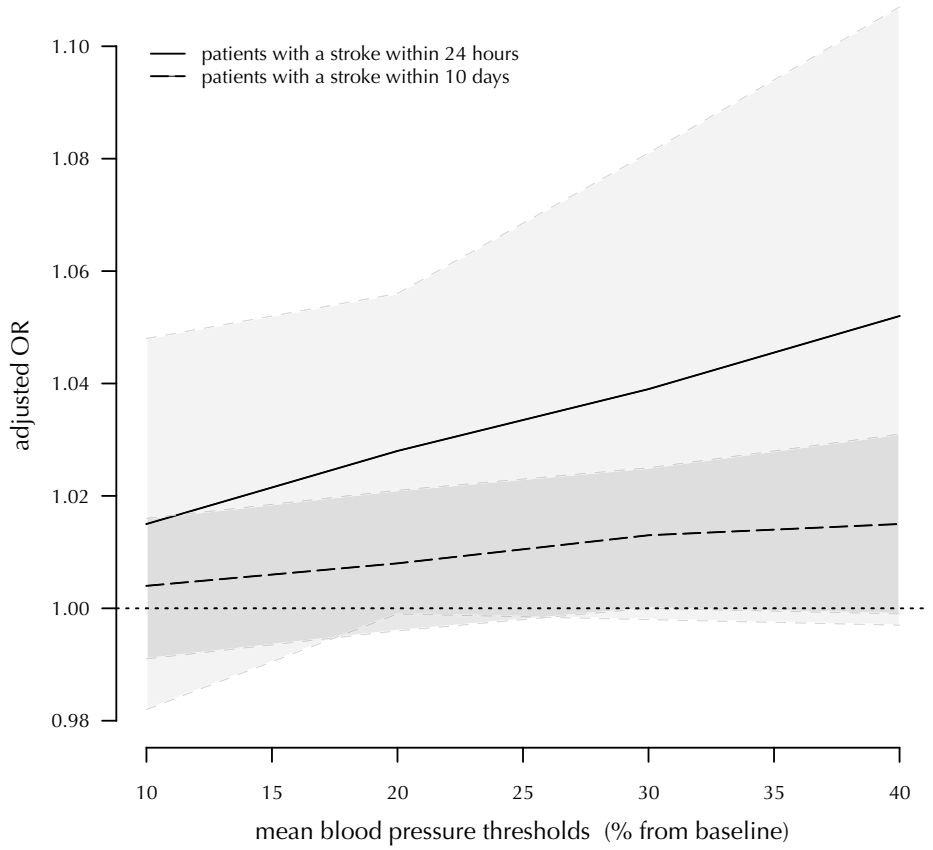

Figure 5.2 Adjusted odds ratios for the associations between duration of intraoperative hypotension and postoperative stroke for cases within 24 hours (n = 22) and 10 days (n = 42) after surgery. The *dashed* lines and *grey* shaded areas represent the 99.9% confidence intervals. The horizontal *dotted* line represents the level of no effect (odds ratio = 1).

OR = odds ratio.

period and a questionable association with postoperative events when using a very long period. To investigate the influence of IOH on the occurrence of stroke early after surgery, a posthoc sensitivity analysis with stroke cases within 24 hours after surgery was performed.

Moreover, as with IOH, it is likely that postoperative hypotension plays a comparable role. Postoperative hypotension might be even more important than hypotension in the highly monitored and controlled intraoperative and early postoperative period, especially since a postoperative stroke most commonly occurs after an asymptomatic interval.[5]

Possibly, IOH predicts postoperative hemodynamic instability. However, postoperative blood pressures were measured at highly variable intervals, ranging from continuous or at least hourly at the intensive care unit to once or twice per shift on the ward. Therefore, when no hypotensive measurements were found in the patient charts, this by no means could imply that indeed no postoperative hypotension had occurred. On the contrary, if a low blood pressure reading was found in the patient chart, this contained no information on the length or severity of the hypotensive episode. Thus, we regarded the postoperative blood pressure data from the patient charts to be too unreliable and did not use them in the analyses to prevent significant bias.

In theory, it could also be possible that IOH is a consequence and not the cause of a postoperative stroke. However, it is more common for the blood pressure to increase after a stroke. Furthermore, IOH could only have been preceded by a stroke when the stroke occurred during surgery, which is very rare. Therefore, we feel this is an unlikely explanation for the possible association between IOH and postoperative stroke.

In the present study, only 42 stroke cases were found. Since this was an observational, hypothesis-generating study, we used all stroke cases that we could find and did not perform *a priori* sample-size calculations. These stroke cases were matched to controls on age and type of surgery. The control was then chosen so that the date of surgery was as close to the case as possible. Still, the median time between the surgery of the case and control was 20 months (interquartile range: 9–36 months). Nevertheless, since no temporal trend in the occurrence of postoperative strokes was observed, it is not likely that this has largely influenced our findings.

Another factor to be taken into account is the need to correct for multiple testing because of the range of IOH definitions that were used. As the different definitions of IOH are correlated, traditional methods such as the Bonferroni correction are likely to be too conservative. Therefore we chose to consider a P value smaller than 0.001

to be statistically significant. It should be noted that although the range of cutoff values for IOH might give the impression that the blood pressure was included as a dichotomized variable, this was not the case. In all analyses, IOH was used as a continuous variable, expressed as the number of minutes that the blood pressure was below the designated IOH threshold.

After publication of the results of the POISE-trial, IOH received renewed interest as a possible explaining factor for the increased stroke rate (from 0.5% in the control group to 1.0% in the metoprolol group).[8] The results of the present study are consistent with this hypothesis, although the magnitude of the effect is much less. Our results suggest that IOH accounts for an increase in stroke risk of approximately 1.3% per minute hypotension (*i.e.* the risk is increased 1.013 times for every minute of hypotension), depending on the definition of IOH that is used (in this case a decrease in mean blood pressure more than 30% from baseline). For example, a cumulative duration of 10 minutes of hypotension will result in a 1.14 times increased stroke risk (1.013^10). If applied to the POISE-trial this would mean an increase in absolute stroke risk from 0.5% (POISE-trial control patients) to 0.57%. This difference with the POISE-trial might be explained by the wide variety of beta-blockers that patients used in different dosages in the present study as opposed to the high-dose metoprolol that patients received in the POISE-trial.[20]

The most often proposed mechanism of a postoperative stroke is an embolism originating from the heart or great vessels. Hypoperfusion, leading to a watershed infarction, is thought to be responsible for only 9% of ischemic strokes after cardiac surgery, and deliberate hypotension does not seem to adversely affect cerebral perfusion.[1] Nevertheless, in the present study we found 7 (17%) strokes in watershed areas. Furthermore, we hypothesized that even in the presence of an embolic stroke, hypotension might aggravate the clinical course by compromising blood flow to potential ischemic, but still viable brain areas (the so-called penumbra). Support for this hypothesis is found in studies on cross-clamping of noncritical segmental arteries of pigs, which makes the spinal cord more vulnerable to hypotension.[21] Thus, the present study suggests that IOH might indeed play a role, albeit limited, in the occurrence of a postoperative stroke.

Defining IOH using blood pressure thresholds relative to a patient's baseline blood pressure offers more information (association with postoperative stroke when mean blood pressure decreases > 30% from baseline and smaller confidence intervals) on associations with postoperative stroke than fixed blood pressure levels. When generalized, this supports the clinical reasoning that defining IOH relative to a baseline

blood pressure is a better way to assess a patient's risk on adverse outcome than using fixed, arbitrarily chosen threshold values, disregarding a patient's comorbidities.[13]

However, the combination of a low stroke incidence, the complexity of the postoperative stroke mechanism and the absence of a uniform definition of IOH makes it challenging to study the association between IOH and postoperative stroke. This is further hampered by the limited effect that IOH appears to have on the occurrence of a postoperative stroke. These associations should therefore be interpreted cautiously and do not automatically imply causality. Nevertheless, although case-control studies are generally considered to be hypothesis generating, these hypotheses are of valuable clinical importance because perioperative blood pressures are controllable, potentially providing an opportunity to alter the postoperative stroke risk, especially in high-risk patients.

In conclusion, the most widely proposed mechanism of a postoperative stroke is arterial embolism. Nonetheless, the results of the present study support the hypothesis that hypotension can influence the evolution of a postoperative stroke by compromising (collateral) blood flow to ischemic areas. In this context hypotension is best defined as a decrease in mean blood pressure relative to a preoperative baseline, rather than an absolute low blood pressure value.

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180
160
140
120
100
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60
40
20
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mmHg

Chapter 6

Intraoperative hypotension and one-year mortality

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Abstract

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

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

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

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

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

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

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

Materials and Methods

Study design

This study was an observational cohort study. Patients were selected from a previously conducted prospective cohort study: the Outpatient Preoperative Evaluation by Nurses study.[11] In brief, all consecutive adult patients (aged 18 years or older) who visited the outpatient preoperative evaluation clinic of the University Medical Center Utrecht, the Netherlands, between February 2002 and February 2003 for general or vascular surgery were selected for the present study. They underwent surgery in the period from February 2002 to August 2003, during general, spinal, epidural or combined general-epidural anesthesia.

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

Data collection

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

Intraoperative hypotension

Intraoperative hypotension was defined as the duration that the blood pressure was below an *a priori* designated threshold value. The thresholds were selected from a

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

Outcome

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

Potential confounders

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

Table 6.1 Characteristics of the cohort (n = 1,705)

		Intraoperative hypotension*		
	Total cohort (n = 1,705)	Present (n = 652)	Absent (n = 1,053)	***P* value**
Mean age (SD), years	52 (15.8)	57 (14.2)	49 (15.9)	< 0.05‡
Male sex	880 (51.6)	324 (49.7)	556 (52.8)	0.21§
Mean BMI (SD), kg/m2	25 (4.8)	25 (4.9)	25 (4.8)	0.60‡
Smoking	509 (29.9)	195 (29.9)	314 (29.8)	0.97§
ASA physical status				
I	647 (37.9)	186 (28.5)	461 (43.8)	< 0.05§
II	872 (51.1)	374 (57.4)	498 (47.3)	
III or IV	186 (47.3)	92 (14.1)	94 (8.9)	
History of				
Cardiac disease	258 (15.1)	115 (17.6)	143 (13.6)	< 0.05§
Hypertension	380 (22.3)	177 (27.1)	203 (19.3)	< 0.05§
Diabetes mellitus	143 (8.4)	67 (10.3)	76 (7.2)	< 0.05§
Stroke	118 (6.9)	45 (6.9)	73 (6.9)	0.94§
Type of surgery				
Minor general	1,200 (70.4)	366 (56.1)	835 (79.3)	< 0.05§
Major general	303 (17.8)	187 (28.7)	116 (11.0)	
Vascular	199 (11.7)	99 (15.2)	100 (9.5)	
Median surgery duration				
(25th–75th percentile), minutes	112 (73–163)	151 (100–217)	91 (65–134)	< 0.05‖
Type of anesthesia				
General	1,226 (71.9)	457 (70.1)	769 (73.0)	< 0.05§
Regional	201 (11.8)	17 (2.6)	184 (17.5)	
Combined	278 (16.3)	178 (27.3)	100 (9.5)	
Cumulative exposure to anesthetics† (25th–75th percentile)				
Median AUC for sevoflurane	111 (61–201)	151 (74–274)	95 (55–160)	< 0.05‖
Median AUC for isoflurane	96 (44–167)	141 (73–197)	66 (27–125)	< 0.05‖
Median AUX for propofol	310 (179–454)	321 (190–510)	305 (175–441)	< 0.05‖
1-year mortality (KM estimate)	88 (353.7)	53 (346.2)	35 (358.4)	< 0.05#

Values are number (%) unless otherwise specified.

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

Statistical analysis

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

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

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

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

Table 6.2 Causes of death (n = 88)

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

Values are number (%).

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

Results

After application of the inclusion and exclusion criteria, a cohort of 1,705 general and vascular surgery patients was selected. Nine patients (0.5%) were lost to follow-up. The demographic and intraoperative patient characteristics are presented in table 6.1. The mortality rate within one year after surgery was 5.2% (n = 88). Most patients (22%) died of cancer (table 6.2).

Figure 6.1 shows the Kaplan-Meier curves for patients with and without IOH, defined according to four systolic blood pressure thresholds (100, 90, 80 en 70 mmHg) and a minimal episode duration of 1 minute. With decreasing threshold values for IOH, the divergence of the curves increased. The log-rank tests showed significant differences in risk of mortality for all four definitions of IOH (*P* values 0.05, 0.001, < 0.001, and < 0.001 respectively).

The proportional hazards and linearity assumptions were not violated. Therefore, Cox proportional hazards analysis was used and all continuous variables were modeled linearly. The crude hazard ratio of duration of IOH (systolic blood pressure below 80 mmHg for at least 1 minute) was 1.013 (95% CI, 1.007–1.019, table 6.3). When adjusted for all confounders, an effect of duration of IOH on the outcome could not be found (hazard ratio, 1.00; 95% CI, 0.989–1.011, table 6.3). With this definition of IOH, only age (hazard ratio, 1.042; 95% CI, 1.023–1.061), American Society of Anesthesiologists physical status (overall *P* value < 0.05), history of hypertension (hazard ratio, 2.406; 95%

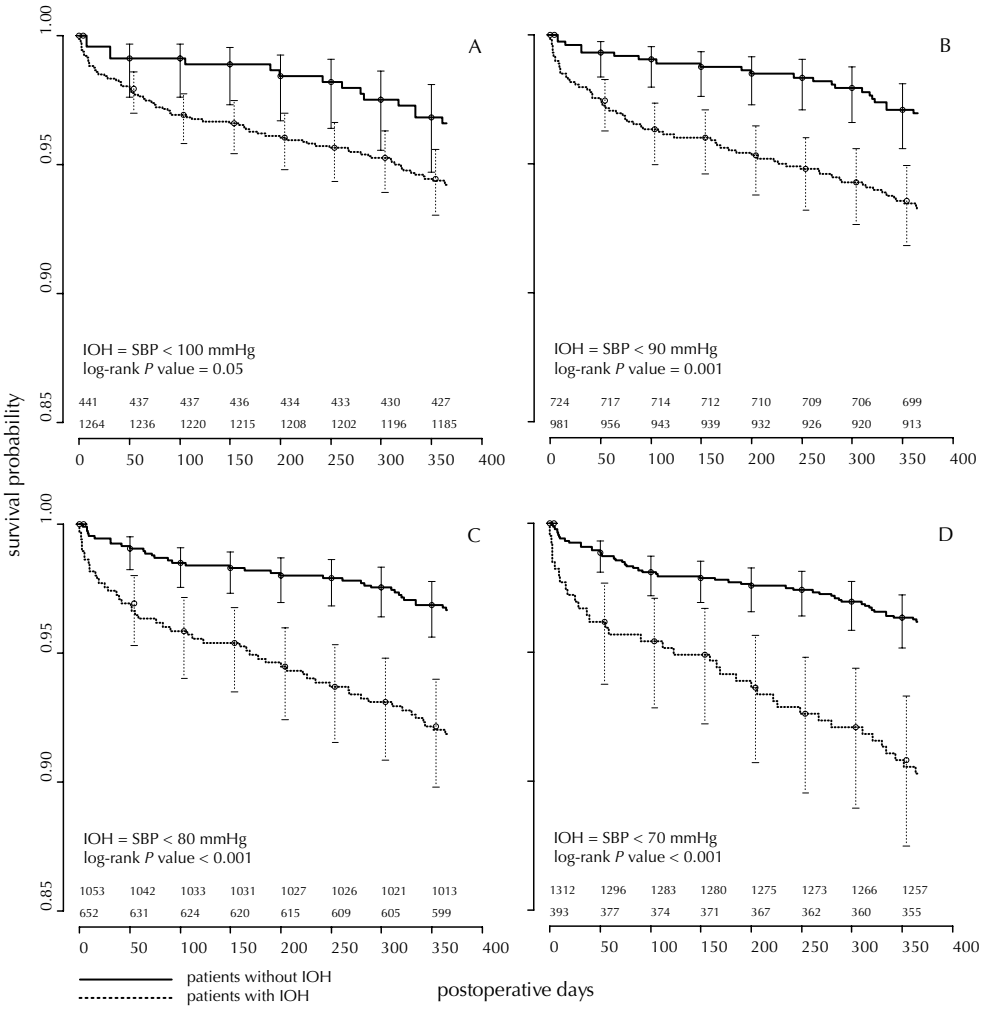

Figure 6.1 Kaplan-Meier curves for all-cause mortality of the cohort (n = 1,705 patients). Intraoperative hypotension (IOH) was defined as a systolic blood pressure (SBP) below 100 mmHg for at least 1 minute (*A*), an SBP below 90 mmHg for at least 1 minute (*B*), an SBP below 80 mmHg for at least 1 minute (C), or an SBP below 70 mmHg for at least 1 minute (D). The differences in survival probabilities were compared using log-rank tests. *Above the x-axis,* the numbers at risk are presented at 50-day intervals. The *upper row* corresponds with the *upper curve,* and the *lower row* corresponds with the *lower curve*. The *horizontal bars* indicate 95% confidence intervals at 50-day intervals.

CI, 1.407–4.112), and duration of surgery (hazard ratio, 1.008; 95% CI, 1.004–1.012) were associated with one-year mortality. Cumulative exposure to sevoflurane showed a hazard ratio of 0.998 (95% CI, 0.995–1.000). No statistically significant effects for interaction were found. It should be noted that these results were not corrected for multiple testing.

Table 6.4 shows the results for all other selected thresholds for IOH and the three minimal episode durations. None of the 48 adjusted hazard ratios were statistically significant. Therefore, a correction for multiple testing was deemed unnecessary. To graphically represent the hazard ratio as a function of the threshold values for low blood pressure, the associations between a wider range of low blood pressure thresholds and one-year mortality were calculated for all three minimal episode durations. Although not statistically significant, the risk of dying within one year after general or vascular surgery seems to increase when the threshold value of IOH was below a systolic blood pressure of 80 mmHg or a mean blood pressure of 60 mmHg or when there is a decrease in both systolic and mean blood pressure of 40–45% from baseline (figure 6.2).

The CART analysis included the duration of IOH in the tree when IOH was defined as a mean blood pressure below 50–75 mmHg for patients older than 46 years. Two trees are presented in figure 6.3 with hypotension defined as a mean blood pressure below 50 mmHg and 60 mmHg for at least 1 minute. With a mean blood pressure below 60 mmHg, IOH was included in the tree with a cutoff value of 30 minutes, whereas a mean blood pressure below 50 mmHg resulted in a cutoff value of only 5 minutes. Therefore, at the lower end of the blood pressure threshold range, the duration at which IOH was included in the classification and regression tree was shorter (table 6.5). The CART analysis with IOH defined by systolic blood pressures yielded less clear results. IOH defined as a systolic blood pressure below 70 mmHg was included in the tree with duration dichotomized at 3 minutes; IOH defined as a systolic blood pressure below 95 mmHg was included with a dichotomized value of 104 minutes. The systolic blood pressure threshold values between 70 and 95 mmHg were not selected with the CART analysis.

Discussion

In this observational study we studied the association between the duration of intraoperative hypotension and the risk of dying within one year after general or vascular surgery. To this aim, a variety of frequently used definitions of IOH

Table 6.3 Crude and adjusted associations (using Cox Proportional Hazards Analysis) of IOH defined as a systolic blood pressure lower than 80 mmHg for at least 1 minute, and one-year mortality

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

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

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

were used. Eighty-eight of 1,705 patients (5.2%) died within one year after surgery.

Using regression techniques, a trend of higher mortality risk within one year after surgery was found for threshold values below a systolic blood pressure of 80 mmHg, below a mean blood pressure of 60 mmHg or for a decrease in both systolic and mean blood pressure of 40–45% from baseline (figure 6.2). The unexpected decrease in hazard ratios to 1 and even below 1 at the extremes (low absolute blood pressure or high relative blood pressure thresholds) are unstable estimates that can be explained by the very low number of patients at these low blood pressure extremes. These hazard ratios are therefore not reliable, which is illustrated by the wide confidence intervals in figure 6.2. Therefore, conclusions on lowest acceptable blood pressure thresholds cannot be drawn from these results.

The CART analysis included duration of IOH in the tree for IOH defined as a mean blood pressure threshold value between 50 and 75 mmHg. For the lower threshold values in this range, shorter durations of IOH were associated with one-year mortality than among the higher thresholds, where longer durations of hypotension were tolerated. Again, no conclusions on causality can be drawn because of the type of this analysis, as residual confounding may still exist. However, these results do seem

Table 6.4 Crude and adjusted hazard ratios for all definition thresholds and episode durations of IOH

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

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

IOH = intraoperative hypotension; MAP = mean arterial pressure; SBP = systolic blood pressure.

to provide support for the widely accepted clinical reasoning that in elderly patients, decreasing blood pressures are tolerated for increasingly shorter durations.

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

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

Third, cumulative deep hypnotic time was previously reported to be associated with one-year mortality by Monk *et al.*,[6] which was recently confirmed by Lindholm *et al.*,[16] and should therefore be considered as a potential confounding factor. However, our patient population was not routinely monitored with an electroencephalography monitor designed to provide information on the intensity of hypnotic effect such as the BIS® monitor (Aspect Medical Systems, Natick, MA) or entropy module (GE Healthcare, Chalfont St. Giles, United Kingdom). Instead, cumulative exposure to propofol or volatile agent was calculated and the area under the effect site concentration curve for propofol-based anesthesia or the area under the inspired concentration curve for volatile-based anesthesia was used in the analysis. Although ideally end-tidal concentrations should have been used to calculate cumulative exposure to volatile anesthetics, only the inspired concentrations were available from the anesthesia record-keeping system. We do not expect this has caused significant bias, because inspiratory and expiratory concentrations of modern volatile anesthetics such as isoflurane and

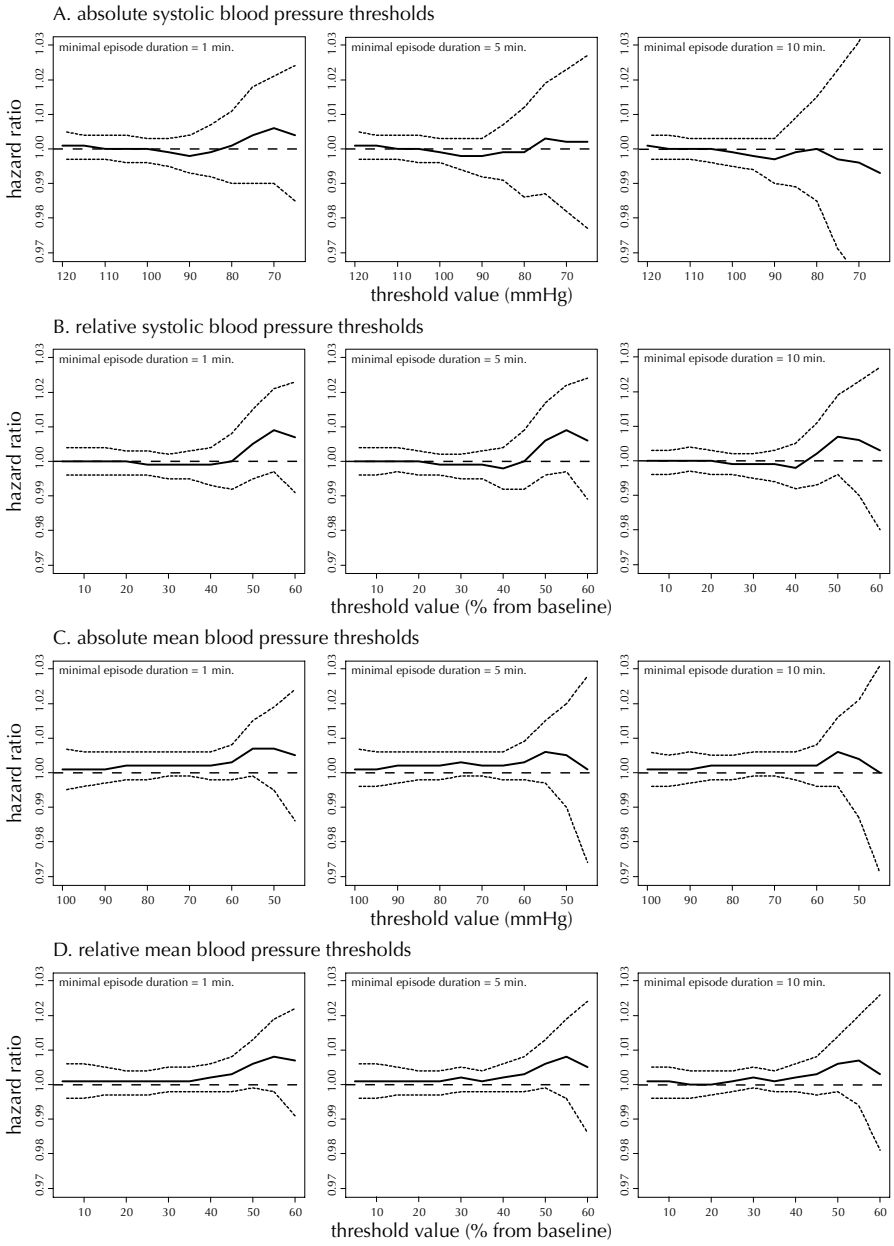

Figure 6.2 Adjusted hazard ratios for the association between duration of intraoperative hypotension and all-cause 1-year mortality plotted against *absolute* (*A* and *C*), *relative* (*B* and *D*), *systolic* (*A* and *B*), and *mean* (C and D) blood pressure threshold values for intraoperative hypotension. The *dotted lines* represent the 95% confidence interval. The *horizontal dotted line* represents the level of no effect (hazard ratio = 1).

sevoflurane rapidly equilibrate. Furthermore, the group of patients with hypotension had a statistically significant higher cumulative exposure to volatile anesthetics than nonhypotensive patients (table 6.1), a difference that was not observed for cumulative exposure to propofol. This might reflect unintended overdose of volatile anesthetics. Because of the observational design of the study, there could be a difference in potential confounders across the studied exposure groups, which is often simply by chance. We adjusted for this difference in potential risk factors in the multivariable analysis.

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

Because preoperative administration of sedation to reduce anxiety might have influenced the baseline blood pressure, the blood pressure measurement from the preoperative evaluation clinic was incorporated in the baseline reference blood pressure. This reduced the blood pressure-decreasing effect of sedation on the baseline blood pressure. Furthermore, in the analyses using a definition of IOH with an absolute threshold value, where baseline blood pressures and the effect of sedation play no role, comparable results were found.

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

The most frequently reported definitions of IOH in the anesthesia literature are a systolic blood pressure below 80 mmHg, a mean blood pressure below 55–60 mmHg, and a decrease in systolic or mean blood pressure of 20–25% from baseline.[7] In the current study, a trend of increasing hazard ratios—not statistically significant—around these blood pressures values was indeed found (figure 6.2). The hazard ratio for mortality seemed to increase with a 40% relative decrease from baseline in systolic or mean blood pressure, which is a much larger relative blood pressure decrease than the

textbook definition of 20–25% decrease in systolic or mean blood pressure. To date, only one study has described an association between IOH and one-year mortality.[6] In that study, the relative risk of dying within one year after major noncardiac surgery was found to increase with 3.6% (95% CI, 0.6–6.6%) for every minute that the systolic blood pressure was below 80 mmHg (measured at 5 minute intervals). Surprisingly, IOH defined as a mean blood pressure below 55 mmHg was also mentioned in that study without being associated with increased one-year mortality. This might be explained by a difference in patient population between the study by Monk *et al.* and the current study (major noncardiac surgery versus major and minor general and vascular surgery). The mortality rate after one year was comparable between the study by Monk *et al.* and the current study (5.5% versus 5.2%), but the 30-day mortality rate of the current study seems higher (1.3% versus 0.7%). However, this difference in 30-day mortality is not statistically significant if tested using a contingency table and chi-square test (current study: 23 deaths, 1,682 alive; Monk *et al.*: 7 deaths, 1,057 alive; $P = 0.09$). Still, the sample size of a study that might report statistically significant and clinically relevant differences in the risk of dying within one year after surgery due to IOH should be

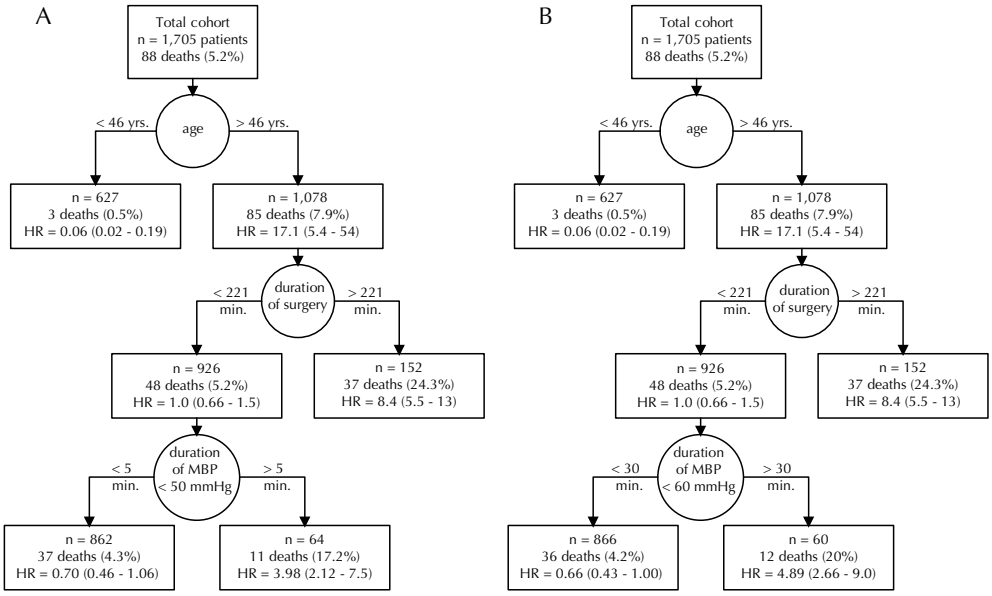

Figure 6.3 Results of the classification and regression tree analysis using two different definitions of intraoperative hypotension: a mean arterial pressure (MAP) below 50 mmHg for at least 1 minute (A) or a MAP below 60 mmHg for at least 1 minute (B). HR = hazard ratio.

Table 6.5 CART cutoff values for the duration of IOH according to different blood pressure threshold values in patients older than 46 years and with a surgery duration less than 221 minutes

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

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

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

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

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

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Part III

Discussion and Summary

180
160
140
120
100
80
60
40
20
mmHg

Chapter 7

General discussion

Anesthesiologists focus on maintaining 'normal' physiology in the perioperative period. To this aim, several vital parameters are monitored. Deviations in hemodynamic parameters, both above and below normal physiological values, have been associated with adverse outcome after surgery.[1,2] Worldwide, monitoring standards therefore include blood pressure measurement as a minimal requirement during anesthesia.[3] However, what constitutes a 'normal' blood pressure during surgery and what is 'too low', remains largely unknown and is at times fiercely debated.

In this chapter, the studies presented in this thesis are put into a larger perspective. The current knowledge of intraoperative hypotension (IOH) is discussed in terms of definition, incidence, risk factors and outcome. Subsequently, the clinical implications of the studies presented in this thesis are discussed, followed by future perspectives including suggestions for further research.

Definition

The exact definition of IOH is difficult.[4] Many different definitions of IOH are in use, both in the anesthesia literature (**chapter 2**) and in daily clinical practice (**chapter 4**).

In defining IOH, it is important to establish what constitutes a normal blood pressure and which deviations from normal will likely result in adverse events. Both are difficult to determine. For example, even in healthy individuals the blood pressure can differ over 10 mmHg between both arms.[5] Moreover, it is important to bear in mind that blood pressure normally fluctuates during the day and declines approximately 10–20% during physiological sleep.[6–9] This temporal pattern in blood pressure is influenced by activity, posture, stress, anxiety, age, gender and comorbidity and puts the question about what is IOH into perspective.[6,10] Furthermore, evidence on safe thresholds of decreased blood pressure is limited. A few old and remarkable studies observed signs of cerebral circulatory insufficiency (dizziness, nausea, yawning, involuntary body movements or fainting) or electroencephalogram abnormalities during a controlled hypotension test in awake volunteers. The results varied widely, but blood pressure could be reduced up to 55% from baseline before signs of cerebral ischemia developed.[11,12] Such studies would nowadays be ethically challenging to perform and current definitions of IOH are therefore more 'eminence or experience-based' than evidence based.

Currently, the most frequently used definitions of IOH use a threshold relative to a baseline blood pressure (**chapter 2** and **4**). Nevertheless, only 50% of the definitions

of IOH requiring a baseline blood pressure actually provide a definition of baseline blood pressure (**chapter 2**). In **chapter 3** we propose that an appropriate baseline blood pressure might be obtained by 'averaging' (using either the mean or the median) of all available blood pressure measurements prior to surgery (**chapter 3**).

Incidence

There are many studies reporting an incidence of IOH.[13–15] However, all these studies used a different definition of IOH and as described in **chapter 2**, the incidence of intraoperative hypotension varies widely with the chosen definition. This was confirmed by Klöhr *et al.* who reported similar varying incidences in patients undergoing a caesarean section under spinal anesthesia.[16] As an example, 9% of patients undergoing general anesthesia were found to experience IOH when using a complex composite definition of a mean blood pressure (MPB) decrease > 40% and below 70 mmHg or a MAP < 60 mmHg.[17] In contrast, 47% of patients undergoing spinal anesthesia experienced a decrease in MAP of 10–20% whereas in 'only' 20% of these patients the MAP dropped 20–30%.[13] When the most frequently used definitions are applied to a large patient dataset, incidences varying between 5% and 99% can be reproduced (**chapter 2**). Even when the threshold value for intraoperative hypotension is changed only slightly, the occurrence frequency of intraoperative hypotension will differ significantly. This can potentially have important implications, both clinically and medicolegally (see clinical implications).[18]

Apart from the definition, both patient characteristics and anesthesia factors can influence the incidence of IOH. For example, the use of general versus spinal anesthesia, or the dosage of local anesthetic used in spinal anesthesia significantly influences the occurrence of IOH.[19] Even though IOH is a frequent (side) effect of anesthesia, it still seems impossible to give a single estimate for the incidence of IOH, which will depend to a large extent on the chosen definition and the presence of risk factors.

Risk factors

Risk factors for the occurrence of IOH can be divided into three categories: patient related, anesthesia related and surgery related.

Patient related

Many risk factors of IOH are associated with a patient's comorbidity or medication use, including age ≥ 50, a history of hypertension, an increased body mass index, ASA physical status III-V, chronic alcohol consumption, a preoperative MAP < 70 mmHg or ≥ 110 mmHg, a decreased exercise capacity (walking distance less than 400 m during 12 minutes) or hypovolemia (plasma volume less than 3000 ml, *e.g.,* in trauma and shock patients).[13,14,17,20]

Common to comorbidity is the use of medication. Especially the long-term use of antihypertensive medication such as renin-angiotensin-aldosterone (RAAS) antagonists, beta-blockers, calcium antagonists or diuretics has been reported to be associated with an increased risk of hypotension after induction of anesthesia.[21–24] However, withdrawal of RAAS antagonists or diuretics on the day of surgery is not associated with a reduction in IOH[25,26] while continuing angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increases the likelihood of intraoperative hypotension.[27] Beta-blockers and calcium channel blockers should be continued on the day of surgery.[27–29]

Anesthesia related

Almost all anesthetics are potent hypotensive agents.[30] It is a misconception that spinal anesthesia induces more IOH than general anesthesia. It is actually the opposite, general anesthesia is associated with greater intraoperative hypotension than spinal anesthesia.[19] Nevertheless, central neuraxis blockade can lead to hypotension.[14] Lowering the dose of local anesthetic will decrease the risk of hypotension in spinal anesthesia.[31] Combined spinal-epidural anesthesia with a sensory block higher than T6 results in more hypotension than spinal anesthesia alone, although this effect might be attributable to the influence of the procedure.[14] In combined epidural-general anesthesia, a block height up to T10 increases the odds of developing hypotension as compared to those with epidural or general anesthesia alone.[32]

In general anesthesia, the largest risk of hypotension is directly after induction of anesthesia and attributable to peak plasma levels of the induction agents.[17] The use of propofol as an induction agent is associated with the largest decrease in blood pressure after induction of anesthesia whereas etomidate and midazolam appear to induce less decrease in blood pressure.[33]

Surgery related

The risk of IOH can also depend on the type of surgery. More complex procedures and/or operations of longer duration impose an increased risk of hypovolemia and

decreased blood pressures, especially after many hours of surgery. For example, IOH has been found to be more common in patients undergoing intra-abdominal or vascular surgery and operations longer than two hours.[20]

Outcome

IOH is considered by some to be the most serious anesthesia concern because of its association with adverse perioperative outcomes[4,34], including myocardial infarction, stroke and even increased risk of death one year after surgery. [17,35–38] However, prospective studies are lacking and studies failing to show an association between IOH and adverse outcome can be found as well.[39–42] Furthermore, as indicated before, different methods to characterize intraoperative hemodynamic patterns pose a significant problem in studying predictors of postoperative complications and comparing such studies.[18,43]

Cardiac events

Data on the association between IOH and cardiac adverse events is very limited. Barone *et al.* conducted a case-control study among low-risk patients undergoing noncardiac surgery and found an association between IOH (defined as a systolic blood pressure < 100 mmHg for 10 consecutive minutes) and postoperative myocardial infarction within one week.[44] Charlson *et al.* reported an increase in myocardial infarctions in high-risk patients who had prolonged MAP decreases of 20 mmHg or more.[43,45] However, Reich *et al.* described low mean blood pressure as a predictor for postoperative mortality and stroke within 2 days, but did not find it predictive for perioperative myocardial infarction. They actually found a decreased risk of myocardial infarction at very low blood pressures, although this was probably due to technical differences in surgical approach between hospitals and not a protective effect.[46] Furthermore, Kheterpal *et al.* found no specific level of IOH to be independently associated with cardiac adverse events within 30 days.[47]

Stroke

In 2008, the POISE study, a randomized trial investigating the effect of perioperative high-dose metoprolol versus placebo in patients undergoing noncardiac surgery on cardiovascular death and nonfatal myocardial infarction or cardiac arrest within 30 days revealed that metoprolol prevented nonfatal myocardial infarction but at the

expense of increased stroke and mortality rates. Metoprolol-induced hypotension was suggested as a potential mechanism for the increased stroke risk. By then, this association between IOH and postoperative stroke had already been subject of discussion for many years. Studies both supporting and rejecting an association between IOH and stroke can thus be found but the hypothesis has never been tested prospectively and a cause-effect relationship could not be established with certainty.[46,48–51] For example, extreme nighttime dipping (*i.e.* a > 20% fall in blood pressure) has been reported to be related to cerebral ischemia.[52] In contrast, no strokes occurred after shoulder surgery in 4,169 patients in the sitting position despite frequent hypotension (*i.e.* a > 30% fall in blood pressure).[53] In **chapter 5** we investigated the relationship between IOH and postoperative stroke in a case-control design. The most widely proposed mechanism of a postoperative stroke is an arterial embolism, which often coexists with hypoperfusion.[54,55] We therefore hypothesized that even in embolic strokes, IOH could play an additive role by compromising collateral blood flow to ischemic, but still viable, areas. We found weak evidence to support this hypothesis: a decrease in MAP of > 30% was found to be associated with an increased postoperative stroke risk.

Mortality

Associations between IOH and perioperative (all-cause) mortality have also been described previously.[1,2,35,46,56] However, as with perioperative stroke, there are also studies that did not find an association between IOH and overall mortality within several years.[57,58] Nevertheless, the mechanism by which IOH might lead to postoperative death (*e.g.,* within one month) is likely to be very complex and all of the studies to date should be considered hypothesis generating. Compelling evidence on the etiology and pathophysiological mechanisms is lacking.[59] In **chapter 6**, we therefore undertook a study to investigate the association between IOH and perioperative mortality. In a traditional logistic regression analysis no association between IOH and one-year mortality could be confirmed. However, additional analyses using nonparametric methods (CART analysis) revealed that the risk of dying within one year after general surgery could be increased for high-risk patients when the duration of IOH becomes long enough. Thus, the effect of IOH on perioperative all-cause mortality remains debatable and there are no studies available that allow firm conclusions.

Other adverse events

Many other adverse outcomes have been linked to IOH. For instance, associations have been suggested with early postoperative renal failure, anastomotic leaks after

esophagectomy or rebleeds after mastectomy.[60–63] However, none are conclusive and mechanisms by which adverse outcomes occur are often multifactorial. For example, Kheterpal *et al.* did not find hypotension to be associated with postoperative acute renal failure within one week after surgery, but patients who experienced renal failure were more likely to have received vasopressor boluses or infusion during the operation. Furthermore, Haase *et al.* demonstrated that blood pressure alone or the administration of vasopressors was not independently associated with acute kidney injury, but the combination of severe hypotension (defined as a MAP < 50 mmHg) with anemia *was* associated with postoperative kidney failure.[64]

In conclusion, associations between IOH and postoperative outcome are mostly based on retrospective studies or coincidental findings from studies designed for other purposes. Furthermore, in everyday anesthesia practice the incidence of hypotension far exceeds the occurrence of adverse outcome, suggesting than only a 'susceptible' minority of patients will have hypotension-induced adverse outcomes.[15]

Clinical implications and recommendations

Clinical implications

Given the arguably still somewhat small number of studies investigating associations between IOH and postoperative adverse outcomes and the methodological limitations of many of these studies, it is challenging to accurately reflect on clinical implications.

Ultimately, the sole purpose of the circulatory system is to transport oxygen and nutrients to cells. For this purpose, blood pressure should be kept sufficient to maintain adequate blood flow to vital organs and as such, pressure is used as a proxy for sufficient perfusion. Many organs have the intrinsic ability to maintain a constant blood flow despite changes in perfusion pressure. This autoregulation allows the blood pressure to drop within certain limits without compromising the oxygen supply to vital organs such as the brain, heart or kidneys.[65] However, general anesthesia potentially influences this autoregulation. For instance, inhalation anesthetics (except sevoflurane) have a dose-dependent depressive effect on cerebral autoregulation, whereas propofol mainly preserves autoregulation.[66] On the other hand, general anesthetics suppress cerebral metabolism, thus possibly allowing the brain to tolerate perfusion pressures that would induce cerebral ischemia in the awake state.[67] This is illustrated by the findings in **chapter 4** where a discrepancy was observed between theoretical definitions of IOH and the (lower) actual treatment thresholds for low

blood pressure in patients under general anesthesia. These findings were confirmed by a similar study demonstrating poor correlation of IOH, defined by the three most frequently found definitions from **chapter 2**, with anti-hypotensive treatment administered by anesthesiologists.[68] On the other hand, awake patients under spinal anesthesia were treated at higher thresholds better corresponding with the self-reported definitions (**chapter 4**). This might be due to patients showing symptoms of hypotension as a result of spinal anesthesia and a profound block, thus triggering prompt treatment of low blood pressure by the attending anesthesiologist. Support for this hypothesis can be found in some old studies where healthy and awake volunteers were subjected to a 'controlled hypotension' test and blood pressure could be decreased up to 55% before signs of cerebral circulatory insufficiency were experienced. However, since the limits of autoregulation are significantly influenced by age and patient comorbidity (*e.g.,* hypertension), the amount of 'allowable' decrease in blood pressure observed in awake patients cannot automatically be extrapolated to patients under general anesthesia. The exact clinical implications of IOH therefore currently remain unknown, especially since it seems that anesthesiologists do not always practice what they preach.

As mentioned before, many different definitions of IOH are in use, resulting in widely varying incidences of IOH (**chapter 2**). This can have important clinical as well as medicolegal consequences. Associations with adverse events found with one definition can possibly not be found using even a slightly different definition. This impairs the ability to compare the results of different studies[43,69], or compare data intended for benchmark purposes. Furthermore, legal experts may come to inappropriate conclusions when different definitions of IOH are used.[18] For example, when a patient suffered a large damaging watershed stroke, a lawyer may build a case of negligence when a physician states that the mean blood pressure during surgery was 'too low', namely 75% of baseline (a decrease of 25% of the patient's awake blood pressure). This could be argued as an example of hindsight bias, because according to this line of reasoning, 30% of patients in most hospitals would daily receive care from 'negligent' anesthesia practitioners.

In daily practice, blood pressure is not considered a static phenomenon with one single cutoff value. Both the magnitude and duration are usually taken into account when assessing the severity of a hypotensive episode. In **chapter 6** we were able to provide some support for this notion by describing a possible relation between IOH and one-year mortality, which revealed that smaller decreases in blood pressure can be accepted for longer durations than deep hypotension, which seems to be tolerated for much shorter periods or not at all.

Recommendations

Even though our current limited understanding of IOH prevents solid evidence-based recommendations, some observations can be made based on the results of the studies presented in this thesis.

First, based on the findings in **chapter 5** and **6**, it seems justified to recommend defining IOH based on a decrease relative to a baseline blood pressure. This would take into account the altered cerebral autoregulation of older and hypertensive patients and has previously been reported to have a much higher predictive ability for adverse outcome than when simply using absolute thresholds.[43] Nevertheless, even for relative blood pressure decrease, no specific threshold value can be supported by the currently available literature. Moreover, one should bear in mind that it might not even be valid to define IOH according to a fixed percentage change from baseline.[70] In **chapter 3** we suggest that the determination of the baseline blood pressure is possibly best based on all available blood pressures before surgery since the variation in blood pressure measurements is very large.

Furthermore, this thesis also provides support that it is probably better to observe and monitor MAP than the more frequently reported systolic blood pressure, since it seems a more robust measurement in the associations with adverse outcomes. In this, the term mean blood pressure might be misleading since it implies that it is a mean of pressures while—at least with noninvasive blood pressure measurements—it is in fact a measured value (the cuff pressure at which the observed oscillations are maximal). In this respect, it is remarkable that current anesthesia monitors have no built-in capability to easily calculate a baseline blood pressure and the subsequent treatment threshold and furthermore that the mean blood pressure is often the smallest figure of the blood pressure reading displayed on the screen.

For research purposes it is recommended to give an exact description of the way IOH is defined. This includes threshold value, threshold type (absolute or relative), baseline (if required), blood pressure type (systolic or mean blood pressure), measurement method (noninvasive or invasive), measurement interval, and minimal episode duration (**chapter 2**). Warner *et al.* argued that even greater granularity might be necessary to describe IOH for future research, including for example the monitor used for the measurements.[18]

In **chapter 4** we could demonstrate that even in daily clinical practice anesthesiologists and anesthesia nurses make use of a wide variety of IOH definitions. In this respect we propose that all anesthesia personnel involved in the monitoring and treatment of blood pressures adhere to an IOH threshold ('treatment trigger') jointly defined prior to the start of the procedure.

Future perspectives

The studies presented in this thesis were generally of an explorative, hypothesis generating nature. The data available until the start of the current work did not yet justify initiating a large interventional trial of aggressive maintenance of perioperative 'normal' blood pressure—using fluids and vasopressors—versus 'care as usual'. Therefore, the results of the studies presented in this thesis require validation using more rigorous study designs.[42,59] In this, the foremost remaining question waiting to be answered is how to properly define IOH.

To come to a proper definition of IOH, this definition should be based on associations with adverse postoperative outcomes. Although there is evidence of an association between aberrant hemodynamics and adverse outcomes, it does not necessarily follow that better hemodynamic control would have led to better outcomes in the patients who experienced complications.[71] The side effects of aggressive maintenance of normotension with vasopressors and fluids should be taken into account. Ideally, one would want to perform a randomized trial assigning patients to various degrees of hypotension to investigate at what threshold values low blood pressure becomes harmful for vital organs, which patients tolerate less IOH and what procedures demand an increased awareness for IOH and adverse outcome. However, such studies are unethical. Furthermore, since adverse outcome after surgery is so rare, such studies would require very large sample sizes to enable finding enough events.[72] Therefore, we propose a randomized interventional study investigating the effect of strict blood pressure control versus 'care as usual' (*i.e.* today's perioperative blood pressure management that appears to be quite permissive with respect to hypotension) on the incidence of adverse outcomes such as stroke or myocardial infarction. Moreover, research comparing different treatments on the effect of global and regional hemodynamics is necessary. For example, it has recently been reported that ephedrine, but not phenylephrine is capable of increasing the cerebral oxygen content when restoring low blood pressure.[73] Such data are necessary to determine the best choice of vasopressor in a large randomized trial. Collaboration between hospitals and countries will likely be essential to include the required large number of patients in such trials.

Furthermore, studies of potential harmful effects of hypotension should be expanded to the investigation of decreased blood pressures in the early postoperative period and on the surgical ward. Postoperative complications usually occur after an asymptomatic interval. The role of postoperative blood pressures has thus far hardly

been studied but offers important opportunities for research. Initially, it would be warranted to perform an explorative study investigating the magnitude of the problem of postoperative hypotension on subsequent outcomes. How often does it occur, are specific patients, procedures or times of day at risk? At first, an observational study design would be recommended in which blood pressures are measured on regular and frequent intervals and subsequent outcomes documented. If an association might be found in such studies, then similar to studies on intraoperative hypotension, intervention studies will be required to unravel the role of postoperative hypotension in the etiology of adverse postoperative outcome.

Finally, further progress in IOH research can be achieved in the field of organ function monitoring. It is important to realize that blood pressure is merely a derivative of organ perfusion, which in turn is a measure for oxygen delivery to tissues of vital organs. Many factors can influence this process, independent of blood pressure. For instance, cerebral perfusion parameters were unchanged in patients undergoing laparoscopic surgery in prolonged Trendelenburg position while they commonly experienced a period of postoperative confusion, which was possibly attributable to cerebral edema preventing oxygen transport into brain tissue.[74] This supports the need for monitors that can reliably measure the function of vital organs. To date, no such monitor exists. For instance electroencephalogram derivatives (*e.g.,* the BIS® monitor) are promising but have so far failed to show good correlation with signs of ischemia.[75]

Based on the studies presented in this thesis it becomes increasingly evident that IOH cannot be defined according to fixed, arbitrarily chosen thresholds, but should be defined according to decreases relative to a baseline blood pressure. The threshold values however have yet to be determined and should be based on clinical consequences of IOH. There is a need to assess the effectiveness and safety of interventions aimed to reduce the risk of adverse outcomes in large-scale randomized trials before proposing any recommendations.[15]

Conclusion

In this thesis, an attempt was made to gain insight into the definition, occurrence, etiology and consequences of intraoperative hypotension. The main difficulty in defining IOH is to determine the patient's 'normal' blood pressure and subsequently

define which deviations from this baseline blood pressure are safe for a particular individual patient. Even though this thesis was not able to provide exact threshold values, it did provide evidence that it is best to define intraoperative hypotension according to mean blood pressure thresholds relative to the patient's preoperative baseline blood pressure. This 'hypotension threshold' value however, will also depend on the duration of a hypotensive episode. Smaller decreases will be tolerated for longer durations than deep hypotension, which is tolerated for much shorter durations or not at all.

Furthermore, support was found for the hypothesis that IOH does not always have to be the primary mechanism for adverse outcome, but can also contribute to the etiology of adverse outcome, for example by compromising blood flow to ischemic but still viable tissue of vital organs in case of embolic stroke.

Contrary to current usage, the definition of intraoperative hypotension should be based on a patient's comorbidity, surgical procedure and type of anesthesia. In the search for the ideal definition, intraoperative hypotension should not be defined according to arbitrary chosen threshold values, but rather regarded as a complex dynamic phenomenon depending on many patient-, surgery- and anesthesia-related factors.

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Chapter 8

Summary

Approximately 234 million surgical procedures are performed every year all around the world. Most of these operations require some form of anesthesia and blood pressure measurement is part of the minimal requirements of intraoperative monitoring in the majority of the cases. However, a uniform interpretation of these measurements does not exist and what exactly constitutes 'too low' blood pressure is unknown. Furthermore, controversy exists on the consequences of intraoperative hypotension (IOH), in particular its influence on adverse postoperative outcomes such as stroke, myocardial infarction or renal failure. In **chapter 1**, a brief historical overview is given on intraoperative blood pressure measurement and management. Recently, several landmark studies have renewed the interest in the topic of IOH but also led to extensive discussions regarding the strength of the evidence of proposed mechanisms by which IOH potentially causes delayed adverse outcomes. This—still ongoing—debate prompted the initiation of the studies presented in this thesis. The goal of this thesis is therefore to refine the understanding of intraoperative hypotension and gain insight in its definitions, etiology and outcome.

Defining intraoperative hypotension

Intraoperative hypotension is a common and frequent side effect of anesthesia and has been reported to be associated with various adverse perioperative outcomes. However, many different definitions of IOH have been used to study these associations. In **chapter 2** we investigated which definitions could be found in the recent anesthesia literature and subsequently applied these different definitions on a large cohort of 15,509 adult patients that underwent noncardiac surgery. The systematic literature search resulted in 48 different definitions of IOH. When applied to the cohort of patients, the incidence of IOH varied between 5% and 99% with the relationship between IOH definition and incidence showing an S-shaped cumulative incidence curve. When the minimal duration for an episode of low blood pressure to be qualified as IOH is increased, the cumulative incidence curves shift to the right. These widely varying incidences make comparisons between studies using different definitions of IOH impossible.

The majority of the definitions of IOH that resulted from the systematic literature search used a threshold value relative to a baseline blood pressure. However, only 50% of the definitions requiring a baseline blood pressure actually provided a

definition of this baseline. When it was defined, is was mostly based on blood pressures obtained in the operating room (OR) just prior to induction of anesthesia. Whether this is an appropriate way to define the baseline blood pressure is however unknown since widespread clinical belief suggests that blood pressures measured in the OR are potentially anxiety and stress-related and might therefore give an overestimation of the patient's 'normal' blood pressure. In **chapter 3** we therefore investigated the difference between the blood pressure measured at the outpatient preoperative evaluation (OPE) clinic and the mean of all preinduction blood pressure measurements in the operating room in a retrospective cohort of 14,044 patients. The differences between OPE and OR blood pressures varied widely and approximately half of the patients had a lower OR blood pressure than at the OPE. Furthermore, the difference between OPE and OR blood pressure was not constant but at higher blood pressure levels, the OR blood pressure became increasingly higher than the OPE measurement. Nevertheless, on average the blood pressure in the OR was slightly higher than at the outpatient evaluation clinic but this was not considered clinically relevant. The widespread clinical thinking that admission or OPE blood pressure is lower and possibly a better baseline than the allegedly stress-related OR blood pressure could not be confirmed.

So far, only theoretical definitions had been studied and it is unknown whether these literature definitions also represent the definitions used by anesthesia team members in daily clinical practice. Therefore, in **chapter 4** a survey of the definitions of IOH used among anesthesia personnel was conducted and the differences between these self-reported definitions and actual treatment thresholds for low blood pressure were studied. As in the literature, a wide range of 33 different definitions could be found using a questionnaire. Subsequently, a cohort of 7,149 patients undergoing an arthroscopy of the knee under either general of spinal anesthesia was studied. Under general anesthesia, low blood pressures were generally treated at the often self-reported threshold of a mean arterial pressure below 60 mmHg or systole of 80 mmHg, corresponding with a decrease of 37–40% from baseline. In contrast, patients under spinal anesthesia were treated at a mean arterial pressure of 74 mmHg or a systole of 100 mmHg, corresponding with the often self-reported 25–30% decrease from baseline. This might imply that in patients under general anesthesia, where the decision to treat low blood pressure is left solely at the discretion of the attending anesthesia team member, hypotension is treated preferably according to absolute thresholds (contrary to self-reporting), often allowing the blood pressure to decrease up to 40% from baseline. In contrast, in awake patients under spinal anesthesia,

where treatment might also be prompted by patient symptoms of hypotension (*e.g.*, dizziness, nausea or vomiting, transpiration, pallor), blood pressures were treated in general at higher absolute thresholds that better correspond with the self-reported definitions of IOH that use a threshold relative to a baseline.

The effect of intraoperative hypotension on postoperative outcome

The second part of this thesis is focused on possible associations between IOH and adverse postoperative outcome. To this aim, the role of IOH in the occurrence of a postoperative ischemic stroke was studied in **chapter 5**. Although rare, a stroke is a major complication after surgery. The most widely accepted mechanism of a postoperative stroke is an arterial embolism, but the role of IOH in the occurrence and evolution of a stroke is largely unknown. From a cohort of 48,241 patients undergoing noncardiac and nonneurosurgical surgery 42 stroke cases were matched to 252 controls on age and type of surgery. For the analyses, IOH was defined according to a range of threshold values and after correction for potential confounding and multiple testing, only the duration that the mean arterial pressure was decreased > 30% from baseline remained significantly associated with the occurrence of a postoperative stroke. This provides support for the hypothesis that IOH can play a role in the development of postoperative ischemic stroke by compromising (collateral) blood flow to ischemic but still viable tissue.

IOH has also previously been associated with mortality within one year after surgery. In **chapter 6** we therefore tested this association in a cohort of 1,705 patients that underwent general and vascular surgery, again using a variety of definitions of IOH. Two different techniques were used to reduce the influence of confounding variables: multivariable Cox proportional hazard regression modeling and classification and regression tree analysis (CART). The mortality within one year after surgery was 5.2% (n = 88). Cox regression analysis did not show any causal relation between any of the definitions of IOH and one-year mortality. CART analysis however, identified IOH as a predictor for one-year mortality and demonstrated that lower blood pressures were tolerated for shorter durations, which is consistent with our clinical reasoning in daily practice. Nevertheless, the effect of IOH on one-year mortality remains debatable and no firm conclusions on the lowest acceptable intraoperative blood pressures can be drawn.

Finally, in **chapter 7**, the studies presented in this thesis are put into a larger perspective. The main difficulty in defining IOH remains the determination of the patient's 'normal' blood pressure and which deviations from this baseline blood pressure are safe for a particular individual patient. Even though it was impossible to present exact threshold values, evidence to support the idea that IOH seems best defined according to a decrease in mean blood pressure relative to a baseline blood pressure could be provided. This threshold value in turn, depends on the duration or the hypotensive episode with smaller decreases being tolerated better than deep hypotension, which seems to be tolerated for much shorter durations or not at all. Future prospective and possibly interventional studies on IOH should expand their focus to the postoperative period and base appropriate definitions of IOH on associations with adverse postoperative outcomes.

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Chapter 9

Samenvatting

(summary in Dutch)

Wereldwijd worden er jaarlijks ongeveer 234 miljoen chirurgische ingrepen uitgevoerd. De meeste van deze operaties behoeven enige vorm van anesthesie en in de meeste gevallen is de meting van de bloeddruk onderdeel van de standaard voor minimale monitoring. Een eenduidige interpretatie van deze metingen bestaat echter niet en wat precies een 'te lage' bloeddruk inhoud is onbekend. Verder bestaat er onduidelijkheid over de gevolgen van intraoperatieve hypotensie (IOH), met name over de invloed op postoperatieve complicaties zoals bijvoorbeeld een cerebrovasculair accident, myocard infarct of nierfalen. In **hoofdstuk 1** wordt een kort historisch overzicht gegeven over de meting en behandeling van bloeddrukken tijdens operaties. Recent hebben enkele belangrijke studies de interesse in IOH hernieuwd maar hebben ook tot uitvoerige discussie geleid over de kracht van het bewijs voor de voorgestelde mechanismes hoe IOH mogelijk lange termijn complicaties kan veroorzaken. Deze—nog steeds voortdurende—discussie gaf aanleiding tot de uitvoering van de studies die in dit proefschrift worden beschreven. Het doel van dit proefschrift is daarom om de kennis van IOH te verfijnen en inzicht te krijgen in haar definitie, etiologie en gevolgen.

Het definiëren van intraoperatieve hypotensie

Intraoperatieve hypotensie is een veel voorkomende bijwerking van anesthesie en is in verband gebracht met diverse postoperatieve complicaties. Echter, deze associaties zijn bestudeerd met gebruik van een verscheidenheid aan definities van IOH. In **hoofdstuk 2** onderzochten we welke definities in de recente anesthesie literatuur gevonden konden worden en hebben deze verschillende definities vervolgens toegepast op een groot cohort van 15,509 volwassen patiënten die niet-cardiale chirurgie ondergingen. Het systematische literatuur onderzoek leverde 48 verschillende definities op. Wanneer toegepast op het patiënten cohort varieerde de incidentie van IOH tussen 5% en 99%, waarbij de relatie tussen de definitie van IOH en de incidentie een S-vormige cumulatieve incidentie curve liet zien. Indien de minimale duur van een episode van lage bloeddruk die gekwalificeerd kan worden als IOH wordt verhoogd, schuift de cumulatieve incidentie curve naar rechts. Deze sterk uiteenlopende incidenties maken vergelijkingen tussen studies die verschillende definities gebruiken onmogelijk.

De meerderheid van de definities van IOH uit het systematische literatuur onderzoek gebruikten een grenswaarde ten opzichte van een uitgangsbloeddruk. Slechts 50% van de definities die een uitgangswaarde nodig hebben verstrekten echter

ook een definitie van die uitgangswaarde. Indien deze was gedefinieerd dan was hij meestal gebaseerd op bloeddrukken verkregen in de operatiekamer (OK) net voor de inductie van anesthesie. Of dit een geschikte manier is om de uitgangsbloeddruk te definiëren is echter onbekend omdat algemeen wordt aangenomen dat de bloeddruk gemeten in de OK mogelijk beïnvloed kan zijn door angst en stress en daarom een overschatting kan zijn van de 'normale' bloeddruk van de patiënt. In **hoofdstuk 3** bestudeerden we daarom het verschil tussen de bloeddruk gemeten op de polikliniek voor preoperatieve screening (POS) en het gemiddelde van alle pre-inductie bloeddrukken in de operatiekamer in een retrospectief cohort van 14,044 patiënten. De verschillen tussen de bloeddrukken gemeten op de POS en OK liepen sterk uiteen en ongeveer de helft van de patiënten had een lagere bloeddruk op OK dan op de POS. Bovendien was het verschil tussen de bloeddrukken op de POS en OK niet constant maar nam toe bij hogere bloeddruk waarden. Desalniettemin was de bloeddruk op de OK gemiddeld iets hoger dan op de POS, al werd dit niet klinisch relevant geacht. De algemene indruk dat de bloeddruk bij opname of op de POS lager en mogelijk een betere uitgangswaarde is dan de vermeend stress gerelateerde OK bloeddruk kon niet worden bevestigd.

Tot op heden zijn alleen theoretische definities bestudeerd en het is onbekend of deze literatuur definities ook de definities vertegenwoordigen die gebruikt worden door het anesthesieteam in de dagelijkse klinische praktijk. In **hoofdstuk 4** werd daarom een onderzoek uitgevoerd naar de definitie van IOH zoals die wordt gebruikt door het anesthesie personeel en tevens werd het verschil tussen deze zelf gerapporteerde definities en daadwerkelijke behandelgrenzen voor lage bloeddruk bestudeerd. Net als in de literatuur kon met behulp van een enquête een grote variëteit van 33 verschillende definities worden gevonden. Vervolgens werd een cohort van 7.149 patiënten bestudeerd die een arthroscopie van de knie ondergingen onder algehele of spinale anesthesie. Onder algehele anesthesie werden lage bloeddrukken over het algemeen behandeld volgens de zelf gerapporteerde grens van een gemiddelde arteriële druk onder 60 mmHg of een systole onder 80 mmHg, welke corresponderen met een daling van 37–40% ten opzichte van de uitgangswaarde. Daarentegen werden patiënten onder spinale anesthesie behandeld bij een gemiddelde arteriële druk van 74 mmHg of een systole van 100 mmHg, corresponderend met de vaak gerapporteerde 25–30% daling vanaf de uitgangswaarde. Dit zou kunnen betekenen dat bij patiënten onder algehele anesthesie, waar de keuze om lage bloeddruk te behandelen enkel wordt overgelaten aan het oordeel van het behandelend anesthesie teamlid, hypotensie bij voorkeur wordt behandeld volgens absolute grenzen (en tegenstelling

tot de zelfrapportage), waarbij de bloeddruk vaak daalt tot 40% van de baseline. In wakkere patiënten onder spinale anesthesie daarentegen, waar de behandeling ook zou kunnen worden ingegeven door symptomen van hypotensie (bijv. duizeligheid, misselijkheid of braken, transpiratie, bleekheid), werden bloeddrukken over het algemeen behandeld bij hogere absolute grenzen die beter overeen kwamen met de zelf gerapporteerde definities van IOH die een grenswaarde gebruiken relatief ten opzichte van een uitgangsbloeddruk.

Het effect van intraoperatieve hypotensie op postoperatieve complicaties

Het tweede deel van dit proefschrift richt zich op de mogelijke associaties tussen IOH en postoperatieve complicaties. Hiertoe werd de rol van IOH in het optreden van een postoperatieve beroerte bestudeerd in **hoofdstuk 5**. Ook al is het zeldzaam, een beroerte is een ernstige complicatie na chirurgie. Het meest geaccepteerde mechanisme van een postoperatieve beroerte is een arteriële embolie, maar de rol van IOH in het optreden en ontwikkeling van een beroerte is grotendeels onbekend. In een cohort van 48.241 patiënten die niet-cardiale en niet-neurochirurgische ingrepen ondergingen werden 42 patiënten met een beroerte vergeleken met 252 controle patiënten van dezelfde leeftijd die hetzelfde type ingreep ondergingen. Voor de analyse werd IOH gedefinieerd volgens een reeks van grenswaarden en na correctie voor mogelijk verstorende variabelen en het meervoudig testen bleef de duur dat de gemiddelde arteriële druk > 30% gedaald was ten opzichte van de uitgangswaarde significant geassocieerd met het optreden van een postoperatieve beroerte. Dit ondersteund de hypothese dat IOH een rol zou kunnen spelen in de ontwikkeling van een postoperatieve ischemische beroerte door de bloedtoevoer naar ischemisch maar nog steeds levensvatbaar weefsel in gevaar te brengen.

IOH is ook eerder in verband gebracht met mortaliteit binnen een jaar na chirurgie. In **hoofdstuk 6** onderzochten we daarom deze associatie in een cohort van 1.705 patiënten die algemene of vaatchirurgie ondergingen, weer gebruik makend van een verscheidenheid aan definities van IOH. Twee verschillende technieken werden gebruikt om de invloed van mogelijk verstorende variabelen te verminderen: multivariate 'Cox proportional hazards regression modelling' en 'classification and regression tree analysis' (CART). De mortaliteit binnen een jaar na chirurgie was 5.2% (n = 88). Cox regressie analyse liet geen causaal verband zien tussen enige van de definities van IOH en 1-jaars mortaliteit. CART analyse echter, identificeerde IOH als

een voorspeller voor 1-jaars mortaliteit en liet zien dat lagere bloeddrukken werden getolereerd voor kortere periodes, wat consistent is met ons klinisch redeneren in de dagelijkse praktijk. Desalniettemin, het effect van IOH op 1-jaars mortaliteit blijft betwistbaar en er kunnen geen harde conclusies getrokken worden over de laagst accepteerbare intraoperatieve bloeddruk.

Tot slot, in **hoofdstuk 7** worden de studies uit dit proefschrift in een breder perspectief gezet. Het grootste probleem in het definiëren van IOH blijft de bepaling van de 'normale' bloeddruk van de patiënt en welke afwijkingen van deze uitgangsbloeddruk veilig zijn voor een specifieke individuele patiënt. Ook al was het onmogelijk om een exacte drempelwaarde te geven kon er wel bewijs worden gevonden ter ondersteuning van het idee dat IOH het best gedefinieerd lijkt te kunnen worden als een daling in de gemiddelde arteriële bloeddruk ten opzichte van een uitgangsbloeddruk. Deze grenswaarde op zijn beurt, hangt af van de duur van de hypotensieve episode waarbij kleinere dalingen beter getolereerd worden dan diepe hypotensie, die voor veel kortere periodes of helemaal niet getolereerd wordt. Toekomstige prospectieve en mogelijk interventie studies over IOH zouden hun focus uit moeten breiden naar de postoperatieve periode en geschikte definities moeten baseren op associaties met ongunstige postoperatieve uitkomsten.

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Epilogue

Dankwoord

Tot slot is een woord van dank aan eenieder zonder wie dit proefschrift nooit mogelijk was geweest op zijn plaats. De moeilijkheid van een dankwoord is echter dat het nooit compleet is. Dus ook voor al diegenen die hun steentje hebben bijgedragen maar die hieronder niet bij naam worden genoemd is mijn dank niet minder groot.

Professor Kalkman, beste Cor, toen ik in maart 2003 bij je kwam om voor het begin van mijn opleiding tot anesthesioloog kennis te maken met de wetenschap, kon ik niet vermoeden dat de daaropvolgende vingeroefeningen met de 'Vierkleurenpen' database de basis zouden leggen voor de ideeën die hebben geleid tot dit proefschrift. Ik ben je heel dankbaar voor de geboden mogelijkheid om mijn opleiding te combineren met promotieonderzoek. Ik waardeer en bewonder je eerlijkheid, oprechtheid en bescheidenheid. Ik heb het als een voorrecht ervaren om bij jou te mogen promoveren.

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Beste Wilton, als co-promotor was je altijd bereikbaar voor raad en daad. Ik bewaar dierbare herinneringen aan de brainstormsessies, congresbezoeken en aan de bemoedigende woorden als de dingen weer eens anders gingen dan gehoopt of gepland. Heel veel dank en succes met je nog lopende onderzoeksprojecten over

perioperatieve outcomes, waaraan we hopelijk in de nabije toekomst nog veel mogen samenwerken. De ideeën zijn nog lang niet op.

De leden van de beoordelingscommissie: professor Kappelle, professor Moll, professor Absalom, heel veel dank voor de bereidheid om tijd in jullie drukke agenda's vrij te maken om mijn pennenvruchten kritisch te beoordelen en zitting te nemen in de promotiecommissie op de openbare verdediging van mijn proefschrift.
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Utrecht, december 2011

List of publications

Publications included in this thesis

1 Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: Literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; 107(2): 213–220.

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3 Bijker JB, Persoon S, Peelen LM, Moons KG, Kappelle LJ, van Klei WA. Intraoperative hypotension and perioperative ischemic stroke after general surgery: A nested case control study. *Under revision at Anesthesiology*.

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5 Bijker JB, Houweling P, Siccama I, van Klei WA, Kalkman CJ. Differences between self-reported definitions of intraoperative hypotension and actual treatment thresholds for low blood pressure. *Under review at British Journal of Anaesthesia*.

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6 Ahmadian L, Cornet R, Kalkman C, de Keizer NF; NVA Working Group 'Minimal Dataset for Preoperative Assessment'. Development of a national core dataset for preoperative assessment. *Methods of Information in Medicine* 2009; 48(2): 155–161.

7 Bijker JB, Kalkman CJ. The role of intraoperative blood pressure in the association between low bispectral index values and mortality within two years after surgery. *Anesthesia & Analgesia* 2010; 110(2): 639.

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1 Bijker JB, van Klei WA, van Wolfswinkel L, Kalkman CJ. Intraoperative hypotension and one-year mortality. *ASA Annual Meeting Atlanta (Georgia, U.S.A.)* October 25, 2005

2 Bijker JB, van Klei WA, van Wolfswinkel L, Kalkman CJ. Volatile anesthetics and one-year mortality. *ASA Annual Meeting, Atlanta (Georgia, U.S.A.)* October 26, 2005

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6 de Jager JA, Bijker JB, Persoon S, Kalkman CJ, van Klei WA. Intraoperative hypotension and postoperative stroke: A case control study. *Dutch Society of Anesthesiology Annual Scientific Meeting, Utrecht (Netherlands)* September 26, 2008

7 Bijker JB, van Klei WA, Houweling PL, Kalkman CJ. Self reported definitions of intraoperative hypotension and actual treatment thresholds for low blood pressure. *ASA Annual Meeting, Orlando (Florida, U.S.A.)* October 18, 2008

8 Bijker JB, van Klei WA, Houweling PL, Kalkman CJ. Intraoperative hypotension, how low do we go? A questionnaire amongst anesthesia personnel. *ASA Annual Meeting, Orlando (Florida, U.S.A.)* October 18, 2008

9 de Jager JA, Bijker JB, Persoon S, Kalkman CJ, van Klei WA. Intraoperative hypotension and postoperative stroke: A case control study. *ASA Annual Meeting, Orlando (Florida, U.S.A.)* October 18, 2008

Curriculum Vitæ

Jilles Bijker was born on September 1, 1975 in Utrecht, the Netherlands. After graduating from high school (VWO) at Het Nieuwe Lyceum in Bilthoven in 1993, he started his medical training (first candidature) at the Catholic University of Leuven (Belgium). The next year he continued his medical study at the Utrecht University where he obtained his Medical Degree in 2003.

In 2004, he started his Ph.D. training and the research described in this thesis (promotores: prof. dr. C.J. Kalkman and prof. dr. K.G.M. Moons; co-promotor: dr. W.A. van Klei). Simultaneously, he began his specialist training in anesthesiology at the Department of Perioperative Care and Emergency Medicine of the University Medical Center Utrecht (chair: prof. dr. J.T.A. Knape). In 2008 he obtained a Master of Science degree in Clinical Epidemiology at the Utrecht University/Julius Center for Health Sciences and Primary Care.

As from July 1, 2011 he is registered as an anesthesiologist and since September he is working at the Gelderse Vallei Hospital in Ede. He is still associated to the University Medical Center Utrecht to continue his research activities.