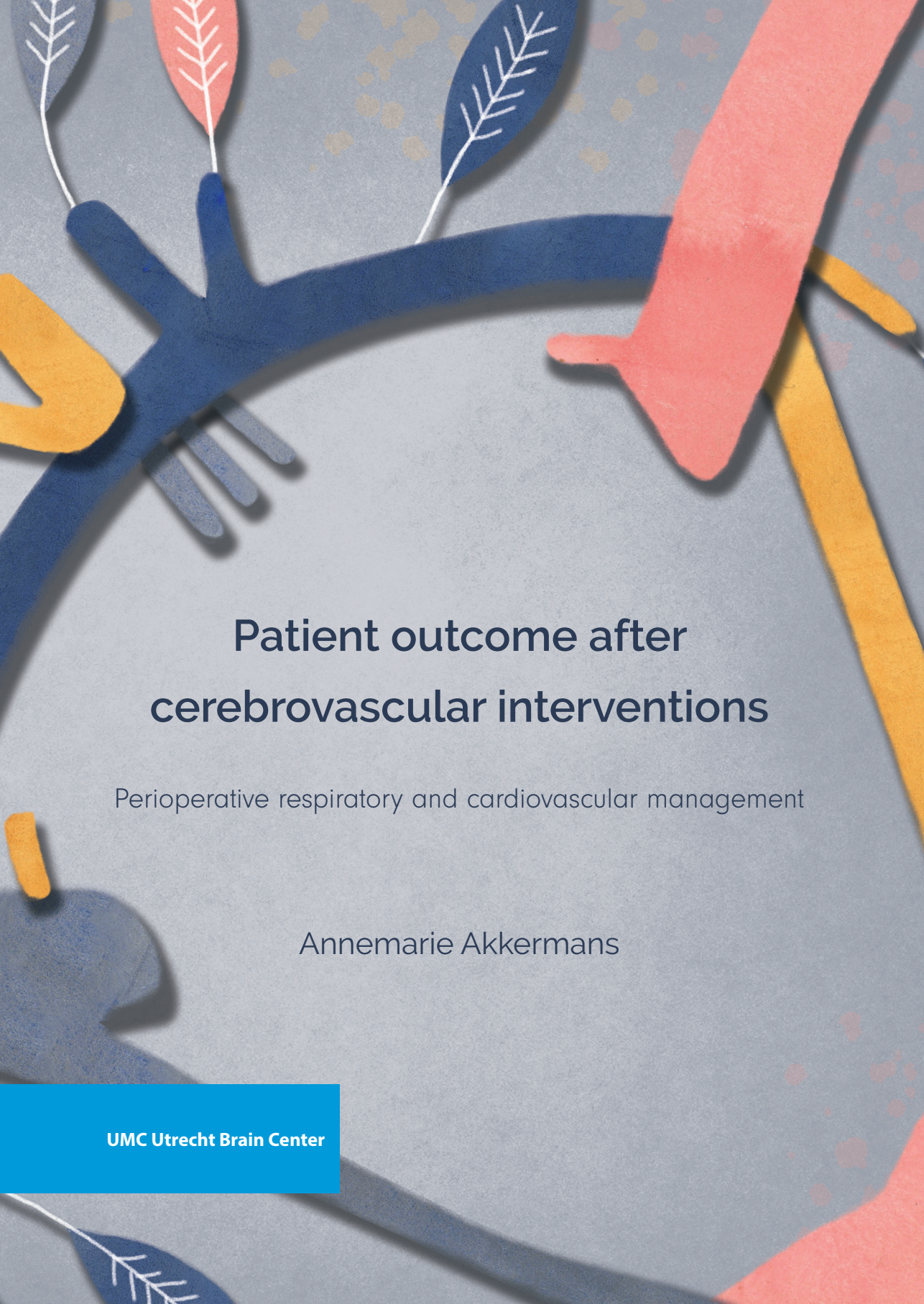

Patient outcome after cerebrovascular interventions

Perioperative respiratory and cardiovascular management

Annemarie Akkermans

UMC Utrecht Brain Center

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Patient outcome after cerebrovascular interventions

Perioperative respiratory and cardiovascular management

Het effect van perioperatief respiratoir en cardiovasculair beleid op patiënt-gerelateerde uitkomsten na cerebrovasculaire interventies

(met een samenvatting in het Nederlands)

Proefschrift

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

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des middags te 12.45 uur

door

Annemarie Akkermans

geboren op 21 maart 1988
te Oosterhout

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Dr. J.A.R. van Waes

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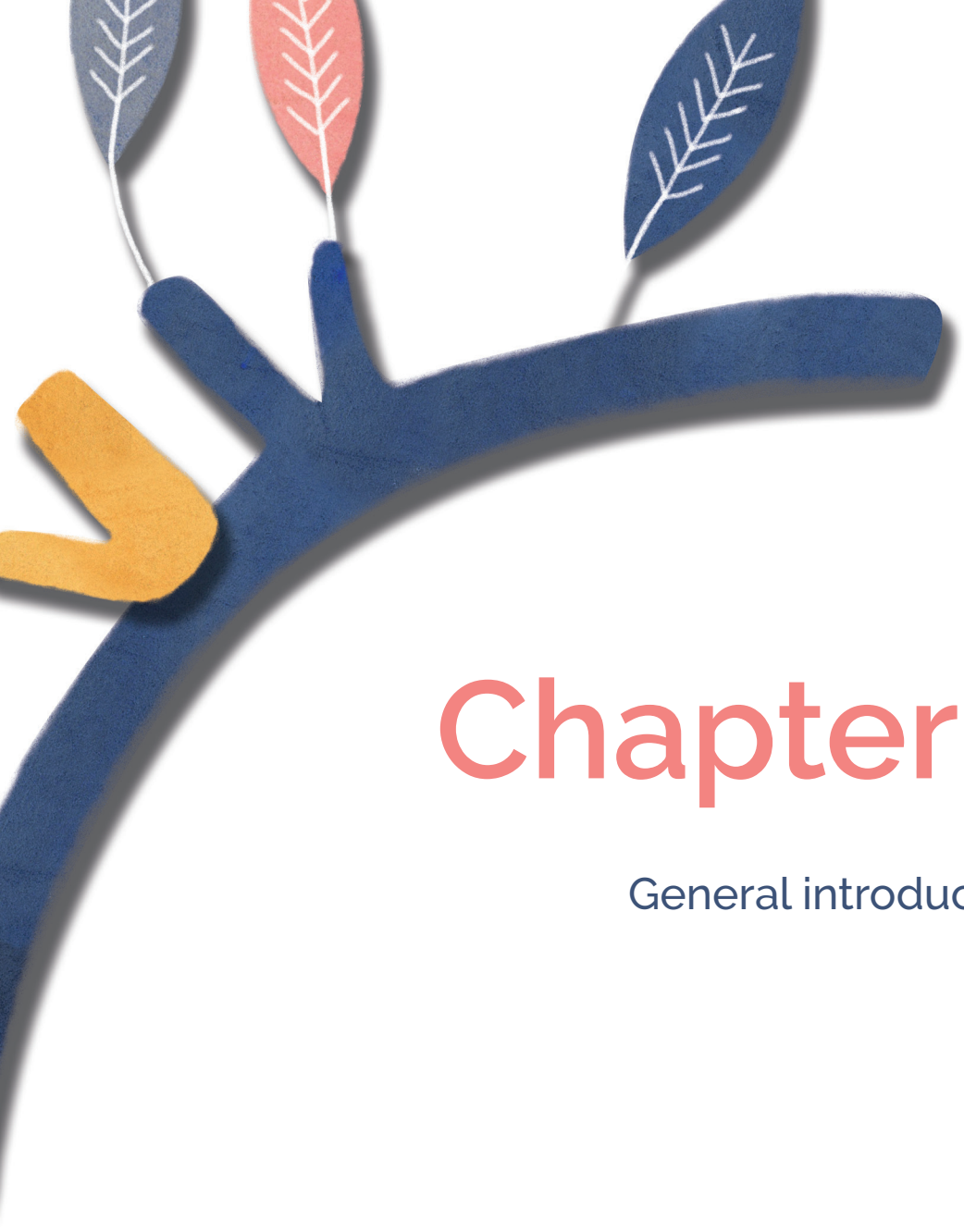

Chapter 1

General introduction

GENERAL INTRODUCTION

Adequate cerebral blood flow is crucial in patients with cerebrovascular disease, especially during anesthesia for neurosurgical or neurovascular interventions. Unfortunately, adequacy of cerebral perfusion is difficult to determine during procedures under general anesthesia and optimal intraoperative management of cerebral blood flow is matter of debate.[1,2] Cerebral blood flow autoregulation has been graphically depicted by Lassen, already in 1959.[3] Based on this famous graph (see Figure 1 for a simplified version), it is believed that the lower limit of cerebral blood flow autoregulation is located at a mean arterial pressure (MAP) of 50 mmHg, the upper limit of autoregulation is at a MAP of 150 mmHg and there is a plateau in between, considering that other factors are held relatively constant. Over decades, this has been taught to residents in the field of anesthesiology, neurology, neurosurgery, and intensive care medicine. In patients with severe cerebrovascular disease, cerebral autoregulation likely becomes disrupted and cerebral blood flow may become almost linearly dependent on blood pressure.[4,5] As simple as this sounds, neuro-anesthesiologists and neurocritical care physicians struggle to consent on targets, since evidence to support Lassen's figure is limited.[2,6–9] Limits of cerebral blood flow autoregulation are not fixed, as they are known to shift upwards in patients with chronic hypertension.[10] To complicate things further, carbon dioxide levels are known to influence the limits and plateau of cerebral autoregulation,[11] while cardiac output can also influence cerebral perfusion.[1]

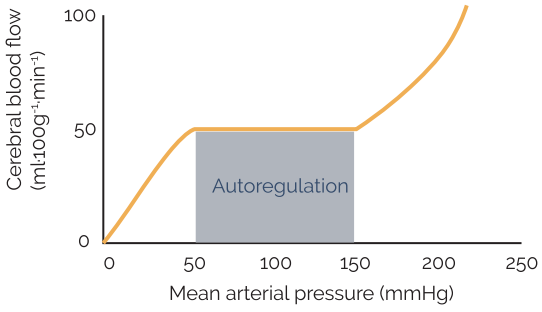

Figure 1. The "classic" cerebral blood flow autoregulation curve depicting the relationship between mean arterial pressure and cerebral blood flow

First, this chapter will provide a short introduction into two entities of severe cerebrovascular disease seen in patients presenting for neurovascular interventions, namely an aneurysmal subarachnoid hemorrhage (ASAH) and moyamoya disease. Second, this chapter will explore the potential role of blood pressure levels,

intraoperative end-tidal carbon dioxide ($ETCO_2$) concentrations and cardiac output in relation to patient outcome after cerebrovascular interventions. Third, this chapter will shortly introduce the potential for perioperative cardiovascular risk identification as a tool for anesthesiologists to improve patient outcome. Finally, this chapter describes the objectives and outline of this thesis.

Subarachnoid hemorrhages and the need for outcome improvement

ASAH is characterized by extravasation of blood into the cerebrospinal fluid surrounding the central nervous system.[12] It occurs in approximately 8 per 100,000 patient-years[13] and is associated with case fatality rates as high as 30%, despite advances in treatment over the past decades.[7,14,15] Approximately 20% of all survivors still has substantial restrictions in daily life ten years after ASAH[16] and only a third returns to their profession.[17] Not only poor recovery from the initial bleeding is an issue of concern. After experiencing ASAH, patients have an increased risk of vascular events and death compared to the general population.[14] Standardized mortality rates of 1.8 (95% confidence interval 1.6–2.1) for all-cause death and 2.0 (95% confidence interval 1.6–2.5) for vascular death are reported in patients who were alive three months after the ictus. An increased risk of all-cause mortality remains present for up to 20 years after ASAH.[14] In the past decades, several attempts have been made to improve the outcome after ASAH, but with varying success. This leaves room for further improvement.[15,18,19]

Most ASAH patients require neurosurgical clipping or endovascular coiling to occlude the ruptured aneurysm. Anesthesiologists are intensely involved during these interventions and their treatment can potentially influence short- and long-term outcome in ASAH patients. For example, anesthesiologists can target specific ranges for respiratory and hemodynamic parameters. However, the exact influence of these parameters, including intraoperative $ETCO_2$ concentrations, blood pressure and cardiac output, on (postoperative) outcome in ASAH patients is unknown.

Moyamoya disease

Moyamoya disease is a rare progressive cerebrovascular disorder, characterized by narrowing of the distal internal carotid arteries and their proximal branches.[20] As a consequence of reduced cerebral blood flow in major vessels, a collateral system of small vessels develops. Moyamoya patients are predisposed to both ischemic and hemorrhagic stroke, as these collaterals can be too small to supply sufficient blood flow and are fragile and prone for rupture.[20] Currently, there is no treatment available to reverse the primary disease process and treatment is focused on preventing adverse events. A cerebral bypass is a revascularization technique often used for flow augmentation in these patients.[21] During this procedure, an anastomosis is

made between two arteries, mostly from an extracranial to an intracranial artery, to circumvent a diseased part of the cerebral vasculature. Although cerebral bypass surgery aims to prevent future ischemic strokes, patients are at risk for perioperative cerebral ischemia.[21]

The potential role of carbon dioxide in improving cerebral perfusion

Carbon dioxide is a waste product of human metabolism and is secreted via the lungs. It presumably has vasoactive and immune-modulating properties, influencing the central nervous system, the cardiovascular system and the respiratory tract, among others.[11,22] Currently, there are no recommendations on carbon dioxide targets during mechanical ventilation under general anesthesia in international guidelines for management of ASAH patients or neurosurgical patients alike.[7] However, it is known that hypocapnia can aggravate cerebral ischemia through vasoconstriction[23] and is associated with a poor neurologic outcome in patients with traumatic brain injury, an ischemic stroke or after a cardiac arrest.[24–26] Two small studies in ASAH patients investigated the association between carbon dioxide concentrations and neurologic outcome and found that cerebral blood flow increased during hypercapnia.[27,28] Interestingly, results from a large retrospective study suggest a potential harmful role for hypercapnic acidosis in patients with acute cerebral injury.[29] In conclusion, the effect of carbon dioxide concentrations on neurologic outcome in ASAH patients remains matter of debate. This discussion is even further fueled by the fact that carbon dioxide does not only have vasoactive properties affecting cerebral perfusion, but can also potentially influence the development of pulmonary complications. Permissive hypercapnia might have protective, immune-modulating properties and enables lung protective ventilation strategies.[22,30] Pulmonary complications are common following non-cardiac surgery and in ASAH patients.[31–33] They are associated with an increase in length of stay, case fatality rates and healthcare costs, in addition to a worse neurologic outcome in ASAH patients.[31,32] Potentially, intraoperative permissive hypercapnia can decrease the incidence of postoperative pulmonary complications,[22,34,35] while improving cerebral perfusion. However, evidence is lacking to define intraoperative $ETCO_2$ targets in ASAH patients and others presenting for cerebrovascular interventions.

The potential role of blood pressure in improving cerebral perfusion

In patients with a disrupted cerebral autoregulation, as seen in ASAH and moyamoya disease, preservation of adequate blood pressure levels is considered important to avoid both hypotension-related cerebral ischemia or, in case of ASAH, hypertension-related re-bleeding. Unfortunately, general anesthesia affects cerebral perfusion via a variety of pathways, including a disturbance in systemic hemodynamics.[1] A few small studies looked at the effect of different intraoperative blood pressure levels on neurologic

outcome in ASAH patients.[36–40] The results from these studies provided insufficient evidence for solid recommendations on intraoperative blood pressure targets. A survey among European neuro-anesthesiologists showed that most anesthesiologists keep the MAP above 60 mmHg. However, there is a large variability in arterial blood pressure management.[6] The American Heart Association/American Stroke Association advises in their 2012 guidelines to keep the systolic blood pressure <160 mmHg in patients with unsecured ruptured aneurysms. This is a consensus opinion, rather than an evidence-based advice. Once the aneurysm is secured, higher blood pressures are allowed, but no exact boundaries (or targets) are known.[7]

Up to 46% of ASAH patients develop cerebral vasospasm, which is associated with cerebral ischemia and poor neurologic outcome.[12] Several strategies have been proposed to prevent or treat cerebral vasospasm and increase cerebral blood flow, including hypervolemia, hemodilution and hypertension. All three components combined are called triple-H therapy, a concept that dates back to the 1970s and is based on the Hagen-Poiseuille Law (see formula below).[41] Blood flow is dependent on the difference in pressure over the vessel (ΔP), the radius of the vessel (r), viscosity of blood (η) and the length of the blood vessel (λ). When the vessel is narrowed (in cerebral vasospasm "r" decreases and becomes relatively fixed), the only variables that can be manipulated to improve blood flow are viscosity and pressure.

$$blood\ flow\ = \frac{\Delta P r^4}{8\eta\lambda}$$

A review studying the outcomes of eleven studies looking into the effect of (components of) triple-H therapy concluded that out of the three arms of triple-H therapy, hypertension was the most promising strategy.[42] Indeed, the vast majority of neuro-anesthesiologists and neurocritical care physicians applies induced hypertension in case of symptomatic vasospasm.[6] However, the HIMALAIA trial by Gathier et al.[19] was not able to provide evidence for a beneficial effect of induced hypertension to prevent delayed cerebral ischemia in ASAH patients. Unfortunately, this study was preliminary stopped because of slow recruitment.

It should be acknowledged that vasopressors used to initiate hypertension may also cause vasoconstriction and possible decrease the radius ("r") of cerebral vessels even further. An increase in blood pressure with vasopressors and thus an increase in ΔP might eventually surpass the effect of vasoconstriction and increase cerebral blood flow, but at the cost of systemic hypertension, possible leading to adverse events such as atrial fibrillation, myocardial infarction and death.[19]

For patients with moyamoya disease, evidence for intraoperative blood pressure management is lacking. Based on expert opinion, it is suggested to maintain the blood pressure at least at levels comparable to preoperative awake blood pressures.[43]

Is there an additional role for cardiac output in improving cerebral perfusion?
Systemic blood pressure is determined by cardiac output and total peripheral resistance. Therefore, it can be argued that an increase in cerebral blood flow in patients with a disrupted autoregulation can also be accomplished by an increase in cardiac output using inotropes, while preventing vasoconstriction.[44,45] One small study in ASAH patients with cerebral vasospasm found that a 46% increase in cardiac output with dobutamine infusion led to a 42% increase in cerebral blood flow in the brain regions perfused by vasospastic arteries.[45] The increase in cerebral blood flow took place despite a small decrease in MAP (4%). Only up to 22% of neuro-anesthesiologists and neurocritical care physicians reported to use inotropes in the presence of severe cerebral vasospasm in ASAH patients.[6] No studies reported the use of inotropes to improve graft flow and cerebral perfusion in patients with moyamoya disease presenting for a cerebral bypass. In conclusion, there is insufficient evidence to advice on cardiac output management to improve cerebral blood flow in patients presenting for these cerebrovascular interventions.

Perioperative cardiovascular risk identification in patients presenting for cerebrovascular interventions
ASAH patients have an overall increased long-term mortality rate and an increased incidence of cardiovascular events compared to age- and sex-matched groups,[14,46] partly due to an increased incidence of cardiovascular risk factors such as smoking and hypertension.[47] In patients presenting for non-cardiac surgery, perioperative troponin levels (as a proxy for perioperative myocardial injury) can be used to help identifying patients with an increased risk of future major adverse cardiac events (MACE) and mortality.[48,49] Therefore, the University Medical Center (UMC) Utrecht implemented a routine postoperative troponin surveillance program. It is uncertain whether postoperative troponin elevation is also associated with MACE in ASAH patients and whether the routine troponin surveillance program can be used to identify ASAH patients at risk for MACE.

Identification of patients at risk for MACE is one thing. However, it is also essential to implement interventions after identification of a high-risk patient. Preventive measures for the non-cardiac surgery population have been studied, such as initiation of aspirin, clonidine and dabigatran regimes.[50–52] Thus far, only a dabigatran regime improved patient outcome.[52] Initiation of anticoagulation therapy shortly after ASAH might not be desirable. Another potential intervention could be targeted postoperative follow-up by anesthesiologists in an effort to timely diagnose or even prevent complications. Therefore,

the UMC Utrecht implemented a dedicated team of anesthesiologists to conduct visits in patients with postoperative elevated troponin levels. The effect of these postoperative visits by anesthesiologists on clinical outcomes and care utility is yet to be determined.

Objectives of this thesis

The objectives of this thesis were 1) to explore the effects of intraoperative carbon dioxide concentration on pulmonary complications in general and in neurosurgical patients specifically, in addition to the effect on neurologic outcome in ASAH patients, 2) to evaluate the effect of different intraoperative blood pressure thresholds on neurologic outcome in ASAH patients, 3) to disentangle the different effects of blood pressure and cardiac output on cerebral perfusion in patients with a disrupted cerebral autoregulation and 4) to determine the relevance of postoperative troponin surveillance in ASAH patients.

Outline of this thesis

In **Part I**, **Chapter 2 and 3**, we explore the trends in $ETCO_2$ as seen in clinical practice in the non-cardiothoracic surgery population. First, **Chapter 2** reports whether $ETCO_2$ targets have changed over time and whether different practice patterns can be identified in the general population and in several subgroups. Second, **Chapter 3** describes the association between intraoperative $ETCO_2$ levels and postoperative pulmonary complications. Results from these two chapters were used as a starting point to further explore the effect of $ETCO_2$ on neurologic outcome in **Part II**.

In **Part II** we focus more specifically on $ETCO_2$ and hemodynamic parameters in patients presenting for cerebrovascular interventions. **Chapter 4** describes the association between different intraoperative $ETCO_2$ and MAP thresholds used in current clinical practice and neurologic outcome in ASAH patients, whereas **Chapter 5** sets out to explore the differential effect of dobutamine – to increase cardiac output – and phenylephrine – to increase blood pressure - on graft flow (as a proxy for cerebral perfusion) in patients presenting for cerebral bypass surgery.

Part III, **Chapter 6 and 7**, discusses the role of perioperative cardiovascular risk identification. In **Chapter 6** we describe the prognostic relevance of troponin measurements after occlusion of a ruptured cerebral aneurysm to predict MACE in ASAH patients. **Chapter 7** discusses the potential beneficial effect of postoperative follow-up visits by a dedicated team of anesthesiologists in patients with elevated troponins after surgery. In this chapter we also explore the effect of the implementation of such a team on care utility.

Part IV, **Chapter 8** discusses the findings from previous chapters in a broader context, as well as potential future directions.

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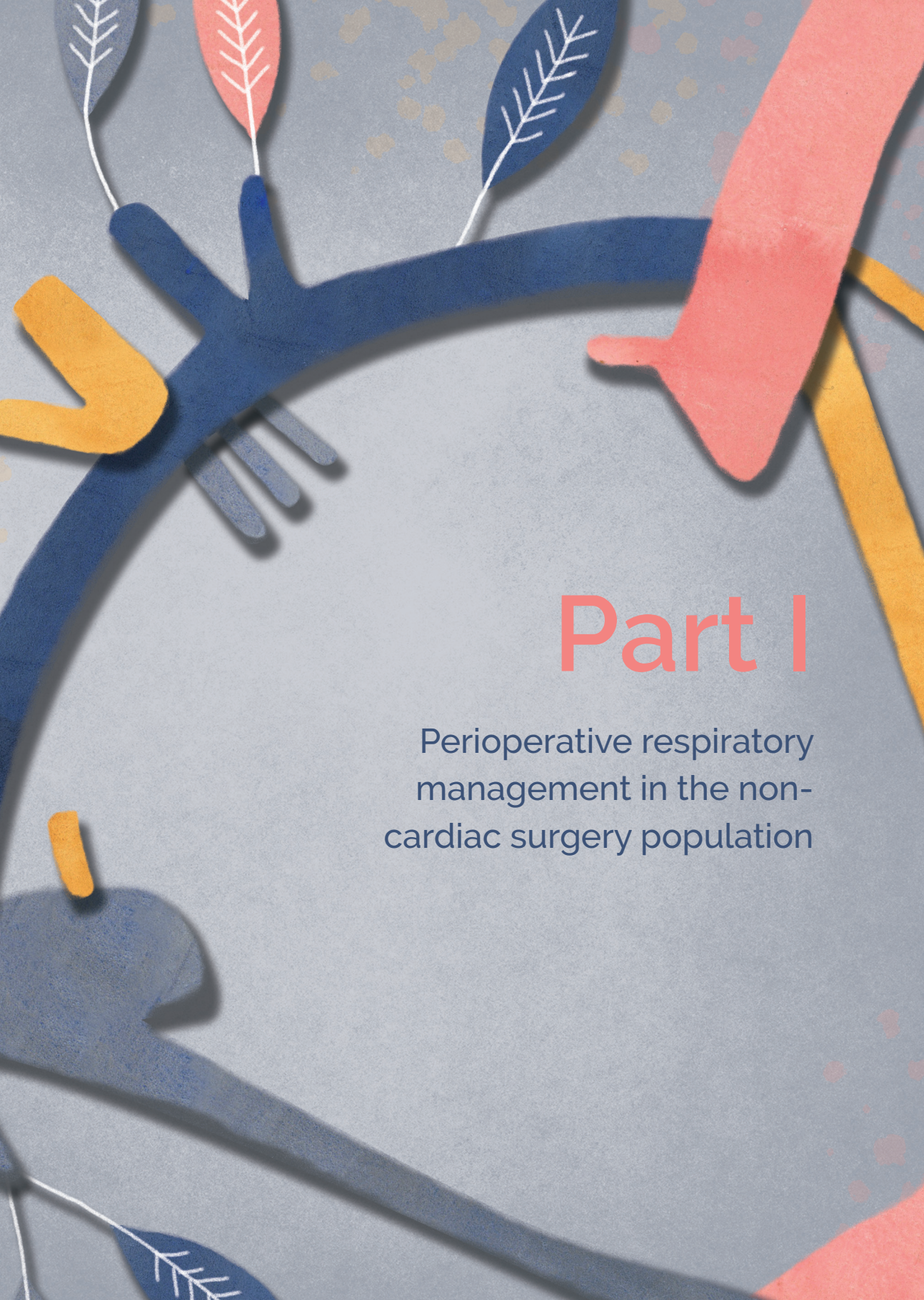
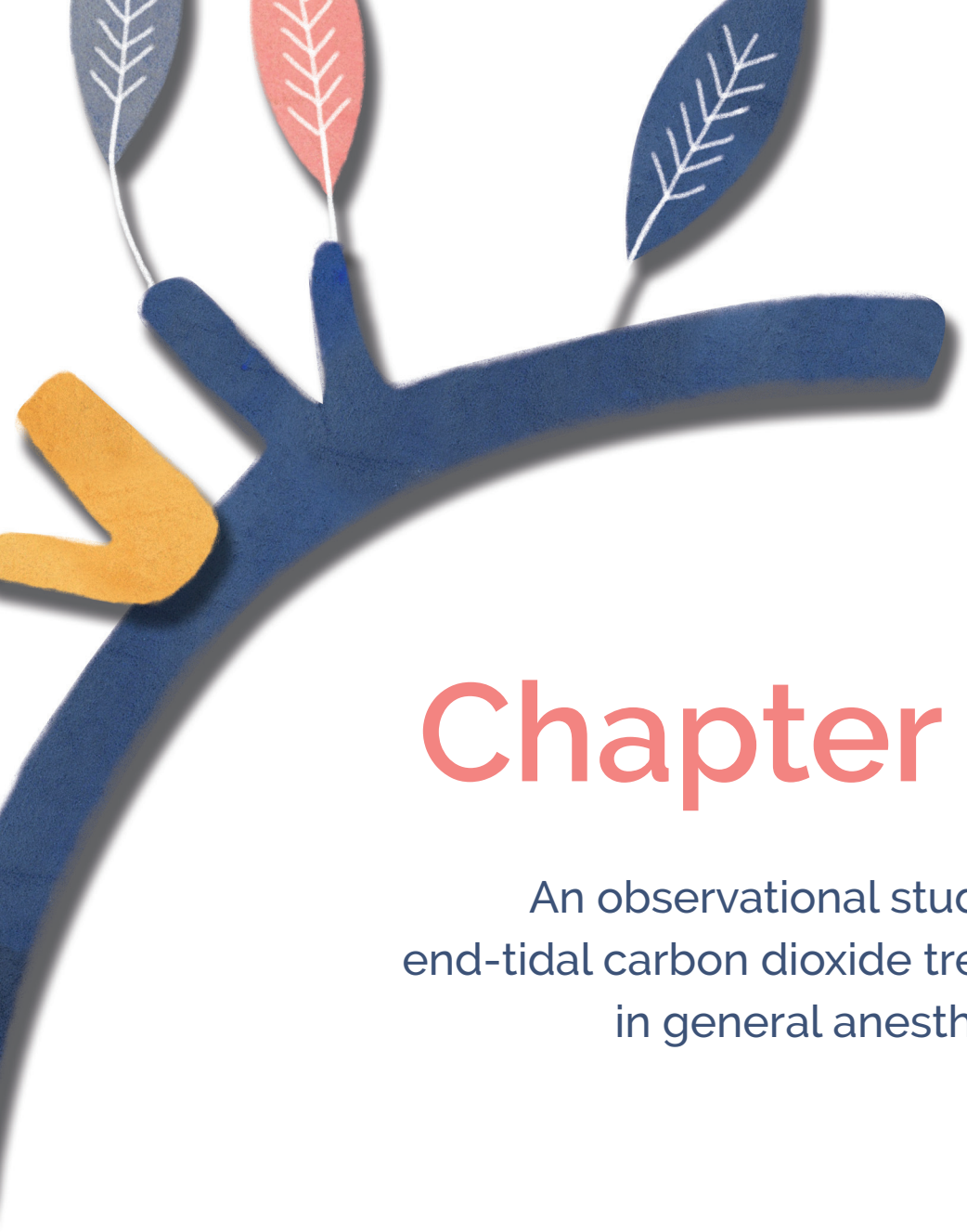


Part I

Perioperative respiratory management in the non-cardiac surgery population



Chapter 2

An observational study of end-tidal carbon dioxide trends in general anesthesia

Annemarie Akkermans, Judith A.R. van Waes, Aleda Thompson, Amy Shanks, Linda M. Peelen, Michael F. Aziz, Daniel A. Biggs, William C. Paganelli, Jonathan P. Wanderer, Daniel L. Helsten, Sachin Kheterpal, Wilton A. van Klei, Leif Saager

Canadian Journal Of Anaesthesia. 2019;66(2):149–160

ABSTRACT

Background Despite growing evidence supporting the potential benefits of higher end-tidal carbon dioxide ($ETCO_2$) levels in surgical patients, there is still insufficient data to formulate guidelines for ideal intraoperative $ETCO_2$ targets. As it is unclear which intraoperative $ETCO_2$ levels are currently used and whether these levels have changed over time, we investigated the practice pattern using the Multicenter Perioperative Outcomes Group database.

Methods This retrospective, observational, multicenter study included 317,445 adult patients who received general anesthesia for non-cardiothoracic procedures between January 2008 and September 2016. The primary outcome was a time-weighted average area-under-the-curve (TWA-AUC) for four $ETCO_2$ thresholds (<28, <35, <45 and >45mmHg). Additionally, a median $ETCO_2$ was studied. A Kruskal-Wallis test was used to analyze differences between years. Random-effect multivariable logistic regression models were constructed to study variability.

Results Both TWA-AUC and median $ETCO_2$ showed a minimal increase in $ETCO_2$ over time, with a median $ETCO_2$ of 33 mmHg [interquartile range (IQR) 31.0-35.0] in 2008 and 35 mmHg [IQR 33.0-38.0] in 2016 (p-value <0.001). A large inter-hospital and inter-provider variability in $ETCO_2$ was observed after adjustment for patient characteristics, ventilation parameters, and intraoperative blood pressure (intraclass correlation coefficient 0.36 [95% CI 0.18-0.58]).

Conclusions Between 2008 and 2016, intraoperative $ETCO_2$ values did not relevantly change. Interestingly, we found a large inter-hospital and inter-provider variability in $ETCO_2$ throughout the study period, possibly indicating a broad range of tolerance for $ETCO_2$, or a lack of evidence to support a specific targeted range. Clinical outcomes were not assessed in this study and they should be the focus of future research.

INTRODUCTION

Historically, it has been common practice to maintain hypocapnia (arterial carbon dioxide pressure ($PaCO_2$) <35 mmHg) during general anesthesia.[1,2] Intraoperative end-tidal carbon dioxide ($ETCO_2$) values around 30 mmHg were frequently targeted, as hypercapnia ($PaCO_2$ >45 mmHg) was considered to contribute to intraoperative tachycardia and hypertension, thereby increasing the oxygen demand of the myocardium.[1,3] In contrast, hypocapnia reduced the need for muscle relaxants and additional anesthetics to prevent spontaneous ventilation. However, there is no good evidence to support the benefit of hypocapnia, and some studies suggest benefits for higher $ETCO_2$ levels.[1,4,5] First, it is easier to implement low tidal volume ventilation.[6,7] Second, hypercapnia increases the cardiac output, resulting in an increase in tissue oxygenation, which in turn may prevent surgical site infections.[1,8–10] Third, studies using different lung injury models showed that hypercapnia has protective, immune-modulating properties, resulting in a decreased inflammatory response.[11–13] Fourth, hypercapnia may increase lung parenchymal compliance[13–15] and can improve ventilation-perfusion matching in the lungs.[1,12,16] Finally, normocapnia is considered to positively influence the neurologic outcome due to vasoactive properties of $PaCO_2$, which is especially pronounced in already injured brains.[17]

Unfortunately, many studies focus on the critical care population, leaving surgical patients underrepresented.[1,2,4,5,8–10] Therefore, there exists no strong evidence of a benefit for higher carbon dioxide tensions compared to hypocapnia in perioperative patients. To generate evidence to formulate guidelines on $ETCO_2$ management during general anesthesia, we first need to understand current clinical practice. To our knowledge, it is unclear which target $ETCO_2$ levels are currently used and whether these levels have changed over time. Therefore, this study aimed to investigate the practice pattern of $ETCO_2$ levels over time in non-cardiothoracic surgery. We did not aim to study clinical outcomes. We hypothesized that the target $ETCO_2$ level may have increased over time in response to the existing evidence described above. To further explore the practice pattern, we aimed to investigate four subgroups separately: patients with chronic obstructive pulmonary disease (COPD, subgroup 1); patients undergoing intracranial or carotid artery surgery (subgroup 2); and patients receiving laparoscopic surgery with (subgroup 3) or without (subgroup 4) robot assistance.

METHODS

For this multicenter, retrospective, observational study, we used data from the Multicenter Perioperative Outcomes Group (MPOG) database. The MPOG registry, data entry process and validation of data has been described in detail previously.[18,19] In brief, MPOG is a consortium of 47 hospitals in North-America and Europe, collecting perioperative data to facilitate outcomes research. Institutional Review Board (IRB) approval for MPOG was obtained from the University of Michigan Health System, as MPOG's coordinating institution. Each participating institution has separate IRB approval to submit a limited set of perioperative data into the centralized database for future use, without any direct patient identifiers. Ethical approval for the current study was provided by the University Medical Center Utrecht, as leading institution for this project (May 2016, Number 16-282/C). The requirement for written informed consent was waived. No additional IRB approval was sought from other institutions. Additionally, the study protocol was reviewed *a priori* and approved by the MPOG Perioperative Clinical Research Committee (PCRC-0032, September 2016).

Patients

This study included all adult patients ≥18 years who received general anesthesia between 01.01.2008 and 09.01.2016 at eight academic institutions affiliated with MPOG: University of Michigan Health System, Ann Arbor, Michigan; Oregon Health & Science University, Portland, Oregon; University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; Washington University School of Medicine, St. Louis, Missouri; University of Vermont Medical Center, Burlington, Vermont; Vanderbilt University, Nashville, Tennessee; University Medical Center Utrecht, Utrecht, the Netherlands; University of Pennsylvania Health System, Philadelphia, Pennsylvania. Only institutions submitting data for all variables mentioned below were selected for this study. For patients who received general anesthesia more than once within 30 days, only the first case was included. Exclusion criteria are presented in Figure 1. These criteria were based on procedure type, a poor clinical condition prior to anesthesia and suspected intraoperative hemodynamic instability in order to limit the risk of artifacts and invalid $ETCO_2$ values. The amount of vasopressor use per hour was used as a proxy for hemodynamic instability. Additionally, we excluded patients who received one-lung ventilation and ventilation by means of a laryngeal mask airway. To ensure sufficient time for data collection, cases with <40 minutes between incision and the end of the surgical procedure were excluded. Furthermore, patients with <20 valid machine-generated $ETCO_2$ measurements were excluded.

A priori we defined four subgroups of patients in whom the target $ETCO_2$ level was considered to possibly differ from other patients: 1) patients with COPD, as their awake $PaCO_2$ level may be increased and therefore a higher $ETCO_2$ may be accepted;[20] 2) patients undergoing intracranial & carotid artery surgery, as these interventions may compromise cerebral perfusion and therefore warrant a strict control of $ETCO_2$;[1,17] and patients receiving laparoscopic surgery with or without robot assistance (subgroups 3 and 4, respectively), as insufflation with carbon dioxide can increase $PaCO_2$ and therefore higher $ETCO_2$ levels may need to be tolerated.[21–23] We differentiated between laparoscopic surgery with and without robot assistance, since Trendelenburg positioning can further increase $PaCO_2$.[22] All four subgroups were excluded from the primary analysis, to avoid confounding the observed change over time in $ETCO_2$ levels, especially due to an increasing utilization of laparoscopic over open procedures. Patients eligible for multiple groups were excluded from all analyses.

Outcome

The primary outcome was $ETCO_2$ stratified into four groups (<28, <35, <45 and >45 mmHg) and the area-under-the-curve for each specific threshold was estimated with adjustment for the total measurement time, resulting in a time-weighted average area-under-the-curve (TWA-AUC) per threshold. Patients could be binned into multiple groups. Patients with at least one valid $ETCO_2$ <28 mmHg were binned into the <28 mmHg group, but this data was also used for the <35 mmHg and <45 mmHg groups, respectively. If patients also had at least one valid $ETCO_2$ values >45 mmHg, the corresponding TWA-AUC was binned into the >45 mmHg group.

To aid interpretation and clinical applicability, a median $ETCO_2$ per case was obtained as a secondary outcome measure. *A priori*, a relative change of 10% in median $ETCO_2$ over the entire study period was considered to be clinically relevant.

Data collection

Data collection for intraoperative variables started ten minutes after surgical incision in order to ignore hyper- and hypocapnia that may follow mask ventilation and intubation during induction of anesthesia, and to allow the $ETCO_2$ to reach a set level. Data collection ended ten minutes prior to the end of the surgical dressing, in order to ignore increased values of $ETCO_2$ that may be accepted to establish spontaneous ventilation. When the exact incision time was not registered, data collection started 20 minutes after anesthesia induction. Only valid $ETCO_2$ values were used (see Table 1S in the Supplemental Material for the artifact filter). Data were collected for ventilation parameters (tidal volume, respiratory rate, positive end-expiratory pressure (PEEP), respiratory minute volume (RMV)) and mean arterial pressure (MAP) as potential

confounders. MAP and ventilation parameters, including $ETCO_2$, were measured continuously during general anesthesia by automated interfaces. An average of these results was recorded every minute in the anesthesia record-keeping system and stored in the centralized MPOG database.

Preoperative data on sex, height, body mass index (BMI), age and American Society of Anesthesiologists (ASA) physical status were collected as covariates.[24] For every case we recorded the institution and determined the primary anesthesia provider, defined as the supervising anesthesiology faculty and primary anesthesia caregiver (either nurse anesthetists or resident) that provided anesthesia for at least 75% of the time.

Statistical analysis

Descriptive statistics were computed using frequencies and percentages for categorical variables and medians with interquartile ranges (IQR; 25^{th} and 75^{th} percentiles) for continuous data, after checking continuous variables for normality using the Kolmogorov-Smirnov test.

Differences in baseline characteristics, ventilation parameters and mean MAP between the general cohort and the subgroups and between the beginning and end of the study were estimated using a Kruskal-Wallis test.

For all four thresholds, the TWA-AUC of each patient was computed from minute-level $ETCO_2$ values using a fitted cubic spline curve (see Figure 1S in the Supplemental Material, showing the method to calculate the area-under-the-curve). For every case a median was calculated for tidal volume, respiratory rate, PEEP and RMV. We determined the mean MAP for every case, as a summary measure for the overall blood pressure. Both the TWA-AUC and median $ETCO_2$ were plotted over time and values were compared between years using a Kruskal-Wallis Test. Medians and IQR were reported.

Prior to the start of this study, we surveyed all participating centers to gain insight into target $ETCO_2$ levels and factors that might have influenced these levels during the study period. The full survey can be found in the Supplemental Material. When abrupt changes in $ETCO_2$ were reported by at least half of all institutions, an Interrupted Time Series analyses would be considered.

To examine variation in $ETCO_2$, patient characteristics were compared between patients with a median $ETCO_2$ $<5^{th}$ percentile, between the 5^{th} and 95^{th} percentile and $>95^{th}$ percentile, using a Kruskal-Wallis test. To examine variation between and within each institution, six mixed-effect multivariable logistic regression models were built.

A positive TWA-AUC $ETCO_2$ >45 mmHg (meaning that at least one $ETCO_2$ value per case was >45 mmHg) was used as a binary outcome measure in all models. Before any regression models were constructed, all variables under consideration for model inclusion were checked for collinearity using the condition index. If the condition index was >30, a Pearson's correlation matrix was developed. Those variables deemed to be collinear (defined as a correlation of ≥ 0.70) were either combined into a single variable or removed. All non-collinear variables were entered into the models. The included fixed effects were selected based upon clinical relevance: age (binned per decade, reference group 18-30), sex, BMI (binned into <18.5, 18.5-24.9 (reference group), 25.0-29.9, 30.0-34.9, 35.0-39.9, ≥40.0 kg/m^2), ASA class (I or II versus III, IV, V), median tidal volume (binned by ideal body weight into <6, 6-8 (reference group), 8-10, >10 ml/kg), median respiratory rate (binned into <12, 12-16 (reference group), 16-20, >20 per minute), median PEEP (binary, <5 or ≥5 cmH_2O), mean MAP (binned into <65, 65-80 (reference group), >80 mmHg) and year of the procedure. All six mixed-effects models contained the same fixed effects, with differing random effects between the models. The first model used institution as a random effect to examine the variation between institutions; the second model used primary anesthesia caregiver and the third used supervising anesthesiology faculty as random effects to examine how much of the variation could be explained by inter-provider variability. The fourth model used supervising anesthesiology faculty nested within institution as the random effect and the fifth model used primary anesthesia caregiver nested within institution, to further explore to variation due to preferences of a provider within a specific institution. The final model was built with primary anesthesia caregiver nested within supervising anesthesiology faculty, which was again nested within institution, as the random effect. This model was built to explore how much of the variation could be explained by a particular anesthesia care team in a specific institution. Measures of effect size for random effects were reported as intraclass correlation coefficients (ICC) and median odds ratios (MOR) with corresponding 95% confidence intervals (CI).[25]

All analyses were conducted for the general cohort and the subgroups separately. A p-value <0.05 was considered statistically significant for all analyses.

The analyses were conducted using SAS v. 9.4 (SAS Institute, Cary, NC, USA) and Stata v. 13.1 (StataCorp LLC; College Station, TX, USA). The study was conducted in adherence to the STROBE statement for observational research.[26]

RESULTS

1,794,773 patients met the initial inclusion criteria of general anesthesia and age. After application of all *a priori* defined exclusion criteria and after exclusion of invalid observations, 317,445 patients were eligible. We included 245,725 patients in our primary analysis and 71,720 patients in different subgroups (Figure 1). Patient characteristics for the general cohort and the subgroups are described in Table 1. Additionally, differences in patient characteristics between 2008 and 2016 are shown in Table 2. Over time, patients were slightly older, had a higher BMI and had a higher ASA class. RMV slightly decreased over time, whereas the mean MAP increased over time. The duration of both the procedure and general anesthesia decreased over time.

Change in $ETCO_2$ over time

The mean TWA-AUC per quarter of a year was plotted for all four $ETCO_2$ thresholds (Figure 2, data for the general cohort) and showed that more time was spent closer to or above the threshold of 45 mmHg. There was a statistically significant decrease in TWA-AUC from 2008 to 2016 for an $ETCO_2$ <28 mmHg, <35 mmHg and <45 mmHg, whereas the TWA-AUC $ETCO_2$ >45 mmHg significantly increased over time (Table 2). The median [IQR] $ETCO_2$ was plotted over time (Figure 3A) and showed a minimal increase from 33 mmHg [IQR 31.0-35.0] in 2008 to 35 mmHg [IQR 33.0-38.0] (p-value <0.001) in 2016.

Similar trends over time were obtained for the subgroups (Figure 3 and Table 2). However, the $ETCO_2$ was lower for patients presenting for intracranial & carotid artery surgery and higher for patients in the (robotic) laparoscopic cohort and for patients with COPD (see also Table 2S in the Supplemental Material, showing the median $ETCO_2$ and TWA-AUC per threshold for the general cohort and all subgroups).

In the survey, two out of eight (25%) institutions reported a decrease in RMV between 2008 and 2016 and one institution (12.5%) reported an increase in RMV. Three institutions (37.5%) reported an increase in target $ETCO_2$ level, varying between 2 and 5 mmHg. Since a minority of institutions reported a change in time, we refrained from conducting an Interrupted Time Series analysis. Results from the survey are summarized in Table 3S in the Supplemental Material.

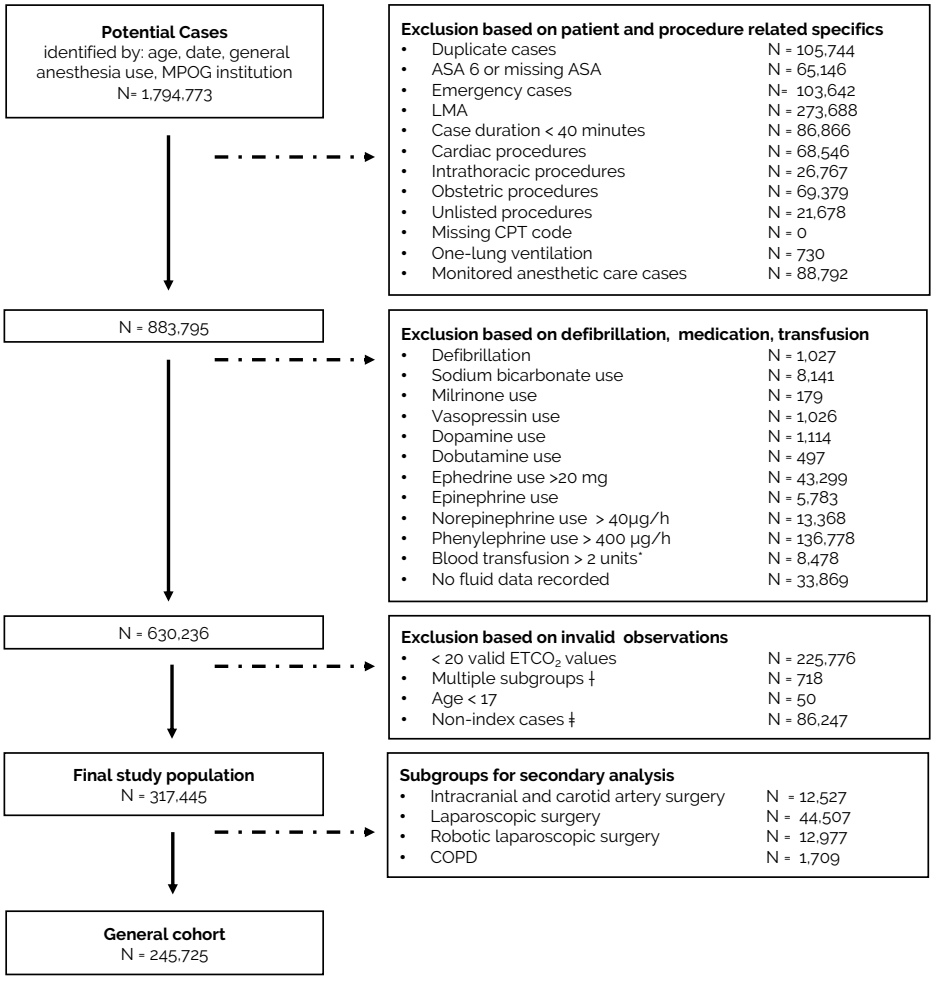


Figure 1. Flow chart

ASA: American Society of Anesthesiologists physical status. COPD: chronic obstructive pulmonary disease. CPT: Current Procedural Terminology. $ETCO_2$: end-tidal carbon dioxide. LMA: laryngeal mask airway. MPOG: Multicenter Perioperative Outcomes Group. * Blood transfusion >2 units was defined as: more than two units of packed cells or whole blood or more than 600 ml of cell saver blood during general anesthesia. ǂ Patients were excluded when they met the inclusion criteria of more than 1 subgroup: e.g. COPD and laparoscopic surgery. ǂ Only the first case within 30 days was included.

Table 1. Baseline characteristics for the general cohort and the subgroups

		General cohort
		N = 245,725
Age (years, median [IQR])		51 [38-63]
Sex (female, %)		124,782 (50.8)
ASA class (%)	I	27,738 (11.3)
	II	125,488 (51.1)
	III	84,835 (34.5)
	IV	7,603 (3.1)
	V	61 (0.02)
Height (cm, median [IQR])		170 [163-178]
BMI (kg/m^2, median [IQR])		27.8 [24.1-32.7]
Median RMV (mL/min, median [IQR])		5,571 [4,660-6,590]
Median respiratory rate (/min median [IQR])		10 [9-12]
Median $ETCO_2$ (mmHg, median [IQR])		34.0 [32.0-36.0]
Mean MAP (mmHg, median [IQR])		78 [72-85]
Duration of general anesthesia (min, median [IQR])		170 [129-232]
Duration of surgery (min, median [IQR])		103 [70-155]

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. COPD: chronic obstructive pulmonary disease. $ETCO_2$: end-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure. RMV: respiratory minute volume.

Variation in $ETCO_2$

The median $ETCO_2$ plots showed a large spread between the 10th and 90th percentile (Figure 3). Patients characteristics for patients with a median $ETCO_2$ <5th percentile (<29 mmHg) between 5th and 95th percentile (29-41 mmHg) and >95th percentile (41 mmHg) were compared (see Table 4S in the Supplemental Material). Patients with a higher median $ETCO_2$ were on average younger, had a higher BMI, a lower ASA class, and were more often male. The median RMV was lower for patients with a higher median $ETCO_2$. The duration of both general anesthesia and surgery was longest for patients with an intermediate $ETCO_2$ (between 29 and 41 mmHg).

Intracranial & carotid artery surgery	Laparoscopic surgery	Robotic laparoscopic surgery	COPD
N = 12,527	N = 44,507	N = 12,977	N = 1,709
53 [39-64]	49 [36-60]	60 [52-66]	65 [55-73]
6,442 (51.4)	28,661 (64.4)	3,364 (25.9)	810 (47.40)
735 (5.9)	4,494 (10.1)	513 (4.0)	0 (0.0)
4,736 (37.8)	23,039 (51.8)	7,705 (59.4)	341 (20.0)
6,447 (51.5)	16,351 (36.7)	4,667 (36.0)	1,173 (68.6)
598 (4.8)	622 (1.4)	92 (0.7)	192 (11.2)
11 (0.1)	1 (0.0)	0 (0.0)	3 (0.2)
170 [163-178]	168 [162-175]	175 [168-182]	170 [160-178]
27.3 [23.8-31.7]	29.8 [25.1-37.3]	28.7 [25.6-32.6]	27.2 [23.4-32.6]
6,012 [4,960-7,238]	6,288[5,391-7,330]	6,720 [5,860-7,692]	5,560 [4,728-6,504]
12 [10-13]	12 [10-14]	12 [10-14]	10 [9-12]
32.0 [29.0-34.0]	36.0 [34.0-38.0]	36.0 [33.0-38.0]	34.0 [32.0-37.0]
81 [75-87]	82 [76-89]	83 [77-89]	80 [74-86]
233 [173-325]	167 [126-225]	251 [213-301]	197 [150-265]
133 [84-211]	106 [72-153]	179 [145-226]	122 [83-186]

After adjusting for patient characteristics, ventilation parameters and mean MAP, an ICC of 0.18 (95% CI 0.07-0.37) was found for a model using institution as a random effect, 0.17 (95% CI 0.16-0.19) for a model with primary anesthesia caregiver as a random effect and 0.12 (95% CI 0.11-0.14) for a model with supervising anesthesiology faculty as a random effect (Table 3). An ICC of 0.36 (95% CI 0.18-0.58) was found for a model with primary anesthesia caregiver nested within a specific supervising anesthesiology faculty, nested within a specific institution, as a random effect. This corresponded with a MOR of 1.98 (95% CI 1.90-2.07). In this, the MOR can be interpreted as the median increase in the odds of having at least one $ETCO_2$ value per case >45 mmHg, when an individual moves from one cluster to another. The subgroup consisting of patients with COPD was too small to conduct random-effect multivariable logistic regression models.

Table 2. Baseline characteristics and $ETCO_2$ levels for 2008 and 2016

		Case year 2008	Case year 2016	p-value
		N = 23,434	N = 18,797	
General cohort				
Age (years, median [IQR])		50 [38-62]	52 [37-64]	<0.001*
Sex (female, %)		11,922 (50.9)	9,511 (50.6)	<0.001*
ASA class (%)	I	3,148 (13.4)	1,965 (10.5)	<0.001*
	II	12,477 (53.2)	9,209 (49.0)	
	III	7,130 (30.4)	6,986 (37.2)	
	IV	672 (2.9)	632 (3.4)	
	V	7 (0.03)	5 (0.03)	
Height (cm, median [IQR])		170 [163-178]	170 [163-178]	0.140
BMI (kg/m^2, median [IQR])		27.4 [23.9-32.1]	28.09 [24.2-33.1]	<0.001*
Median RMV (ml/min, median [IQR])		5,665 [4,744-6,708]	5,480 [4,572-6,468]	<0.001*
Mean MAP (mmHg, median [IQR])		77 [71-84]	80 [73-86]	<0.001*
Duration of general anesthesia (min, median [IQR])		178 [134-241]	167 [127-224]	<0.001*
Duration of surgery (min, median [IQR])		106 [72-160]	102 [69-153]	<0.001*
TWA-AUC $ETCO_2$ <28 mmHg ǂ		0.0 [0.0-1.0]	0.0 [0.0-0.0]	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg ǂ		169.0 [57.8-351.8]	45.4 [2.0-161.9]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg ǂ		986.9 [573.5-1,621.8]	713.2 [385.0-1,218.1]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg ǂ		0.0 [0.0-0.0]	0.0 [0.0-2.73]	<0.001*
Median $ETCO_2$ ǂ		33.0 [31.0-35.0]	35.0 [33.0-38.0]	<0.001*
Intracranial & carotid artery surgeryǂ				
TWA-AUC $ETCO_2$ <28 mmHg		0.0 [0.0-35.0]	0.0 [0.0-17.0]	0.030*
TWA-AUC $ETCO_2$ <35 mmHg		376.5 [145.0-812.5]	181.0 [28.4-658.3]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg		1,581.3 [841.5-2,680.7]	1,238.9 [622.1-2,292.3]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg		0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.001*
Median $ETCO_2$		31.6 [29.0-33.0]	33.0 [30.0-36.0]	<0.001*
Laparoscopic surgeryǂ				
TWA-AUC $ETCO_2$ <28 mmHg		0.0 [0.0-0.0]	0.0 [0.0-0.0]	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg		76.3 [19.0-193.3]	17.3 [0.34-77.1]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg		856.9 [489.7-1408.2]	574.0 [327.5-990.2]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg		0.0 [0.0-1.0]	0.0 [0.0-3.58]	<0.001*
Median $ETCO_2$		35.0 [33.0-37.0]	37.0 [35.0-40.0]	<0.001*

Table 2. Continued

	Case year 2008	**Case year 2016**	**p-value**
	N = 23,434	N = 18,797	
Robotic laparoscopic surgery†			
TWA-AUC $ETCO_2$ <28 mmHg	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.030*
TWA-AUC $ETCO_2$ <35 mmHg	140.2 [31.9-327.9]	58.5 [7.0-187.0]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg	1,538.9 [1,099.0-2,028.5]	1,306.3 [849.1-1,884.4]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg	0.0 [0.0-4.0]	0.0 [0.0-19.0]	<0.001*
Median $ETCO_2$	35.0 [33.0-37.7]	37.0 [35.0-39.0]	<0.001*
COPD†			
TWA-AUC $ETCO_2$ <28 mmHg	0.0 [0.0-2.0]	0.0 [0.0-0.0]	0.059
TWA-AUC $ETCO_2$ <35 mmHg	162.4 [41.3-394.0]	22.8 [1.5-164.5]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg	1,151.0 [658.0-1,989.1]	728.9 [390.4-1,264.8]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg	0.0 [0.0-0.24]	0.0 [0.0-21.6]	<0.001*
Median $ETCO_2$	34.0 [32.0-36.0]	36.0 [34.0-39.0]	<0.001*

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure. RMV: respiratory minute volume. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant at a level of significance of $p < 0.05$. † in mmHg, median [IQR].

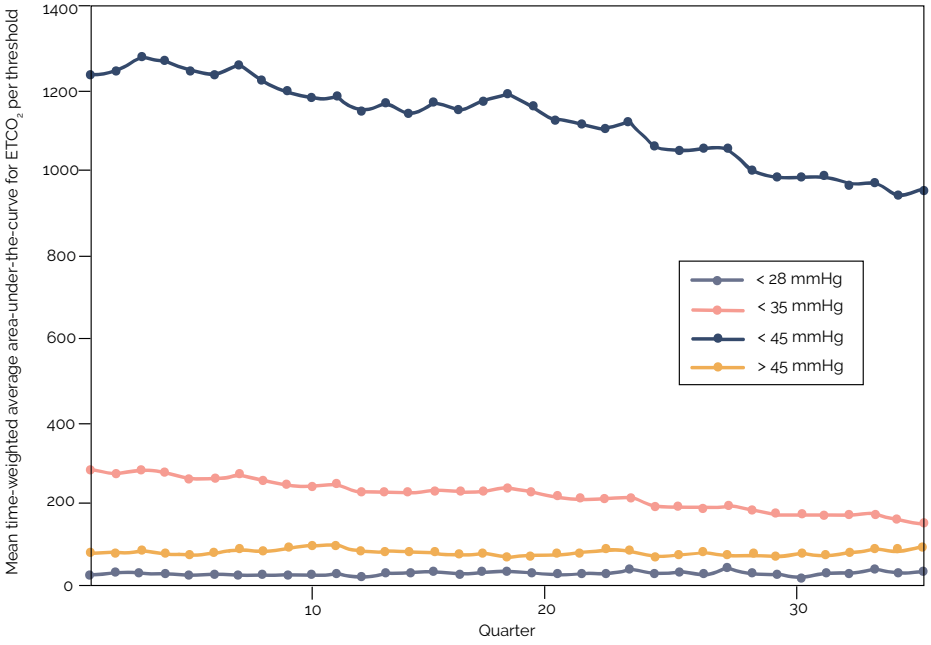


Figure 2. Trend in TWA-AUC $ETCO_2$ for four different thresholds

The trend over time in mean time-weighted average area-under-the-curve (TWA-AUC) per quarter for end-tidal carbon dioxide levels ($ETCO_2$) <28mmHg, <35mmHg, <45mmHg and >45mmHg. The TWA-AUC decreased over time for an $ETCO_2$ threshold of <28, <35 and <45mmHg, whereas the TWA-AUC $ETCO_2$ >45mmHg increased over time.

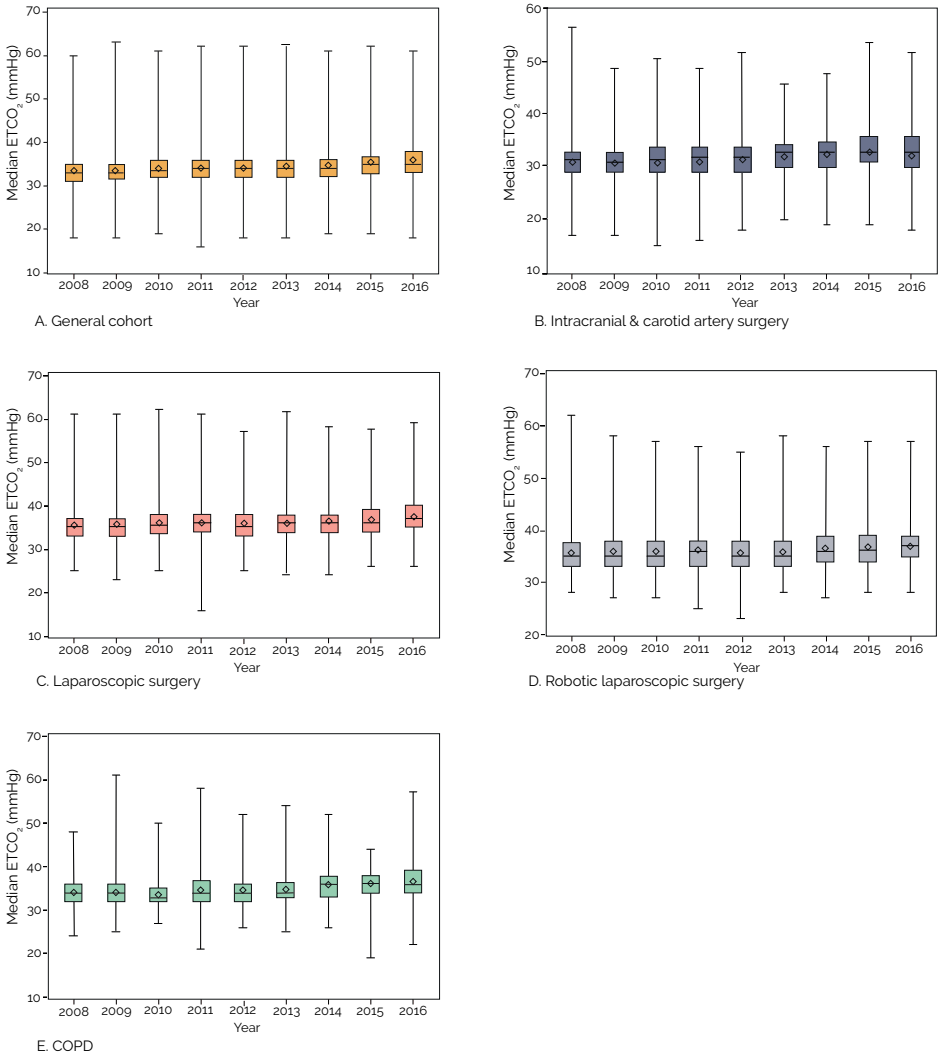


Figure 3. Trend in median $ETCO_2$ over time

The boxplots show an increase in median end-tidal carbon dioxide ($ETCO_2$) values between 2008 and 2016 for the general cohort (A) and the subgroups (B-E). The triangle represents the mean, the whiskers represent the spread between the 10th and 90th percentile. The median $ETCO_2$ was lower for patients presenting for intracranial & carotid artery surgery (B) compared to the general cohort. The median $ETCO_2$ was higher for patients in the (robotic) laparoscopic cohort (C, D) and for patients with chronic obstructive pulmonary disease (COPD) (E) when compared to the general cohort (A).

Table 3. Institutional and provider variation

Random effect per model*		**General cohort**
		N = 245,725
Institution	ICC (95% CI)	0.18 (0.07-0.37)
	MOR (95% CI)	1.96 (1.28-6.32)
Supervising anesthesiology faculty	ICC (95% CI)	0.12 (0.11-0.14)
	MOR (95% CI)	1.56 (1.45-1.69)
Primary anesthesia caregiver	ICC (95% CI))	0.17 (0.16-0.19)
	MOR (95% CI)	1.91 (1.79-2.06)
Supervising anesthesiology faculty nested within institution	ICC (95% CI)	0.23 (0.09-0.49)
	MOR (95% CI)	1.08 (1.06-1.10)
Primary anesthesia caregiver nested within institution	ICC (95% CI)	*Did not converge*
	MOR (95% CI)	*Did not converge*
Primary anesthesia caregiver nested within supervising anesthesiology faculty, nested within institution	ICC (95% CI)	0.36 (0.18-0.58)
	MOR (95% CI)	1.98 (1.90-2.07)

ICC: intraclass correlation coefficient. MOR: median odds ratio. * Dependent variable: positive TWA-AUC $ETCO_2$ >45mmHg (yes/no). Fixed effects: age (binned per decade), body mass index (binned into <18.5, 18.5-24.9, 25.0-29.9, 30.0-34.9, 35.0-39.9, ≥40.0 kg/m^2), sex, ASA class (I or II vs III, IV or V), positive end-expiratory pressure (binary, <5 or ≥5mmHg), tidal volume (binned by ideal body weight into <6, 6-8, 8-10, >10ml/kg),

DISCUSSION

Between 2008 and 2016, median $ETCO_2$ levels showed a minimal increase, however this change did not meet the *a priori* defined clinically relevant threshold of 10%. A large variation in target $ETCO_2$ levels was observed between institutions and between providers for the general cohort and all subgroups. Interestingly, only a minority of this variation could be attributed to institution and anesthesia provider, while controlling for patient characteristics. The amount of variability that could be attributed to institution and primary anesthesia caregiver was overall slightly larger than the amount that could be attributed to the supervising anesthesiology faculty, except for intracranial & carotid artery surgery, where the preference of the supervising anesthesiology faculty seemed to be more important than the effect of institution and primary anesthesia caregiver.

Intracranial & carotid artery surgery	Laparoscopic surgery	Robotic laparoscopic surgery
N = 12,527	N = 44,507	N = 12,977
0.14 (0.05-0.33)	0.11 (0.04-0.26)	0.22 (0.09-0.44)
1.66 (1.19-4.55)	1.44 (1.13-2.95)	2.36 (1.34-12.15)
0.18 (0.12-0.25)	0.05 (0.04-008)	0.19 (0.15-0.24)
1.96 (1.54-2.84)	1.20 (1.13-1.29)	2.10 (1.75-2.69)
0.15 (0.10-0.21)	0.14 (0.12-0.16)	0.30 (0.26-0.35)
1.79 (1.44-2.24)	1.68 (1.55-1.84)	3.86 (2.91-5.51)
0.22 (0.10-0.40)	0.12 (0.03-0.37)	0.18 (0.05-0.46)
1.42 (1.23-1.83)	1.12 (1.03-1.42)	1.05 (1.02-1.13)
0.23 (0.11-4.23)	0.17 (0.08-0.31)	0.31 (0.14-0.55)
1.34 (1.18-1.68)	1.26 (1.20-1.34)	1.39 (1.26-1.60)
0.26 (0.12-0.48)	0.27 (0.16-0.42)	0.37 (0.19-0.59)
1.21 (1.01-31.25)	1.29 (1.16-1.49)	2.06 (1.58-3.12)

median respiratory rate (binned into <12, 12-16, 16-20, >20/min), mean of the mean arterial pressure (binned into <65, 65-80, >80mmHg) and year of procedure. Random effects differed per model and included institution, primary anesthesia caregiver and/or attending anesthesiologist. The subgroup of patients with a history of chronic obstructive pulmonary disease was too small to conduct random-effect multivariable logistic regression analyses.

Practice variation in targeted $ETCO_2$ levels has not been studied previously. Large practice variation across regions, institutions and physicians is reported throughout the medical field.[27] Previously, a variation of 18% in tidal volume was shown to be attributable to institutional variability.[24] The same amount of variation could be attributed to institutional variability in our study.

The large variation in $ETCO_2$ as found in this study, may have several implications. It raises the question whether anesthesia providers do care for any $ETCO_2$ target at all, or at least it could be theorized that $ETCO_2$ levels are not considered as important as maintaining for example adequate blood pressure levels or oxygen saturation. Likely, there is insufficient knowledge about the effects of $ETCO_2$ levels to guide anesthesia providers in targeting specific $ETCO_2$ levels. We believe further exploration of the effect of intraoperative $ETCO_2$ levels on postoperative outcome is required to determine what $ETCO_2$ level should be aimed for to improve patient outcome. This research group has initiated two new projects to study: 1) the association between

intraoperative $ETCO_2$ levels and postoperative pulmonary complications and 2) the association between intraoperative $ETCO_2$ levels and neurologic outcome in the neurosurgical population.

As all retrospective analyses, this study has limitations. First, we did not differentiate between spontaneous and controlled ventilation, but we only included cases with endotracheal tubes placed. By excluding cases managed with laryngeal mask airways the likelihood of spontaneous breathing patterns was reduced significantly. It could be argued that some of the residual spontaneous breathing might lead to a higher $ETCO_2$ level and that this may explain the observed variation. However, we would expect that an inacceptable $ETCO_2$ level (either hyper- or hypocapnia) would be corrected by the anesthesia provider. Therefore, since the aim of this study was to investigate which levels are being accepted, we did not differentiate between these ventilation methods. Second, the use of certain ventilator modes might be associated with the practice pattern in $ETCO_2$ levels, e.g. a volume-controlled ventilation mode with specific default settings, but this was not taken into account in this study. As became apparent from the survey, the majority of institutions used a strictly controlled default ventilation mode. Third, a TWA-AUC is not easily applicable in daily practice. However, our primary aim was to investigate the practice pattern over time for further research purposes and we believe that a median $ETCO_2$ per case would not suffice to summarize a case adequately. Four ranges of $ETCO_2$ and thus four different TWA-AUC values per case allowed us better to summarize a very long case as compared to one overall value. The median $ETCO_2$ was added as a secondary outcome measure to aid interpretation and clinical applicability. Fourth, the intraoperative timeframe used for data collection has been chosen based upon expert consensus. We aimed to collect data during a relatively stable phase of general anesthesia. We checked timeframes in randomly selected cases and found a good correspondence with the maintenance phase of anesthesia. Finally, although we adjusted the results for a large set of potential confounders, residual confounding might be present due to the retrospective nature of this study.

Conclusion

There was no clinically relevant change in intraoperative $ETCO_2$ levels between 2008 and 2016. However, there was a very large practice variation, even within institutions and providers that could not be fully explained by differences in patient or procedure characteristics. Although existing literature suggests that $ETCO_2$ levels of 40 mmHg or higher might be associated with better outcomes in mechanically-ventilated patients,[4,5,9,17,28] this is not reflected in current clinical anesthesia practice. Clinical outcomes were not assessed in this study and should be the focus of future research to formulate clear guidelines.

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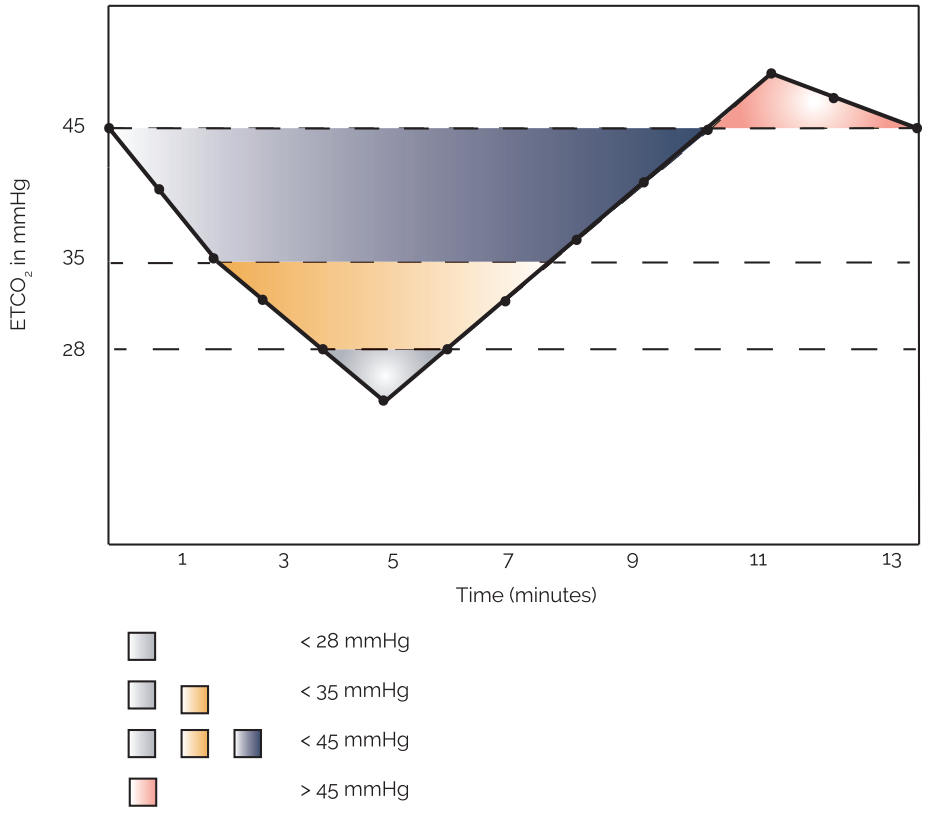
SUPPLEMENTAL MATERIAL



Supplemental Material: Figure 1S. The fitted cubic spline method to calculate the area-under-the-curve for all four $ETCO_2$ thresholds

$ETCO_2$: end-tidal carbon dioxide.

Supplemental Material: Survey.

1. On behalf of which institution are you completing this survey?

Section 1 Current Protocol

2. Is your clinic currently using a protocol entailing an $ETCO_2$ target or target range?
   Example: "40mmHg according to protocol" or "agreed range of 30-35mmHg"
3. If yes: please indicate the target that you are using and also provide the unit of measurement (mmHg, kPa, %)
4. If yes: when was this target (approximately) introduced at your institution?
5. If you have any additional comments regarding the current $ETCO_2$ target, you can leave them here.

Section 2 Protocol in the past

6. Has your institution used a protocol entailing $ETCO_2$ targets in the past (between 2008 and 2016) that it is not using any more?
7. If yes: please indicate the target that you were using and also provide the unit of measurement (mmHg, kPa, %)
8. If yes: when was this target (approximately) introduced at your institution?
9. If yes: when did your institution (approximately) stop using this target?
10. If you have any additional comments regarding this target, you can leave them here

Section 3 Influencing factors

11. Do you think that, over the years, certain events/policies have influenced the $ETCO_2$ level at your institution?
    Example: increased use of spontaneous ventilation mode
12. If yes: what was the most important factor that caused a change?
13. If yes: when did this change (approximately) occur?
14. If yes: do you think this change caused the $ETCO_2$ to increase or to decrease?
15. If yes: by approximately how much did this factor increase/decrease the $ETCO_2$ level? Please provide the unit of measurement (mmHg, kPa, %)
16. If yes: Was there another factor that could have influenced the $ETCO_2$ level as well? If yes, please answer question 13-15 for this factor as well.

Section 4 Ventilation mode and default setting

17. Which ventilation mode is currently used most widely at your institution?
18. What are the default settings?
19. Which ventilation mode was most widely used at your institution in 2008?
20. What were the default settings in 2008?

Supplemental Material: Table 1S. Artifact filter

Artifact criteria for ventilation parameters and MAP	
General criteria	• User entered values: invalid • At least 40 minutes between incision and the end of the surgical procedure. When incision was not available: at least 50 minutes between induction end and end of the surgical procedure • At least 20 valid measurements (not consecutive) per case
$ETCO_2$	• $ETCO_2$ had to be between 10mmHg (1.3kPa or 1.3%) and 65mmHg (8.6kPa or 8.5%) • Invalid when abrupt changes in $ETCO_2$ values were seen, defined as ≥5mmHg change in either direction with a consecutive value correcting back with at least 5mmHg
RMV	• Tidal volume had to be between 100ml and 1,000ml • Respiratory rate had to be between 4 and 25/minute • RMV had to be between 500 and 25,000 ml/min
MAP	• Invalid when <50mmHg or >150mmHg

$ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. RMV: respiratory minute volume.

Supplemental Material: Table 2S. $ETCO_2$ of the general cohort compared to the subgroups

Variable ǂ	**General cohort**
	General cohort (N = 245,835)
Median $ETCO_2$	34.00 [32.00-36.00]
TWA-AUC $ETCO_2$ <28 mmHg	0.00 [0.00-0.00]
TWA-AUC $ETCO_2$ <35 mmHg	108.98 [22.00-262.21]
TWA-AUC $ETCO_2$ <45 mmHg	856.00 [487.10-1,431.66]
TWA-AUC $ETCO_2$ >45 mmHg	0.00 [0.00-0.00]
	Variable ǂ
	Median $ETCO_2$
	TWA-AUC $ETCO_2$ <28 mmHg
	TWA-AUC $ETCO_2$ <35 mmHg
	TWA-AUC $ETCO_2$ <45 mmHg
	TWA-AUC $ETCO_2$ >45 mmHg

COPD: chronic obstructive pulmonary disease. $ETCO_2$: end-tidal carbon dioxide. TWA-AUC: time-weighted average area-under-the-curve.

Supplemental Material: Table 3S. Survey results

Institution	**Ventilator mode 2008**	**Volume* 2008 (ml)**	**Frequency* 2008 (/min)**
1	Controlled†	500	12
2	Controlled	500	12
3	Controlled	500	12
4	Controlled	600	10
5	Controlled	600	8
6	Controlled	10 #	8-10
7	Controlled	600	10
8	Controlled	600	10

$ETCO_2$: end-tidal carbon dioxide. RMV: respiratory minute volume. * Default settings of ventilator for volume and frequency of ventilation. † Controlled ventilator modes included pressure- or volume-controlled, including pressure-controlled modes with a guaranteed volume and volume-controlled modes with pressure regulation. ǂ Synchronized Intermittent Mandatory Ventilation (delivers a mandatory number of breaths while at the same time allowing spontaneous breaths). § Change in default RMV (respiratory minute volume, ml/min), based on reported default settings from 2008 and from 2016. || Assumed change in $ETCO_2$ (mmHg) on average, reported by the institution itself. # Default volume in ml/kg instead of in ml.

Subgroup	p-value ǂ	Subgroup	p-value ǂ
Intracranial & carotid artery surgery	(N = 12,532)	COPD	(N = 1,709)
32.00[29.00-34.00]	<0.001*	34.00 [32.00-37.00]	<0.001*
0.00 [0.00-25.00]	<0.001*	0.00 [0.00-2.73]	<0.001*
295.90 [95.50-775.20]	<0.001*	118.00 [19.25-309.84]	0.010*
1,438.57 [761.68-2,610.63]	<0.001*	1,009.28 [559.88-1,729.16]	<0.001*
0.00 [0.00-0.00]	<0.001*	0.00 [0.00-2.00]	<0.001*
Laparoscopic surgery	(N = 44,526)	Robotic laparoscopic surgery	(N = 12,977)
36.00 [34.00-38.00]	<0.001*	36.00 [33.00-38.00]	<0.001*
0.00 [0.00-0.00]	<0.001*	0.00 [0.00-0.00]	0.492
47.00 [7.00-145.86]	<0.001*	97.50 [17.92-287.81]	0.223
727.46 [409.78-1,211.98]	<0.001*	1,413.50 [904.57-1,968.29]	<0.001*
0.00 [0.00-0.94]	<0.001*	0.00 [0.00-13.00]	<0.001*

* Statistically significant at a level of significance of p <0.05. ǂ P-value obtained with a Kruskal-Wallis test, comparing the general cohort with the subgroup. ǂ in mmHg, median [interquartile range].

Ventilator mode 2016	Volume * 2016 (ml)	Frequency * 2016 (/min)	Changed RMV §	Changed $ETCO_2$ (mmHg) ‖
Controlled	480	15		5
Controlled	500	12	-	2
Controlled	500	12	-	-
Controlled	600	10	-	-
Controlled	600	8	-	-
Controlled	5-7 #	12-16	-	5
Controlled	440	10	-	-
SIMV ǂ	500	12	-	-

Institution 1 assumed an increase in $ETCO_2$ of 5mmHg as of March 2015, due to implementation of a new ventilator mode with different default settings (namely a pressure regulated volume-controlled mode, based on lean body mass and age). Institution 2 assumed an increase in $ETCO_2$ of 2mmHg as of July 2014 due to an increased use of pressure support modes, in addition to emerging evidence for lung protective ventilation strategies. Institution 5 reported a target of 35-40 mmHg for patients receiving colorectal procedures, implemented in November 2013. Institution 6 assumed that $ETCO_2$ increased with 5mmHg since January 2012, due to multiple factors that could not be further defined. Institution 8 reported a major shift in $ETCO_2$ in 2007 (prior to the study period) after implementation of ventilators with pressure support mode.

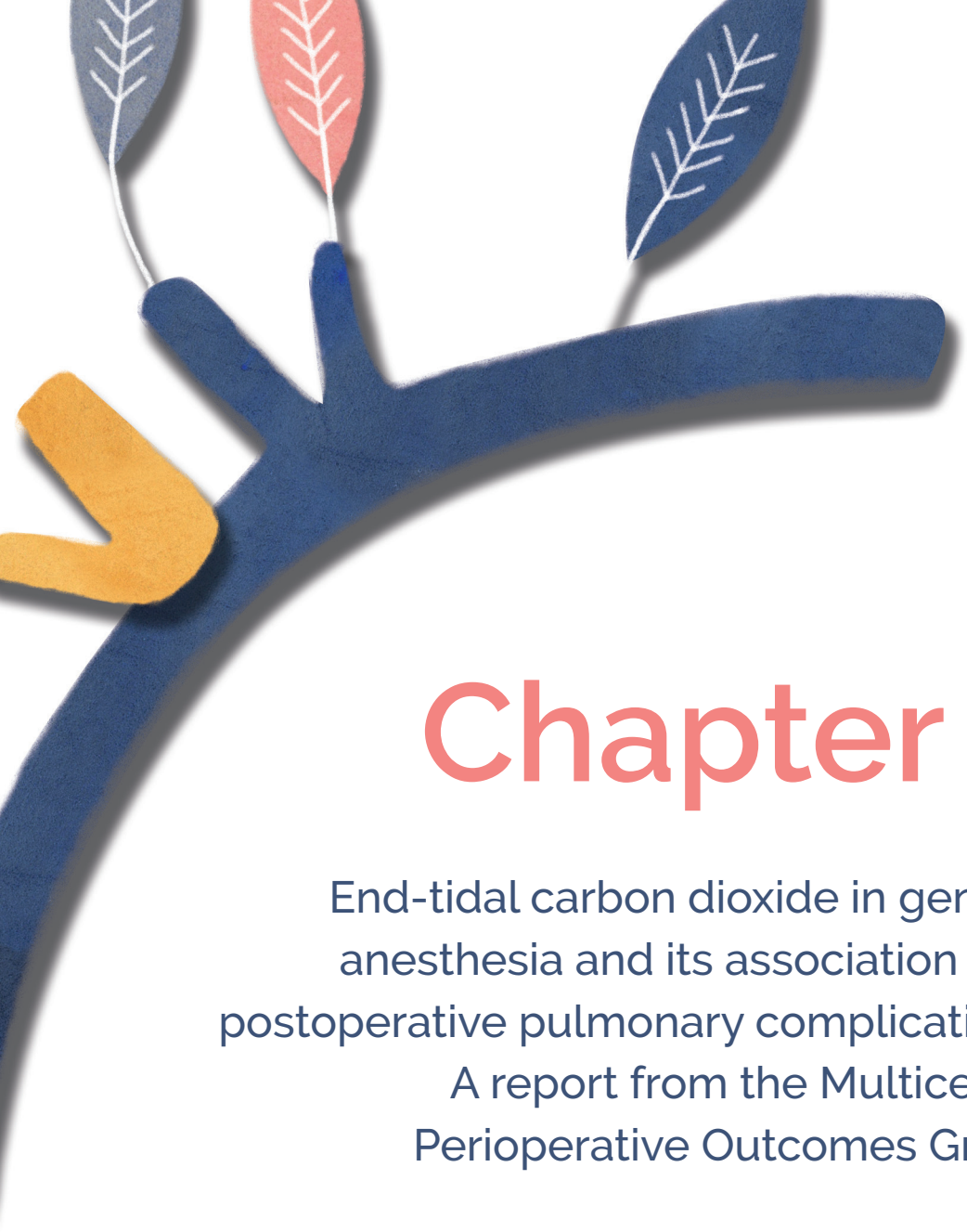
Supplemental Material: Table 4S. Baseline characteristics by $ETCO_2$ percentile

		Median $ETCO_2$ <5th percentile
		N = 7,699
Age (years, median [IQR])		55 [42-67]
Sex (female, %)		4,863 (63.2)
ASA class (%)	I	580 (7.5)
	II	3,371 (43.8)
	III	3,225 (41.9)
	IV	509 (6.6)
	V	14 (0.2)
Height (cm, median [IQR])		167 [160-175]
BMI (kg/m^2, median [IQR])		26.8 [23.4-31.0]
Median RMV (mL/min, median [IQR])		5,544 [4,554-6,635]
Mean MAP (mmHg, median [IQR])		78 [72-85]
Duration of general anesthesia (min, median [IQR])		161 [122-226]
Duration of surgery (min, median [IQR])		88 [61-135]

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. MAP: mean arterial pressure. RMV: respiratory minute volume. [abc] P-values reported are for the difference between the three groups.

Median $ETCO_2$ within 5th – 95th percentile	**Median $ETCO_2$ >95th percentile**	**p-value**
N = 226,174	N = 11,852	
51 [38-63]	48 [34-59]	<0.001[abc]
115,570 (51.1)	4,349 (36.7)	<0.001[abc]
25,665 (11.4)	1,493 (12.6)	<0.001[abc]
116,215 (51.9)	5,902 (49.8)	
77,626 (34.3)	3,984 (33.6)	
6,625 (2.9)	469 (4.0)	
43 (0.02)	4 (0.03)	
170 [163-178]	175 [165-182]	<0.001[abc]
27.8 [24.1-32.7]	29.3 [24.8-35.4]	<0.001[abc]
5,592 [4,684-6,600]	5,175 [4,212-6,292]	<0.001[abc]
78 [72-85]	78 [71-86]	<0.001[bc]
172 [130-234]	148 [112-200]	<0.001[abc]
104 [71-157]	89[60-137]	<0.001[ac]

Pairwise p-values were computed with a = p <0.05 for the difference between the <5th percentile and the 5-95th percentile, b = p <0.05 for the difference between the <5th percentile and the >95th percentile, and c = p <0.05 for the difference between the 5th-95th percentile and the >95th percentile. 5th percentile = 29.00mmHg, 95th percentile = 41.00mmHg.



Chapter 3

End-tidal carbon dioxide in general anesthesia and its association with postoperative pulmonary complications. A report from the Multicenter Perioperative Outcomes Group

Annemarie Akkermans, Judith A.R. van Waes, Sachin Kheterpal, Wietze Pasma, Leif Saager, Aleda Thompson, Wilton A. van Klei

Submitted

ABSTRACT

Background Postoperative pulmonary complications are common and despite several preventive strategies, incidences remain high. Emerging evidence suggests that permissive hypercapnia may reduce the risk of lung injury. This led us to hypothesize that higher intraoperative end-tidal carbon dioxide ($ETCO_2$) concentrations decrease the risk of postoperative pulmonary complications.

Methods This retrospective, observational, multicenter study included patients who received general anesthesia for non-cardiothoracic procedures between January 2010 and December 2017. The primary outcome was a composite of pulmonary complications (pneumonia, respiratory failure, pleural effusion, pulmonary edema, atelectasis, pneumothorax, bronchospasm or aspiration pneumonitis) within 30 postoperative days. Secondary outcomes were pulmonary complications within one week after surgery, postoperative length of stay and in-hospital mortality within 30 days. The association between these outcomes and median $ETCO_2$ and several time-weighted average area-under-the-curve (TWA-AUC) thresholds was studied using a multivariable mixed-effect model and by plotting associated risks.

Results Among 143,769 patients across eleven hospitals, 7,296 experienced a pulmonary complication. A median $ETCO_2$ >40 mmHg was associated with an increase in pulmonary complications within 30 days compared to a median $ETCO_2$ of 35-40 mmHg (median $ETCO_2$ 40-45 mmHg; adjusted OR 1.16 (99% CI 1.00-1.33), p-value 0.008 and median $ETCO_2$ >45 mmHg; OR 1.64 (99% CI 1.33-2.02), p-value <0.001). The occurrence of any $ETCO_2$ <28 mmHg was associated with pulmonary complications within 30 days (OR 1.40 (95% CI 1.33-1.49), p-value <0.001), mortality and length of stay. Any $ETCO_2$ >45 mmHg was also associated with pulmonary complications within 30 days (OR 1.24 (95% CI 1.17-1.31), p <0.001). Plots showed an optimum for an $ETCO_2$ around 35-38 mmHg.

Conclusions Both a very low (<28 mmHg) and a high $ETCO_2$ (>45 mmHg) are associated with postoperative pulmonary complications within 30 days. There may be an optimum around an $ETCO_2$ of 35-38 mmHg, but prospective studies are needed to explore this further.

INTRODUCTION

Postoperative pulmonary complications are common following non-cardiothoracic surgery, with reported incidences varying between 3% and 33%, depending on the definition.[1,2] These complications are associated with an increased length of stay and increased healthcare costs.[2,3] Moreover, postoperative pulmonary complications are associated with a 30-day mortality rate of up to 20%.[2,4] Many risk factors have been identified and several preventive strategies have been proposed.[1,4–6] Intraoperative ventilation strategies supposedly play a crucial role.[7,8] Under the influence of evidence supporting lung protective ventilation strategies,[9] the median intraoperative tidal volume has decreased over the past decades, whereas the percentage of patients receiving positive end-expiratory pressure (PEEP) ≥5 cmH_2O has increased.[10] Despite these developments, the incidence of postoperative pulmonary complications and related poor outcomes remains high.[2]

Permissive hypercapnia might have an additional beneficial effect in preventing pulmonary complications. First, when allowing higher end-tidal carbon dioxide ($ETCO_2$) concentrations, it is easier to implement the principle of low tidal volume ventilation.[9] Second, lung injury models found that hypercapnia and hypercapnic acidosis possess immune-modulating properties through inhibition of the nuclear factor-kB pathway, thus reducing inflammation.[11] A study in patients undergoing a pulmonary lobectomy found that hypercapnia (with an arterial carbon dioxide pressure ($PaCO_2$) of 60-70 mmHg) inhibited local and systematic inflammation, when compared to normocapnia ($PaCO_2$ 35-45 mmHg).[12] Third, hypercapnia might increase lung parenchymal compliance by modulating actin-myosin contraction,[13] improving ventilation to under-ventilated areas in addition to increasing cardiac output, thus improving ventilation-perfusion matching.[14–16]

Thus far, it remains unclear whether intraoperative $ETCO_2$ concentrations are truly associated with postoperative pulmonary complications, although hypocapnia seems to be associated with mortality and length of stay.[17,18] In current practice, there is a large variability in intraoperative $ETCO_2$ concentrations, possibly indicating a lack of evidence to support a specific target.[19] Therefore, this study aimed to investigate possible associations between $ETCO_2$ concentrations and postoperative pulmonary complications in patients presenting for non-cardiothoracic surgery. We hypothesized that an $ETCO_2$ >45 mmHg would be associated with a decreased risk of postoperative pulmonary complications within 30 days after surgery.

METHODS

This multicenter, retrospective, observational study was conducted in adherence to the STROBE statement for observational research[20] and used data from the Multicenter Perioperative Outcomes Group (MPOG) database. The MPOG registry has been described previously.[19,21] Each participating institution has Institutional Review Board approval to submit a limited set of perioperative data into the database. Additional ethical approval was provided by the University Medical Center Utrecht (17-204/C, March 2017) as the coordinating center for this study. The requirement for informed consent was waived. A data analysis and statistical plan was written before data were accessed. This plan was approved and filed by the MPOG Perioperative Clinical Research Committee (PCRC-0041, June 2017) before start of the study.

Patients

All adults (≥18 years) who received general anesthesia for in-patient surgical procedures between 01.01.2010 and 12.31.2017 in eleven U.S. MPOG hospitals were included; eight were academic hospitals and three were private hospitals. Only the first case per patient per admission was included. Exclusion criteria are presented in Figure 1 and were based on procedure type, clinical condition prior to anesthesia and data quality. To limit the risk of a falsely low or high $ETCO_2$, we defined several additional exclusion criteria. First, patients with one-lung ventilation and ventilation by means of a laryngeal mask airway were excluded. Second, patients with suspected intraoperative hemodynamic instability were excluded. Intraoperative hemodynamic instability was defined as need for intraoperative defibrillation or use of inotropes, epinephrine, vasopressin, sodium bicarbonate or transfusion of more than the equivalent of two units of blood products. Additionally, we used vasopressor use as a proxy for hemodynamic instability and excluded those who were given >40 µg/hour norepinephrine, >400µg/hour phenylephrine or >20mg ephedrine during the procedure. Finally, patients with less than 20 valid $ETCO_2$ measurements were excluded.

Outcome

The primary outcome, postoperative pulmonary complications, was slightly modified from the definition established by the European Society of Anesthesiology in view of the retrospective nature of data selection, using ICD-9 and ICD-10 billing codes (see table 1S in the Supplemental Material, listing the relevant codes).[22] Included complications were pneumonia, respiratory failure, pleural effusion, pulmonary edema, atelectasis, pneumothorax, bronchospasm and/or aspiration pneumonitis within 30 days after surgery. Secondary outcomes were pulmonary complications within one week after surgery, postoperative length of stay and in-hospital mortality within 30 postoperative days.

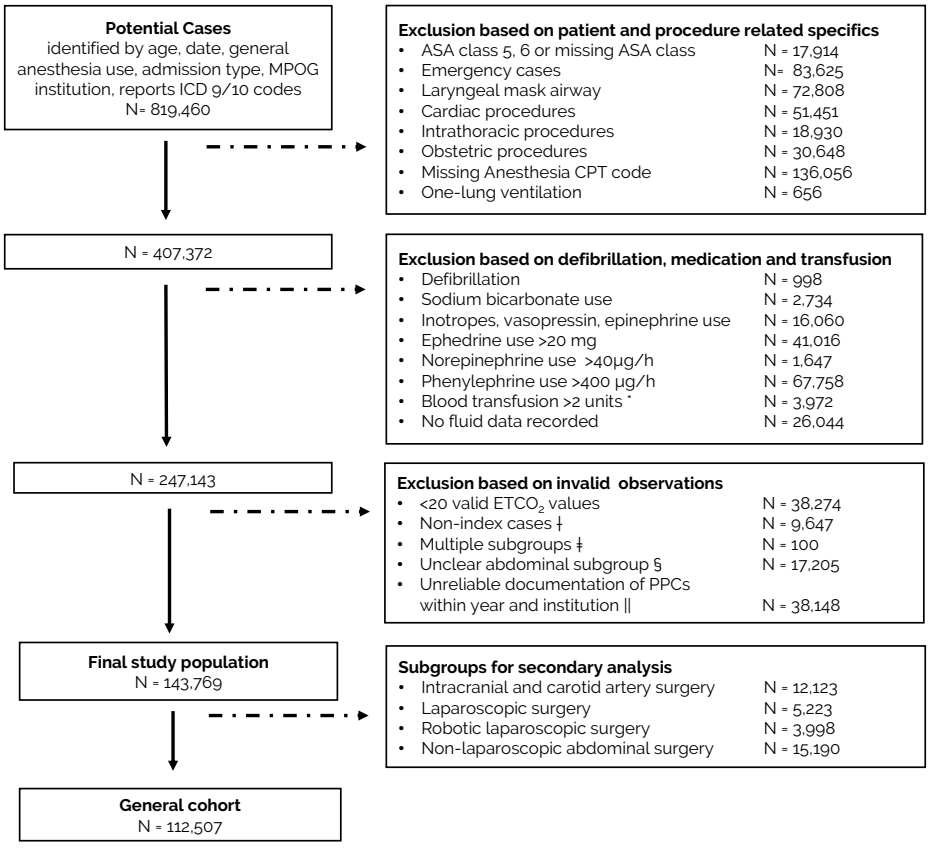


Figure 1. Flow chart

ASA: American Society of Anesthesiologists physical status. CPT: Current Procedural Terminology. $ETCO_2$: end-tidal carbon dioxide. MPOG: Multicenter Perioperative Outcomes Group. PPCs: postoperative pulmonary complications.

* More than two units of packed cells or whole blood or more than 700 ml of cell saver blood, all during anesthesia. ǂ Only the first case per patient per admission was indexed. ǂ Patients were excluded when they met the inclusion criteria for more than 1 group: e.g. intracranial and laparoscopic surgery. § E.g. colectomy without differentiating between open or laparoscopic procedure. || When an institution submitted only a few cases per year, combined with an incidence strongly deviating from other years, these years were excluded for this specific institution.

$ETCO_2$

Two different $ETCO_2$ measures were used per case: a median to enhance clinical applicability and a time-weighted average area-under-the-curve (TWA-AUC) to account for intraoperative variability.[19] For TWA-AUC, $ETCO_2$ was stratified into four groups (<28, <35, <45 and >45 mmHg) and the area-under-the-curve for each specific threshold was calculated with adjustment for the total measurement time, resulting in four different TWA-AUC values per case. This method has been described previously.[19]

Secondary analysis of subgroups

A priori, we defined four subgroups of patients in whom the $ETCO_2$ target and the risk of pulmonary complications might differ.[1,19] Abdominal surgery is associated with an increased risk of pulmonary complications.[1] In patients receiving (robotic assisted) laparoscopic surgery, insufflation with carbon dioxide can increase $PaCO_2$ and thus $ETCO_2$.[19] Trendelenburg positioning potentially influences $ETCO_2$ concentrations and the risk of pulmonary complications as well in these patients.[23] Therefore we aimed to differentiate between 1) non-robotic laparoscopic surgery, 2) robotic laparoscopic surgery and 3) non-laparoscopic abdominal surgery. The fourth subgroup concerned patients undergoing intracranial & carotid artery surgery as lower carbon dioxide targets are used,[19] presumably to preserve cerebral perfusion while preventing an increased intracranial pressure.[16,24] Additionally, these procedures are also associated with an increased risk of pulmonary complications.[1]

The four subgroups were excluded from the primary analysis to prevent them from confounding the trend over time and the association with pulmonary complications. Especially due to increased use of (robotic) laparoscopy, we believe we would otherwise detect the effect of an increase in laparoscopic cases on pulmonary complications. Patients were excluded when they were eligible for more than one subgroup (e.g. when a patient received intracranial surgery and a laparoscopic procedure in the same session).

Data collection

Data on patient-related, procedure-related and anesthesia-related factors associated with $ETCO_2$ concentrations and pulmonary complications were collected from the MPOG database (Table 1).[1,5,9,25–27] Vital and ventilation parameters were measured continuously during anesthesia by means of automated interfaces. An average was recorded every minute and stored in the database. Intraoperative data were collected between 35 minutes after the first $ETCO_2$ capture until 20 minutes prior to the last $ETCO_2$ capture, based on previous experience.[19] In doing so, we aimed to ignore hyper- and hypocapnia that may follow induction and hypercapnia that may be accepted to establish spontaneous ventilation towards the end of a procedure.

All ICD-9 and ICD-10 billing codes, documented within 30 days after surgery, as well as length of stay and mortality before discharge were collected from the MPOG database. The institution ID was, anonymized, documented to account for potential inter-institutional differences.[19] Artifacts were excluded, using criteria defined based on prior work by the researchers.[19] The artifact filter can be found in Table 2S in the Supplemental Material.

Missing values

Missing values were handled using multiple imputation, as complete case analyses are known to lead to biased effect estimates.[28] We used multivariate imputation by chained equations (R mice package), creating 10 imputation sets.[29] Multiple imputation was performed in the general cohort and the subgroups combined.

Statistical analysis

When assuming an incidence of postoperative pulmonary complications of approximately 5%, and a conservative risk reduction of 5% for hypercapnia,[1,4] a total sample size of 56,832 was considered to be sufficient for an 80% power and an alpha of 0.05.

Baseline characteristics were compared between patients with and without pulmonary complications using a Fisher's exact test, $\chi 2$ test, independent *t* test, or Mann–Whitney U test as appropriate. Continuous variables were checked for normality using the Kolmogorov–Smirnov test. For vital and ventilation parameters a median per case was calculated. For mean arterial blood pressure (MAP) a mean per case was calculated to take intraoperative variability into account, as is common in blood pressure analysis.[30] For all four $ETCO_2$ thresholds, the TWA-AUC was computed from minute-level $ETCO_2$ values as has been done previously.[19]

First, analyses were done with median $ETCO_2$. A logistic regression model was built with pulmonary complications as the dependent variable and median $ETCO_2$ as the independent variable. Multivariable analyses were used to adjust for potential confounders. Confounders were selected based upon a known association with ventilation parameters and postoperative pulmonary complications. Log-transformation was applied to continuous variables where applicable. Covariates selected *a priori* for model inclusion were age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, male sex, median tidal volume per predicted body weight (PBW), median PEEP, median respiratory rate and mean MAP. Collinearity was assessed using a Pearson's correlation matrix and collinear variables were combined into one category if feasible. Otherwise, the clinically most relevant variable was included. A list of included

variables can be found underneath Table 3. A restricted cubic spline function was used for median $ETCO_2$ to confirm a nonlinear relationship with pulmonary complications and splines with three, four, and five knots were tested for the best fit. Models were compared using Akaike's Information Criterion, with the model having the smallest value being the best fit.[31] This model was used to plot the associated risk of developing postoperative pulmonary complications against median $ETCO_2$. In this plot, median tidal volume was stratified into <6, 6-8 and >8 $ml \cdot kg^{-1} \cdot PBW^{-1}$ and PEEP into 0-5, 5-8 and >8 cmH_2O, to explore the effect of tidal volume and PEEP. Afterwards, median $ETCO_2$ was binned into the following categories (<28, 28-35, 35-40 (as reference), 40-45, >45 mmHg) based on location of the splines and after inspection of the plot to further study the relationship in a multivariable mixed-effect model and to enhance clinical applicability. Period (defined as year of procedure binned into 2010-2012, 2012-2015 and 2016-2017) and institution were included as a random intercept. All other confounders were included as fixed effects. To assess between-institution and between-period variance, an intraclass correlation coefficient was calculated.[32] Grand mean centering and scaling was used to optimize model fit.[33] All analyses were conducted in each of the imputed datasets and estimates were pooled using Rubin's rule.[34,35]

Second, the same models were build using all four thresholds of TWA-AUC $ETCO_2$. TWA-AUC $ETCO_2$ <28 mmHg, <35 mmHg and >45 mmHg were strongly skewed, even after log transformation and were therefore binned in never below (or above in case of >45 mmHg) the threshold (i.e. TWA-AUC = 0) or at least once surpassing the threshold. TWA-AUC $ETCO_2$ <45 mmHg was normally distributed and was binned to enhance clinical applicability, based on location of the splines and after inspection of the plots. The following categories were formed: a TWA-AUC $ETCO_2$ <45 mmHg of 0-8 (i.e. 37-45 mmHg), 8-10 (i.e. 35-37 mmHg), 10-12 (i.e. 33-35 mmHg, as reference), 12-14 (i.e. 31-33 mmHg) and >14 mmHg (i.e. <31 mmHg). In conclusion: 1) any $ETCO_2$ value below 28 mmHg, 2) any $ETCO_2$ value below 35 mmHg, and 3) any $ETCO_2$ value above 45 mmHg were used as independent, binary variables and 4) TWA-AUC $ETCO_2$ <45 mmHg was used as independent variable, categorized into TWA-AUC <31 mmHg, 31-33 mmHg, 33-35 mmHg (as reference), 35-37 mmHg and 37-45 mmHg to explore the association of TWA-AUC $ETCO_2$ with postoperative pulmonary complications.

For the secondary outcomes mixed-effect logistic and linear regression models were built following the same steps as described above for both median and TWA-AUC $ETCO_2$. Length of stay was log-transformed to satisfy the linear regression normality assumption[36] and beta coefficients were back-transformed to report them as percentage of change.[37] The subgroups were analyzed using a similar approach.

To further explore the effect of institution, we conducted two sensitivity analyses. First, analyses were repeated for the center contributing the most cases. Second, results from the mixed-effect model were compared to results from a fixed-effect model were institution and period were included as fixed effect together with all other covariables.

Since $ETCO_2$ and TWA-AUC were binned, a Bonferroni correction was applied, to correct for multiple testing as has been done before.[38] The corresponding confidence intervals and p-values can be found in Table 3. For all other analyses a p-value of <0.05 was considered to be statistically significant. The statistical analyses were performed with R (Version 3.6.2 – © 2019-12-12, R, Inc., for Windows).[39]

RESULTS

819,460 patients were eligible for inclusion. After application of all exclusion criteria, 143,769 patients were included: 107,235 patients for the general cohort and 36,534 patients for the four subgroups (Figure 1). A total of 5.4% of the data was missing (see table 3S and 4S in the Supplemental Material for distribution of missing data).

Patient characteristics

Baseline characteristics for the general cohort and the four subgroups are shown in Table 1. Table 2 describes baseline characteristics for patients with and without pulmonary complications in the general cohort. Patients with pulmonary complications were older, more often male and suffered from more comorbidities, including chronic obstructive pulmonary disease, obstructive sleep apnea, congestive heart failure and preoperative anemia. Their preoperative albumin was lower. There was no difference in median $ETCO_2$, but the TWA-AUC $ETCO_2$ <35 mmHg was larger for patients with pulmonary complications.

Incidence

Pulmonary complications within 30 days occurred in 7,296/107,235 (6.8%) patients from the general cohort versus 965/12,123 (7.9%), 217/5,223 (4.2%), 101/3,998 (2.5%) and 1,706/15,190 (11.2%) patients presenting for intracranial & carotid artery surgery, laparoscopic procedures, robotic procedures and non-laparoscopic abdominal procedures, respectively (Table 1). The majority of these complications occurred within 7 days after the procedure (87%, 73%, 90%, 88%, 89%, respectively).

Table 1. Baseline characteristics for all groups

		General cohort
		N = 107,235
Preoperative characteristics		
Age (years, median [IQR])		54 [41-65]
Sex (Female, %)		55,906 (52.1)
BMI (kg/m², median [IQR])		28.4 [24.4-34.0]
ASA class (%)	I	6,153 (5.7)
	II	48,300 (45.0)
	III	48,797 (45.5)
	IV	3,985 (3.7)
Chronic obstructive pulmonary disease (%)		7,461 (7.0)
Asthma (%)		34,673 (32.3)
Obstructive sleep apnea (%)		38,926 (36.3)
Congestive heart failure (%)		5,110 (4.8)
Preoperative albumin (g/dl, median [IQR])		4.1 [3.6-4.4]
Anemia (%)		12,759 (11.9)
Intraoperative characteristics		
Prone positioning (%)		11,923 (11.1)
Trendelenburg positioning (%)		7,554 (7.0)
Epidural analgesia (%)		7,093 (6.6)
Use of neuromuscular blockers (%)		95,588 (89.1)
Reversal of neuromuscular blockers (%)		88,334 (82.4)
Use of corticosteroids (%)		76,241 (71.1)
Total blood product transfusion (ml, median [IQR]) *		0 [0-0]
Total fluids in crystalloid equivalents (ml, median [IQR])		1,500 [1,000-2,100]
Mean MAP (mmHg, median [IQR])		80 [73-87]
Data collection duration (min, median [IQR])		112 [66-180]
Respiratory parameters		
Median $ETCO_2$ (mmHg, median [IQR])		35 [33-37]
TWA-AUC $ETCO_2$ <28 mmHg (mmHg, median [IQR]) *		0.00 [0.00-0.00]
TWA-AUC $ETCO_2$ <35 mmHg (mmHg, median [IQR])		0.84 [0.14-2.08]
TWA-AUC $ETCO_2$ <45 mmHg (mmHg, median [IQR])		9.69 [7.59-11.52]
TWA-AUC $ETCO_2$ >45 mmHg (mmHg, median [IQR]) *		0.00 [0.00-0.01]

	Intracranial & carotid artery surgery	**Laparoscopic surgery**	**Robotic surgery**	**Non-laparoscopic Abdominal surgery**
	N = 12,123	N = 5,223	N = 3,998	N = 15,190
	53 [39-65]	50 [38-62]	60 [53-66]	53 [41-64]
	6,325 (52.2)	3,378 (64.7)	1,057 (26.4)	8,117 (53.4)
	27.7 [24.0-32.1]	29.9 [24.7-39.5]	28.2 [25.1-32.6]	27.2 [23.5-32.1]
	167 (1.4)	210 (4.0)	122 (3.1)	423 (2.8)
	4,039 (33.3)	2,293 (43.9)	2,383 (59.6)	4,964 (32.7)
	7,253 (59.8)	2,666 (51.0)	1,473 (36.8)	8,574 (56.4)
	664 (5.5)	54 (1.0)	20 (0.5)	1,229 (8.1)
	699 (5.8)	115 (2.2)	76 (1.9)	773 (5.1)
	3,575 (29.5)	3,318 (63.5)	2,063 (51.6)	5,682 (37.4)
	3,930 (32.4)	3,088 (59.1)	2,540 (63.5)	5,780 (38.0)
	486 (4.0)	176 (3.4)	75 (1.9)	812 (5.3)
	4.2 [3.8-4.4]	4.0 [3.7-4.3]	4.2 [3.9-4.5]	4.0 [3.5-4.3]
	727 (6.0)	438 (8.4)	89 (2.2)	2,805 (18.5)
	768 (6.3)	129 (2.5)	74 (1.9)	121 (0.8)
	256 (2.1)	180 (3.4)	290 (7.2)	149 (1.0)
	344 (2.8)	373 (7.1)	59 (1.5)	3,398 (22.4)
	11,278 (93.0)	5,166 (98.9)	3,964 (99.1)	14,955 (98.5)
	9,890 (81.6)	4,994 (95.6)	3,813 (95.4)	14,371 (94.6)
	9,038 (74.6)	3,306 (63.3)	2,022 (50.6)	10,031 (66.0)
	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
	1,700 [1,050-2,500]	1,500 [1,000-2,000]	1,500 [1,150-2,000]	2,200 [1,400-3,500]
	79 [73-85]	83 [77-90]	84 [78-91]	80 [74-87]
	160 [99-258]	121 [71-188]	141 [105-197]	147 [88-221]
	33 [30-35]	36 [34-38]	36 [34-38]	34 [33-36]
	0.00 [0.00-0.11]	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.00]
	2.41 [0.90-4.47]	0.61 [0.13-1.53]	0.56 [0.11-1.39]	1.25 [0.37-2.47]
	11.97 [9.93-14.18]	8.89 [6.91-10.66]	8.79 [6.50-10.61]	10.54 [8.89-12.08]
	0.00 [0.00-0.00]	0.00 [0.00-0.00]	0.00 [0.00-0.04]	0.00 [0.00-0.00]

Table 1. Continued

	General cohort
	N = 107,235
Median tidal volume (ml, median [IQR])	500 [446-567]
Median tidal volume per PDW (ml, median [IQR])	7.9 [7.0-9.0]
Median respiratory rate (/min, median [IQR])	12 [10-14]
Median RMV (ml/min, median [IQR])	5,916 [4,994-7,000]
Median PEEP (cmH_2O, median [IQR])	5 [5-5]
Median preoperative saturation (%, median [IQR])	98 [96-100]
Median intraoperative saturation (%, median [IQR])	99 [97-100]
Outcome	
Postoperative pulmonary complications within 30 days (%)	7,296 (6.8)
Postoperative pulmonary complications within 7 days (%)	6,325 (5.9)
Length of stay (days, median [IQR])	3 [2-5]
Mortality at discharge (%)	706 (0.7)

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure.

In the general cohort, patients with pulmonary complications stayed in the hospital for a median of 7 days [IQR 3-13] versus 3 days [IQR 2-5] for patients without pulmonary complications and in-hospital mortality was seen in 349 (4.8%) and 357 (0.4%) patients, respectively (Table 2).

Primary analysis: the general cohort

A model including a restricted cubic spline function with 3 knots at the 10th, 50th and 90th percentile resulted in the best fit using Akaike's Information Criterion. This model was used to plot the associated risk of pulmonary complications against median $ETCO_2$ and TWA-AUC $ETCO_2$ <45 mmHg (Figure 2). There appeared to be an optimum for a median $ETCO_2$ around 38 mmHg and a TWA-AUC $ETCO_2$ <45mmHg around 10 mmHg (i.e. 35 mmHg).

The adjusted effect estimates using the binned independent variables are presented in Table 3; univariable results are presented in Table 5S of the Supplement Material. First, the association of categories in median $ETCO_2$ was explored. In the general cohort, a median $ETCO_2$ >40 mmHg was associated with an increase in pulmonary complications

Intracranial & carotid artery surgery	Laparoscopic surgery	Robotic surgery	Non-laparoscopic Abdominal surgery
N = 12,123	N = 5,223	N = 3,998	N = 15,190
496 [442-564]	510 [450-575]	550 [490-610]	490 [439-556]
7.8 [7.0-9.0]	8.4 [7.4-9.5]	8.0 [7.2-9.0]	7.8 [6.9-8.9]
12 [10-14]	12 [12-14]	14 [12-15]	11 [10-12]
5,990 [5,028-7,163]	6,570 [5,604-7,560]	7,280 [6,380-8,250]	5,500 [4,640-6,480]
5 [4-5]	5 [5-6]	5 [4-5]	5 [5-5]
98 [96-99]	99 [98-100]	99 [98-100]	99 [97-100]
99 [98-100]	99 [98-100]	99 [98-100]	99 [98-100]
956 (7.9)	217 (4.2)	101 (2.5)	1,706 (11.2)
806 (6.6)	196 (3.8)	89 (2.2)	1,518 (10.0)
3 [2-6]	4 [3-6]	2 [2-3]	5 [4-9]
172 (1.4)	19 (0.4)	1 (0.0)	222 (1.5)

PBW: predicted body weight. PEEP: positive end-expiratory pressure. RMV: respiratory minute volume. TWA-AUC: time-weighted average area-under-the-curve. * Strongly skewed distribution.

at 30 days and within one week compared to the reference category of median $ETCO_2$ 35-40 mmHg (at 30 days: for the category of median $ETCO_2$ 40-45 mmHg; adjusted OR 1.16 (99% CI 1.00-1.33), p-value 0.008 and for the category of median $ETCO_2$ >45 mmHg; adjusted OR 1.64 (99% CI 1.33-2.02), p-value <0.001). Postoperative length of stay was longer for those with a median $ETCO_2$ of <35 mmHg as compared to the reference category (for category of median $ETCO_2$ 28-35 mmHg; adjusted percentage of change 1.71% (99% CI 0.41-3.03), p-value 0.002).

Second, the association of TWA-AUC $ETCO_2$ thresholds was explored. Any value <28 mmHg was associated with pulmonary complications at 7 and 30 days (at 30 days; adjusted OR 1.40 (95% CI 1.33-1.49), p-value <0.001), mortality and an increased length of stay. Also, any value >45 mmHg was associated with pulmonary complications at 7 and 30 days (at 30 days; OR 1.24 (95% CI 1.17-1.31), p <0.001). For categories of TWA-AUC $ETCO_2$ <45 mmHg, a TWA-AUC $ETCO_2$ 37-45 mmHg was associated with an increase in pulmonary complications at 7 and 30 days (at 30 days; OR 1.16 (99% CI 1.05-1.27), p-value < 0.001) as compared to the reference category (i.e. TWA-AUC $ETCO_2$ 33-35 mmHg).

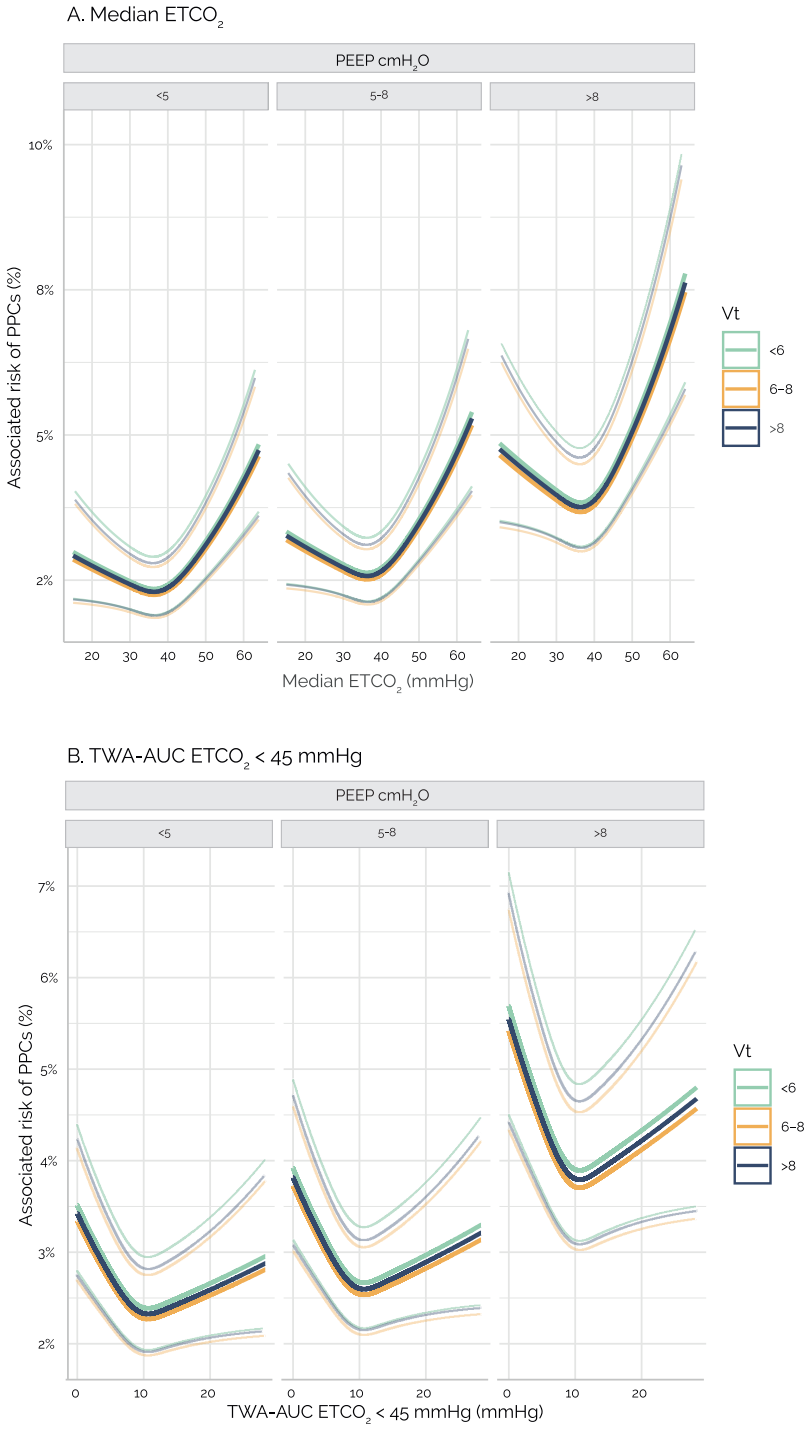
Table 2. Baseline characteristics for patients with and without postoperative pulmonary complications within 30 days in the general cohort

		No pulmonary complications	Pulmonary complications	p-value
		N = 99,939	N = 7,296	
Preoperative characteristics				
Age (years, median [IQR])		54 [40-65]	58 [45-68]	<0.001*
Sex (Female, %)		52,572 (52.6)	3,334 (45.7)	<0.001*
BMI (kg/m², median [IQR])		28.5 [24.4-33.9]	28.0 [24.0-33.7]]	<0.001*
ASA Class (%)	I	6,025(6.0)	128 (1.8)	<0.001*
	II	46,642 (46.7)	1,658 (22.7)	
	III	44,491 (44.5)	4,306 (59.0)	
	IV	2,781 (2.8)	1,204 (16.5)	
Chronic obstructive pulmonary disease (%)		6,602 (6.6)	859 (11.8)	<0.001*
Asthma (%)		32,263 (32.3)	2,410 (33.0)	0.191
Obstructive sleep apnea (%)		36,018 (36.0)	2,908 (39.9)	<0.001*
Congestive heart failure (%)		3,871 (3.9)	1,239 (17.0)	<0.001*
Preoperative albumin (g/dL, median [IQR])		4.1 [3.7-4.4]	3.7 [3.0-4.2]	<0.001*
Anemia (%)		10,379 (10.4)	2,381 (32.6)	<0.001*
Intraoperative characteristics				
Prone positioning (%)		11,149 (11.2)	774 (10.6)	0.157
Trendelenburg positioning (%)		7,084 (7.1)	470 (6.4)	0.039*
Epidural analgesia (%)		6,719 (6.7)	374 (5.1)	<0.001*
Use of neuromuscular blockers (%)		88,992 (89.0)	6,597 (90.4)	<0.001*
Reversal of neuromuscular blockers (%)		82,411 (82.5)	5,923 (81.2)	0.006*
Use of corticosteroids (%)		71,576 (71.6)	4,665 (63.9)	<0.001*
Total blood product transfusion (ml, median [IQR]) ǂ		0 [0-0]	0 [0-0]	<0.001*
Total fluids in crystalloid equivalents (ml, median [IQR])		1,500 [1,000-2,100]	1,400 [800-2,400]	<0.001*
Mean MAP (mmHg, median [IQR])		80 [74-87]	79 [73-87]	<0.001*
Data collection duration (min, median [IQR])		111 [66-178]	121 [63-221]	<0.001*

Table 2. Continued

	No pulmonary complications	**Pulmonary complications**	**p-value**
	N = 99,939	N = 7,296	
Respiratory parameter			
Median $ETCO_2$ (mmHg, median [IQR])	35 [33-37]	35 [33-37]	0.977
TWA-AUC $ETCO_2$ <28 mmHg (mmHg, median [IQR]) ǂ	0.00 [0.00-0.00]	0.00 [0.00-0.01]	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (mmHg, median [IQR])	0.84 [0.14-2.07]	0.88 [0.16-2.26]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg (mmHg, median [IQR])	9.69 [7.60-11.51]	9.71 [7.44-11.72]	0.239
TWA-AUC $ETCO_2$ >45 mmHg (mmHg, median [IQR]) ǂ	0.00 [0.00-0.01]	0.00 [0.00-0.02]	<0.001*
Median tidal volume (ml, median [IQR])	500 [447-567]	492 [435-559]	<0.001*
Median tidal volume per PDW (ml, median [IQR])	7.9 [7.0-9.0]	7.7 [6.8-8.8]	<0.001*
Median respiratory rate (/min, median [IQR])	12 [10-14]	12 [10-14]	<0.001*
Median RMV (ml/min, median [IQR])	5,904 [4,990-6,984]	6,070 [5,080-7,224]	<0.001*
Median PEEP (cmH_2O, median [IQR])	5 [4-5]	5 [5-6]	<0.001*
Median preoperative saturation (%, median [IQR])	98 [96-100]	97 [96-99]	<0.001*
Median intraoperative saturation (%, median [IQR])	99 [97-100]	99 [97-100]	0.085
Outcome			
Length of stay (days, median [IQR])	3 [2-5]	7 [3-13]	<0.001*
Mortality at discharge (%)	357 (0.4)	349 (4.8)	<0.001*

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure. PBW: predicted body weight. PEEP: positive end-expiratory pressure. RMV: respiratory minute volume. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant at a level of significance of $P < 0.05$. ǂ Strongly skewed distribution.


A. Median ETCO2
PEEP cmH2O
<5
5-8
>8
10%
8%
5%
2%
Associated risk of PPCs (%)
20 30 40 50 60
Median ETCO2 (mmHg)
Vt
<6
6–8
>8
B. TWA-AUC ETCO2 < 45 mmHg
PEEP cmH2O
<5
5-8
>8
7%
6%
5%
4%
3%
2%
Associated risk of PPCs (%)
0 10 20
TWA-AUC ETCO2 < 45 mmHg (mmHg)
Vt
<6
6–8
>8

◂ **Figure 2.** Associated risks of postoperative pulmonary complications for median $ETCO_2$ and TWA-AUC $ETCO_2$ <45 mmHg

$ETCO_2$: end-tidal carbon dioxide. PEEP: positive end-expiratory pressure. PPCs: postoperative pulmonary complications. TWA-AUC: time-weighted average area-under-the-curve. Vt: median tidal volume in $ml \cdot kg^{-1} \cdot PBW^{-1}$. The associated risks of postoperative pulmonary complications are plotted against median $ETCO_2$ (Panel A) and TWA-AUC $ETCO_2$ <45 mmHg (Panel B). Results were stratified for a median tidal volume of <6, 6-8 and >8 $ml \cdot kg^{-1} \cdot PBW^{-1}$ and PEEP 0-5, 5-8 and >8 cmH_2O. Panel A shows that the associated risk of pulmonary complications is lowest for a median $ETCO_2$ around 38 mmHg. Panel B shows that a small TWA-AUC <45 mmHg (below 8 mmHg; i.e. few values below 45 mmHg or many values close to the threshold of 45 mmHg) increases the risk of pulmonary complications. The same happens with a large TWA-AUC $ETCO_2$ <45 mmHg (above 20 mmHg, i.e. many values far from the threshold of 45 mmHg, so very low $ETCO_2$). There appeared to be an optimum for a TWA-AUC $ETCO_2$ <45mmHg around 10 mmHg (i.e. TWA-AUC $ETCO_2$ 35 mmHg). There is no clear effect of tidal volume, but there appeared to be more pulmonary complications in patients with higher levels of PEEP.

Secondary analysis: the subgroups

Since only 5,223 patients could be included in the laparoscopic subgroup and 3,998 in the robotic subgroup, these two groups were merged for analyses in the mixed-effect model to increase statistical power.

In patients presenting for intracranial & carotid artery surgery any value >45 mmHg was associated with an increase in pulmonary complications at 7 and 30 days. A median $ETCO_2$ <28 mmHg decreased length of stay (-7.32% (99% CI -12.28 - -2.07), p-value 0.002).

For all included abdominal procedures, any value <28 mmHg was associated with an increase in pulmonary complications within 30 days. For non-laparoscopic abdominal procedures, any value <35 mmHg was associated with a decrease in pulmonary complications at 7 and 30 day and a decreased length of stay. For categories of TWA-AUC $ETCO_2$ <45 mmHg, 37-45 mmHg was associated with an increase in pulmonary complications in non-laparoscopic abdominal procedures, as was any value >45 mmHg.

The mixed-effect model did not converge for mortality at discharge in the subgroups due to sample sizes and complexity issues of the model.

Table 3. Association between $ETCO_2$ and postoperative pulmonary complications obtained with a mixed-effect model

	Count		**PPCs - 30 days**	
Thresholds ǂ	Total	PPC 30 days	Adjusted OR (CI)	p-value
General cohort	107,235	7,296		
Median $ETCO_2$ (CI 99%, p <0.010)				
<28 mmHg	2,123	260	1.15 (0.93-1.42)	0.080
28-35 mmHg	58,997	3,854	0.97 (0.90-1.05)	0.300
35-40 mmHg	37,161	2,463	Ref	
40-45 mmHg	6,717	500	1.16 (1.00-1.33)	0.008*
>45 mmHg	2,237	219	1.64 (1.33-2.02)	<0.001*
TWA-AUC $ETCO_2$<28 mmHg (CI 95%)				
No value <28 mmHg	82,652	4,767	Ref	
Any value <28 mmHg	24,583	2,529	1.40 (1.33-1.49)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	13,146	809	Ref	
Any value <35 mmHg	94,089	6,487	0.96 (0.88-1.04)	0.342
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	6,373	608	1.12 (0.97-1.29)	0.041
31-33 mmHg	14,627	1,003	1.03 (0.92-1.15)	0.537
33-35 mmHg	27,945	1,758	Ref	
35-37 mmHg	27,256	1,745	1.04 (0.94-1.14)	0.323
37-45 mmHg	31,034	2,182	1.16 (1.05-1.27)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	76,358	4,897	Ref	
Any value >45 mmHg	30,877	2,399	1.24 (1.17-1.31)	<0.001*
Intracranial & carotid artery	12,123	956		
Median $ETCO_2$ (CI 98.3%, p <0.017) ǂ				
<28 mmHg	1,612	131	0.88 (0.67-1.17)	0.286
28-35 mmHg	8,245	672	Ref	
>35 mmHg	2,266	153	0.91 (0.72-1.16)	0.374
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,794	467	Ref	
Any value <28 mmHg	5,329	489	1.13 (0.96-1.32)	0.138
TWA-AUC $ETCO_2$<35 mmHg (CI 95%)				
No value <35 mmHg	474	31	Ref	
Any value <35 mmHg	11,649	925	0.98 (0.66-1.47)	0.937

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
1.18 (0.95-1.47)	0.054	1.47 (0.82-2.62)	0.090	4.29 (0.08-8.68)	0.011
0.98 (0.90-1.06)	0.426	1.00 (0.77-1.28)	0.962	1.71 (0.41-3.03)	0.002*
Ref		Ref		Ref	
1.20 (1.03-1.39)	0.002*	0.92 (0.58-1.47)	0.657	0.30 (-2.00-2.65)	0.716
1.70 (1.36-2.12)	<0.001*	1.28 (0.69-2.37)	0.304	1.11 (-2.98-5.36)	0.483
Ref		Ref		Ref	
1.43 (1.34-1.52)	<0.001*	1.50 (1.24-1.82)	<0.001*	5.54 (4.34-6.76)	<0.001*
Ref		Ref		Ref	
0.98 (0.90-1.08)	0.697	1.12 (0.86-1.46)	0.408	0.39 (-1.02-1.82)	0.587
1.13 (0.97-1.31)	0.036	1.46 (0.97-2.21)	0.020	1.19 (-1.56-4.02)	0.270
1.01 (0.89-1.14)	0.870	1.08 (0.74-1.56)	0.600	-0.49 (-2.40-1.45)	0.513
Ref		Ref		Ref	
1.04 (0.94-1.15)	0.307	1.00 (0.71-1.40)	0.998	-1.18 (-2.77-0.44)	0.064
1.17 (1.06-1.29)	<0.001*	0.95 (0.70-1.30)	0.693	-1.65 (-3.28-0.00)	0.012
Ref		Ref		Ref	
1.27 (1.20-1.35)	<0.001*	1.08 (0.87-1.34)	0.496	-0.34(-1.38-0.72)	0.530
0.94 (0.70-1.25)	0.603	DNC		-7.32 (-12.28- -2.07)	0.002*
Ref		DNC		Ref	
0.90 (0.69-1.18)	0.368	DNC		-1.29 (-5.23-2.81)	0.450
Ref		Ref		Ref	
1.12 (0.94-1.33)	0.193	DNC		1.21 (-1.72-4.23)	0.453
Ref		Ref		Ref	
0.90 (0.58-1.38)	0.621	DNC		-1.29 (-7.47-5.30)	0.698

Table 3. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC 30 days	Adjusted OR (CI)	p-value
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	3,213	283	1.03 (0.78-1.36)	0.798
31-33 mmHg	2,793	227	1.02 (0.78-1.33)	0.861
33-35 mmHg	2,984	227	Ref	
35-37 mmHg	1,980	139	0.91 (0.67-1.23)	0.420
37-45 mmHg	1,153	80	0.98 (0.68-1.43)	0.896
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	10,078	753	Ref	
Any value >45 mmHg	2,045	203	1.10 (1.05-1.50)	0.012*
Laparoscopic & Robotic	9,221	318		
Median $ETCO_2$ (CI 98.8%, p <0.013)ǂ				
<35 mmHg	4,135	161	1.19 (0.85-1.67)	0.188
35-40 mmHg	4,032	123	Ref	
40-45 mmHg	855	27	0.97 (0.55-1.73)	0.908
>45 mmHg	199	7	0.96 (0.33-2.78)	0.926
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,901	199	Ref	
Any value <28 mmHg	2,320	119	1.40 (1.08-1.81)	0.012*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,004	25	Ref	
Any value <35 mmHg	8,217	293	1.10 (0.70-1.74)	0.669
TWA-AUC $ETCO_2$ <45 mmHg (CI 98.8%, p <0.013)ǂ				
<33 mmHg	996	49	1.22 (0.75-2.00)	0.308
33-35 mmHg	2,067	82	Ref	
35-37 mmHg	2,596	77	0.82 (0.53-1.25)	0.242
37-45 mmHg	3,562	110	0.84 (0.56-1.27)	0.294
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	6,292	193	Ref	
Any value >45 mmHg	2,929	125	1.16 (0.90-1.49)	0.241
Non-laparoscopic abdominal	15,190	1,706		
Median $ETCO_2$ (CI 99%, p <0.01)				
<28 mmHg	199	41	1.23(0.71-2.12)	0.326
28-35 mmHg	10,309	1,076	0.88 (0.75-1.04)	0.044
35-40 mmHg	4,250	511	Ref	
40-45 mmHg	369	59	1.13 (0.73-1.76)	0.461
>45 mmHg	63	19	2.32 (0.98-5.52)	0.012

PPCs - 7 days		Mortality		Length of stay ǂ	
Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
1.06 (0.79-1.43)	0.612	DNC		-3.34 (-9.14-2.82)	0.149
1.01 (0.76-1.36)	0.909	DNC		1.01 (-3.82-6.07)	0.617
Ref		DNC		Ref	
0.93 (0.66-1.30)	0.584	DNC		0.10 (-5.17-5.66)	0.959
1.03 (0.68-1.54)	0.874	DNC		1.71 (-4.38-8.20)	0.480
Ref		Ref		Ref	
1.24 (1.02-1.50)	0.031*	DNC		0.90 (-2.97-4.94)	0.669
1.28 (0.90-1.81)	0.084	DNC		3.98 (0.15-7.95)	0.011*
Ref		DNC		Ref	
1.00 (0.55-1.83)	0.993	DNC		-4.40 (-9.74-1.25)	0.048
0.64 (0.17-2.44)	0.400	DNC		-9.43 (-18.85-1.10)	0.024
Ref		DNC		Ref	
1.52 (1.16-1.98)	0.002*	DNC		2.02 (-1.13-5.27)	0.218
Ref		DNC		Ref	
1.40 (0.83-2.36)	0.201	DNC		3.36 (-1.01-7.91)	0.146
1.20 (0.72-1.99)	0.377	DNC		2.74 (-3.48-9.36)	0.283
Ref		DNC		Ref	
0.77 (0.50-1.21)	0.151	DNC		-1.09 (-5.68-3.71)	0.556
0.82 (0.53-1.26)	0.243	DNC		-4.50 (-8.92-0.15)	0.021
Ref		DNC		Ref	
1.19 (0.91-1.54)	0.206	DNC		-4.78 (-7.36- -2.13)	<0.001*
1.26 (0.73-2.20)	0.273	DNC		5.13 (-8.29-20.50)	0.350
0.90 (0.75-1.07)	0.110	DNC		-2.08 (-5.30-1.26)	0.123
Ref		DNC		Ref	
1.08 (0.68-1.71)	0.660	DNC		5.55 (-5.27-17.61)	0.204
2.38 (0.98-5.73)	0.011	DNC		8.76 (-14.85-38.92)	0.377

Table 3. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC 30 days	Adjusted OR (CI)	p-value
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	11,337	1,158	Ref	
Any value <28 mmHg	3,853	548	1.38 (1.22-1.57)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,065	160	Ref	
Any value <35 mmHg	14,125	1,546	0.75 (0.61-0.93)	0.008*
TWA-AUC $ETCO_2$ <45 mmHg (99%, p <0.01)				
<31 mmHg	1,033	151	1.28 (0.96-1.71)	0.028
31-33 mmHg	2,953	337	1.22 (0.99-1.50)	0.017
33-35 mmHg	4,962	493	Ref	
35-37 mmHg	3,816	384	1.00 (0.82-1.22)	0.990
37-45 mmHg	2,426	341	1.36 (1.09-1.69)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	12,544	1,375	Ref	
Any value >45 mmHg	2,646	331	1.18 (1.03-1.36)	0.021*

CI: confidence interval. DNC: did not converge. $ETCO_2$: end-tidal carbon dioxide. OR: odds ratio. PPCs: postoperative pulmonary complications. Ref: reference category. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant. ǂ There was limited variation in $ETCO_2$ for patients presenting for intracranial & carotid artery surgery and (robot assisted) laparoscopic procedures. Therefore, the number of categories for median $ETCO_2$ and TWA-AUC <45 mmHg was reduced, compared to other groups. ǂ Length of stay was log transformed before analysis. The obtained b-coefficient was transformed using (exp(coefficient)-1)*100 to obtain a percentage of change in length of stay.

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
Ref		DNC		Ref	
1.44 (1.26-1.64)	<0.001*	DNC		-1.00 (-4.05-2.16)	0.525
Ref		DNC		Ref	
0.77 (0.62-0.96)	0.020*	DNC		-10.24 (-14.70- -5.54	<0.001*
1.28 (0.94-1.72)	0.038	DNC		4.71 (-2.83-12.83)	0.120
1.24 (1.00-1.55)	0.010	DNC		2.43 (-1.96-7.01)	0.178
Ref		DNC		Ref	
1.01 (0.82-1.25)	0.897	DNC		3.25 (-0.66-7.32)	0.039
1.36 (1.08-1.71)	0.001*	DNC		4.92 (0.16-9.90)	0.009*
Ref		DNC		Ref	
1.20 (0.98-1.46)	0.018*	DNC		-2.37 (-5.57-0.94)	0.176

In the multivariable analyses adjustments were made for age, male sex, body mass index, American Society of Anesthesiologist physical status, chronic obstructive pulmonary disease, obstructive sleep apnea, congestive heart failure, preoperative albumin, epidural analgesia, total amount of fluids administered in crystalloid equivalents, mean of the mean arterial pressure, median tidal volume per predicted body weight, median positive end-expiratory pressure, median respiratory rate, median intraoperative saturation and duration of data collection as proxy for intraoperative duration. A random intercept was used for period and for institution. Bonferroni correction was used to correct for the number of categories within a threshold and p-values and CIs are reported accordingly. For example, when five categories were made within a threshold, p <0.010 was considered statistically significant after a Bonferroni correction (0.05/5), with a corresponding CI of 99%. For TWA-AUC $ETCO_2$ < 28 mmHg, < 35 mmHg and > 45 mmHg no correction was used, since the variable was binned into two categories only.

Sensitivity analyses

Comparable results were obtained for the association between $ETCO_2$ and pulmonary complications within the general cohort using data from the largest institution only and are presented in Table 6S in the Supplemental Material. Additionally, comparable results were found for pulmonary complications and mortality using a fixed-effect model. However, results from the mixed- and fixed-effect model differed for length of stay, with a large intraclass correlation coefficient for institution (see Table 7S and 8S in the Supplemental Material for results of the fixed-effect model and the intraclass correlation coefficients, respectively). The mixed-effect models did not converge for in-hospital mortality when analyzing the subgroups. Results from the fixed-effect models indicate that there was only a possible association between any value <28 mmHg and mortality for the non-laparoscopic abdominal subgroup.

DISCUSSION

This study aimed to explore the association between intraoperative $ETCO_2$ concentrations and pulmonary complications after non-cardiothoracic surgery. While we hypothesized that an $ETCO_2$ >45 mmHg would be associated with a decreased risk of postoperative pulmonary complications, we found that the occurrence of any $ETCO_2$ concentration >45 mmHg was associated with an increase in pulmonary complications within 30 days. Any $ETCO_2$ <28 mmHg during the data collection period was also associated with an increase in pulmonary complications within 30 days. There was a clear non-linear U-shaped relationship between intraoperative $ETCO_2$ concentrations and pulmonary complications and there appeared to be an optimum for a median $ETCO_2$ around 38 mmHg and a TWA-AUC $ETCO_2$ <45mmHg around 10 mmHg (i.e. 35 mmHg).

Clinical implications

Several intraoperative ventilatory settings such as high PEEP levels, recruitment maneuvers and low tidal volumes have been reported to protect against pulmonary complications, with the latter being the most important determinant according to a meta-analysis.[9] Interestingly, in the trials studying the effect of low tidal volume ventilation, patients were ventilated with higher PEEP levels, respiratory rates, plateau pressures and a higher $PaCO_2$, as compared with those receiving conventional ventilation.[9] A recent randomized clinical trial studying the effect of intraoperative ventilation with a tidal volume of 6 $ml \cdot kg^{-1} \cdot PBW^{-1}$ versus 10 $ml \cdot kg^{-1} \cdot PBW^{-1}$ in non-cardiothoracic non-intracranial surgery used a fixed PEEP level of 5 cmH_2O and found no difference in postoperative pulmonary complications.[40] Again, $PaCO_2$ levels were higher in the low tidal volume group. Permissive hypercapnia has been suggested to reduce the risk

of pulmonary complications, primarily by facilitation of low tidal volume ventilation[9] and immune-modulating properties.[11,12] However, the results from the present study suggest that both a very low (<28 mmHg) and high $ETCO_2$ (>45 mmHg) are associated with postoperative pulmonary complications within 30 days. Intraoperative $ETCO_2$ concentrations <28 mmHg were also associated with in-hospital mortality and increased length of stay. Additionally, a TWA-AUC $ETCO_2$ of 37-45 mmHg and a median $ETCO_2$ of >40 mmHg seem to be associated with pulmonary complications. The optimum appears to be around a median $ETCO_2$ of 38 mmHg, which is higher than found in current practice, namely a median $ETCO_2$ of 35 [IQR 33-38].[19] By excluding all potentially hemodynamic unstable patients and analyzing several procedure types separately, the $ETCO_2$ concentrations found in this study reflect values that are currently targeted by anesthesiologists during maintenance of anesthesia, rather than randomly occurring values based on patient or procedure characteristics. A stricter $ETCO_2$ management might be warranted based on our results. One can wonder if a median $ETCO_2$ of 38 mmHg truly results in a clinically relevant reduction in pulmonary complications when compared to a median $ETCO_2$ of 40 mmHg. This needs to be studied further in a prospective, preferable randomized, setting. However, we do believe that our results show an important u-shaped relationship, where both too low (i.e. <28 mmHg) and too high $ETCO_2$ concentrations (i.e. >45 mmHg) may need to be prevented.

It is very well possible that different $ETCO_2$ concentrations are preferred for different organ systems. Hypercapnia can increase cardiac output and cause a shift in the oxyhemoglobin dissociation curve, resulting in increased tissue perfusion and oxygenation.[41] It has been hypothesized that hypercapnia can prevent surgical site infections, but a randomized trial was unable to confirm this.[42] Also, hypercapnia can increase myocardial oxygen demand.[16] In injured brains, hypocapnia can worsen cerebral ischemia, whereas hypercapnia can increase cerebral blood flow, potentially at the cost of an elevate intracranial pressure. In conclusion, especially severe hypocapnia seems to be harmful, but future studies exploring the effect of $ETCO_2$ on pulmonary complications should consider to take patient-centered outcomes such as disability-free survival into account as well.[43] Based on findings from this study, we suggest that future studies also take severity and duration of hypo- and hypercapnia into account, as well as institutional practice. First, others found that an $ETCO_2$ <35 mmHg was associated with mortality and length of stay which was in contrast to our results.[17,18] These studies only studied hypocapnia as a binary variable (mean $ETCO_2$ <35 mmHg) or used a median $ETCO_2$, without taking severity or duration of hypo- or hypercapnia into account.[17,18] We believe this may have influenced the associations found in these studies. Second, institutional practice might have an important effect on complications and especially length of stay, as reflected by the large intraclass correlation coefficient for length of stay in our study.

Strengths and limitations

This study has several strengths. First, we were able to include a large number of patients, enabling us to correct for many potential confounders. Despite a comprehensive and highly granular database, sample sizes for our subgroups were still relatively small and these results should be interpreted with caution. Second, as we included both academic and private hospitals, we believe that our findings are generalizable to a large set of patients. To account for between-institution variation, we used a mixed-effect model. Third, we used a standardized definition for postoperative pulmonary complications and found an incidence of 6.8%. A prospective cohort study using a similar definition, found a comparable incidence of 5%.[4] Finally, we summarized $ETCO_2$ using TWA-AUC. A systematic review studying the effect of intraoperative hypotension in non-cardiac surgery revealed that both severity and duration are important to consider when studying vital parameters rather than just a mean or median, as regression to the mean can occur.[44] Therefore, we believe that AUC is a more appropriate measure to summarize $ETCO_2$ concentrations than a mean or median. As the duration of the procedure can potentially have a large influence on postoperative outcome (i.e. a difficult and complicated procedure often takes longer), we chose to correct AUC for duration, resulting in a TWA-AUC.

This study has some obvious limitations. First, as with all retrospective observational studies, the risk of residual confounding is evident. However, we believe that we defined a fairly broad panel of confounders. We were unable to include tobacco use, ventilator mode, driving pressure and recruitment maneuvers, since data for these variables were not sufficiently and reliably submitted to the MPOG registry. A previous study from the MPOG consortium found that most institutions use a controlled ventilation mode.[19] Also, there is no clear benefit for one specific intraoperative ventilation mode with regard to pulmonary complications.[8] To not make the mixed-effect model overly complex, the use of (reversal of) neuromuscular blocking agents was not included, as use was standardized in most institutions. Second, we had to exclude 217,453 patients (27%) due to missing or invalid data points, underlining the difficulty of conducting outcome research using large multicenter databases. Third, when no ICD codes were documented within 30 days after surgery, we classified this as "no pulmonary complication". This assumption potentially diluted the found effect. Additionally, we used a Bonferroni correction, which potentially results in overcorrection as well.[45] Fourth, TWA-AUC values described in this cohort differ from those previously described.[19] In the previous study, TWA-AUC values were transformed for interpretation purposes.[19] Fifth, the intraoperative timeframe used for data collection was relatively narrow and excluded $ETCO_2$ values during the beginning and end of anesthesia. However, this timeframe was chosen to collect data during a stable phase of anesthesia. In randomly selected cases, these timeframes were found to correspond well with the maintenance phase of anesthesia.

Conclusion

The occurrence of any intraoperative $ETCO_2$ >45 mmHg as well as any $ETCO_2$ value <28 mmHg appears to be associated with an increased risk of postoperative pulmonary complications. The latter was also associated with mortality and an increased length of stay. The optimal $ETCO_2$ seems to be around 35-38 mmHg but due to its retrospective design, causality could not be determined. Prospective, preferably randomized, studies are required to explore the effect of intraoperative $ETCO_2$ concentrations on postoperative pulmonary complications further.

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SUPPLEMENTAL MATERIAL

Supplemental Material: Table 1S. Definition of pulmonary complications

ESA definition		Definition in this study	
Respiratory infection	Patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count >12×10^9/L	**Pneumonia**	
		ICD 9	481-486, 997.31,
		ICD-10	J13-18, J95.851
Respiratory failure	Postoperative PaO2 <8kPa (60mmHg) on room air, a PaO2:FI02 ratio <40kPa (300mmHg) or arterial oxyhemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy	**Respiratory failure**	
		ICD-9	518.51, 518.52, 518.53, 518.7, 518.81, 518.82, 518.84, 997.39, 799.02, 779.1
		ICD-10	J80, J95.2, J95.821, J95.822, J95.84, J95.859, J95.89, J96.0, J96.00, J96.01, J96.02, J96.20, J96.21, J96.22, J96.9, J96.90, J96.91, J96.92, R09.02, R09.2
Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemi-diaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemi-thorax with preserved vascular shadows	**Pleural effusion / pulmonary edema**	
		ICD-9	511.9, 518.4
		ICD-10	J81.0
Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemi-diaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung	**Atelectasis**	
		ICD 9	514, 518.0
		ICD-10	JJ98.11, J98.19
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura	**Pneumothorax**	
		ICD 9	512
		ICD-10	J93.0, J93.1, J93.8, J93.9, J95.81, J95.82, J95.850

Supplemental Material: Table 1S. Continued

ESA definition		Definition in this study	
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators	**Bronchospasm**	
		ICD-9	519.11
		ICD-10	J98.01
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents	**Aspiration pneumonitis**	
		ICD-9	507.0, 997.32
		ICD-10	J69.0, J95.4

ESA: European Society of Anesthesiologist. ESA definition based on: Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, Leva B, Rhodes A, Hoeft A, Walder B, Chew MS, Pearse RM: Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015; 32(2):88–105

Supplemental Material: Table 2S. Artifact filter

Parameter	Definition
General criteria	• User entered values: invalid • Data collection between 35 minutes after the first $ETCO_2$ capture until 20 minutes prior to the last $ETCO_2$ capture • At least 20 valid measurements (not consecutive) per case during the data collection timeframe
Height	• Invalid when <120cm or >220 cm
Weight	• Invalid when <15 kg or >250 kg
$ETCO_2$	• $ETCO_2$ had to be between 15 mmHg (2 kPa or 2%) and 65 mmHg (8.6 kPa or 8.5%)
Tidal volume	• Invalid when tidal volume <100 mL or >2000 ml
Tidal volume per PBW	• PBW male = 50 + (0.91*height (cm) – 152.4) • PBW female = 45.5 + (0.91*height (cm) – 152.4) • Invalid when <1 or >25
Respiratory rate	• Invalid when <4 and >25/minute
Respiratory minute volume	• See Tidal volume and Respiratory rate • Also; invalid when <500 ml/min and >25,000 ml/min
PEEP	• Invalid when <0 cmH_2O
SpO2	• Invalid when <0 %

Supplemental Material: Table 2S. Continued

Parameter	Definition

MAP	• Invalid when
	  • SBP >150 and PP <30
	  • SBP ≥100 AND SBP ≤150 AND PP <15
	  • SBP <100 AND PP <10
	  • SBP >200 AND PP <50
	  • SBP ≤10 OR DBP ≤10
	  • SBP = DBP = MAP
	  • MAP ≥140
	  • MAP ≤10
	  • marked as artifact in real-time by the provider. If any blood pressure is marked as artifact then all measurements for that time were marked as artifact
	  • If only a MAP is returned on arterial line (e.g. no SBP or DBP), then MAP was marked as artifact for that timestamp
	• For each intraoperative minute with SBP values simultaneously recorded from multiple sources, the highest available SBP was determined as the true SBP. This process was similarly applied to MAP and DBP, respectively.
	• For all minutes with continued missing MAP values but with SBP and DBP present, MAP was computed by the formula: (MAP) = (SBP) * (1/3) + (DBP) * (2/3)

Fresh frozen plasma	• Invalid when >20,000ml
Cryoprecipitate	• Invalid when >2,500 ml
Colloids	• Invalid when >2,500ml
Crystalloids	• Invalid when >20,000ml
Packed cells	• Invalid when >10,000ml
Total fluids in ml of crystalloid equivalents	Definition: sum of all colloid, crystalloid and blood products converted to crystalloid equivalents. The conversion formula used is based on conversion ratio of 1:1.5 (Orbegozo Cortés D, Gamarano Barros T, Njimi H, Vincent JL: Crystalloids versus colloids: Exploring differences in fluid requirements by systematic review and meta-regression. Anesth Analg 2015; 120:389–402) and is standardized practice at MPOG. (See https://collations.mpogresearch.org/Detail.aspx?name=Total%20Fluid%20-%20Crystalloid%20Equivalents%20(ml)) • Invalid when >40,000ml

DBP: diastolic blood pressure. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. MPOG: Multicenter Perioperative Outcomes Group. PBW: predicted body weight. PEEP: positive end-expiratory pressure. PP: pulse pressure. SBP: systolic blood pressure. SpO2: pulse oximetry.

Supplemental Material: Table 3S. Missing data distribution

Variable	Count (%)
	N = 143,769*
Preoperative characteristics	
Age	0 (0%)
Sex	39 (0%)
Height	7,950 (6%)
Weight	5,033 (4%)
PBW	7,984 (6%)
BMI	8,479 (6%)
ASA class	0 (0%)
Chronic obstructive pulmonary disease	0 (0%)
Asthma	0 (0%)
Obstructive sleep apnea	0 (0%)
Congestive heart failure	0 (0%)
Preoperative albumin	58,452 (41%)
Anemia	22,207 (15%)
Intraoperative characteristics	
Prone positioning	27,168 (19%)
Trendelenburg positioning	27,869 (19%)
Epidural analgesia	0 (0%)
Use of neuromuscular blockers	13,706 (10%)
Reversal of neuromuscular blockers	13,706 (10%)
Use of corticosteroids	13,706 (10%)
Packed cells	0 (0%)
Whole blood	0 (0%)
Cell saver	0 (0%)
Fresh frozen plasma	0 (0%)
Thrombocytes	0 (0%)
Cryoprecipitate	1 (0%)
Other blood products	0 (0%)
Colloids	15 (0%)
Crystalloids	26 (0%)
Total fluids in crystalloid equivalents	8 (0%)

Supplemental Material: Table 3S. Continued

Variable	**Count (%)**
	N = 143,769*
Mean MAP	2,715 (2%)
Data collection start time	0 (0%)
Data collection end time	0 (0%)
Respiratory parameters	
Median $ETCO_2$	0 (0%)
TWA-AUC $ETCO_2$ <28 mmHg	0 (0%)
TWA-AUC $ETCO_2$ <35 mmHg	0 (0%)
TWA-AUC $ETCO_2$ <45 mmHg	0 (0%)
TWA-AUC $ETCO_2$ >45 mmHg	0 (0%)
Median tidal volume	19,422 (14%)
Median respiratory rate	421 (0%)
Median PEEP	13,356 (9%)
Median preoperative saturation	26,750 (19%)
Median intraoperative saturation	9,299 (6%)
Outcome	
Postoperative pulmonary complications within 30 days	0 (0%)
Postoperative pulmonary complications within 7 days	0 (0%)
Length of stay	32,199 (22%)
Mortality at discharge	26,002 (18%)

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. PBW: predicted body weight. PEEP: positive end-expiratory pressure. TWA-AUC: time-weighted average area-under-the-curve * Missingness for general cohort and all subgroups combined

Supplemental Material: Table 4S. Baseline characteristics for patients with and without missing mortality data in the general cohort

		Mortality not missing	Mortality missing	p-value
N = 107,235		N = 87,267	N = 19,968	
Preoperative characteristics				
Age (years, median [IQR])		55 [41-66]	51 [38-62]	<0.001*
Sex (Female, %)		4,043 (51.6)	10,850 (54.4)	<0.001*
BMI (kg/m², median [IQR])		28.8 [24.6-34.2]	27.8 [23.9-33.4]	<0.001*
ASA class (%)	I	4,616 (5.3)	1,537 (7.7)	<0.001*
	II	38,580 (44.2)	9,720 (48.7)	
	III	40,982 (47.0)	7,815 (39.1)	
	IV	3,089 (3.5)	896 (4.5)	
Chronic obstructive pulmonary disease (%)		3,737 (4.3)	167 (0.8)	<0.001*
Asthma (%)		9,616 (11.0)	1,259 (6.3)	<0.001*
Obstructive sleep apnea (%)		14,251 (16.3)	1,157 (5.8)	<0.001*
Congestive heart failure (%)		4,254 (4.9)	567 (2.8)	<0.001*
Preoperative albumin (g/dL, median [IQR])		4.1 [3.6-4.4]	3.8 [3.3-4.2]	<0.001*
Anemia (%)		9,147 (11.8)	2,246 (18.5)	<0.001*
Intraoperative characteristics				
Prone positioning (%)		8,359 (11.5)	2,045 (10.7)	0.003*
Trendelenburg positioning (%)		6,610 (9.2)	672 (3.5)	<0.001*
Epidural analgesia (%)		5,990 (6.9)	1,103 (5.5)	<0.001*
Use of neuromuscular blockers (%)		70,627 (88.6)	14,795 (90.9)	<0.001*
Reversal of neuromuscular blockers (%)		66,647 (83.6)	12,491 (76.8)	<0.001*
Use of corticosteroids (%)		60,436 (75.8)	9,696 (59.6)	<0.001*
Total blood product transfusion (ml, median [IQR]) ǂ		0 [0-0]	0 [0-0]	<0.001*
Total fluids in crystalloid equivalent (ml, median [IQR])		1,500 [1,000-2,100]	1,400 [1,000-2,100]	<0.001*
Mean MAP (mmHg, median [IQR])		80 [74-88]	78 [72-86]	<0.001*
Data collection duration (min, median [IQR])		111 [66-181]	114 [68-179]	0.241

Supplemental Material: Table 4S. Continued

	Mortality not missing	**Mortality missing**	**p-value**
N = 107,235	N = 87,267	N = 19,968	
Respiratory parameters			
Median $ETCO_2$ (mmHg, median [IQR])	35 [33-37]	34 [32-36]	<0.001*
TWA-AUC $ETCO_2$ <28 mmHg (mmHg, median [IQR]) ǂ	0.00 [0.00-0.00]	0.00 [0.00-0.01]	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (mmHg, median [IQR])	0.74 [0.12-1.89]	1.40 [0.33-2.84]	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg (mmHg, median [IQR])	9.52 [7.47-11.28]	10.58 [8.25-12.47]	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (mmHg, median [IQR]) ǂ	0.0 [0.0-0.01]	0.00 [0.00-0.00]	<0.001*
Median tidal volume (ml, median [IQR])	495 [443-560]	492 [440-560]	0.026*
Median respiratory rate (/min, median [IQR])	12 [10-14]	11 [10-12]	<0.001*
Median PEEP (cmH_2O, median [IQR])	5 [5-5]	5 [4-5]	<0.001*
Median preoperative saturation (%, median [IQR])	98 [96-99]	99 [96-100]	<0.001*
Median saturation (%, median [IQR])	99 [97-100]	99 [98-100]	<0.001*
Outcome			
Postoperative pulmonale complications within 30 days (%)	6,248 (7.2)	1,048 (5.2)	<0.001*
Postoperative pulmonale complications within 7 days (%)	5,323 (6.1)	1,002 (5.0)	<0.001*
Length of stay (days, median [IQR])	3 [2-5]	1 [1-1]	<0.001*
Mortality at discharge (%)	562 (0.6)	0 (NA)	NA

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure. NA: not applicable. PBW: predicted body weight. PEEP: positive end-expiratory pressure. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant at a level of significance of $p < 0.05$. ǂ Strongly skewed distribution

Supplemental Material: Table 5S. Result from univariable analyses for the association between $ETCO_2$ and postoperative pulmonary complications obtained with a mixed-effect model

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC 30 days	Unadjusted OR (CI)	p-value
General cohort	107,235	7,296		
Median $ETCO_2$ (CI 99%, p <0.010)				
<28 mmHg	2,123	260	1.78 (1,48-2.14)	<0.001*
28-35 mmHg	58,997	3,854	1.00 (0.93-1.07)	0.937
35-40 mmHg	37,161	2,463	Ref	
40-45 mmHg	6,717	500	1,26 (1.11-1.44)	< 0.001*
>45 mmHg	2,237	219	1.84 (1.52-2.22)	<0.001*
TWA-AUC $ETCO_2$<28 mmHg (CI 95%)				
No value <28 mmHg	82,652	4,767	Ref	
Any value <28 mmHg	24,583	2,529	1.82 (1.72-1.91)	0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	13,146	809	Ref	
Any value <35 mmHg	94,089	6,487	1.01 (0.94-1.09)	0.708
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	6,373	608	1.49 (1.31-1.70)	<0.001*
31-33 mmHg	14,627	1,003	1.09 (0.98-1.22)	0.031
33-35 mmHg	27,945	1,758	Ref	
35-37 mmHg	27,256	1,745	1.00 (0.92-1.10)	0.944
37-45 mmHg	31,034	2,182	1.17 (1.08-1.28)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	76,358	4,897	Ref	
Any value >45 mmHg	30,877	2,399	1.27 (1.21-1.34)	<0.001*
Intracranial & carotid artery	12,123	956		
Median $ETCO_2$ (CI 98.3%, p <0.017) ǂ				
<28 mmHg	1,612	131	1.05 (0.82-1.34)	0.635
28-35 mmHg	8,245	672	Ref	
>35 mmHg	2,266	153	0.86 (0.68-1.07)	0.101
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,794	467	Ref	
Any value <28 mmHg	5,329	489	1.32 (1.15-1.51)	<0.001*

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Unadjusted OR (CI)	p-value	Unadjusted OR (CI)	p-value	% Change (CI)	p-value
1.78 (1.47-2.15)	<0.001*	4.11 (2.45-6.90)	<0.001*	1.14 (1.09-1.19)	<0.001*
0.99 (0.92-1.07)	0.810	1.12 (0.88-1.42)	0.243	1.03 (10.01-1.04)	<0.001*
Ref		Ref		Ref	
1.30 (1.13-1.50)	<0.001*	1.20 (0.78-1.86)	0.276	0.99 (0.97-1.02)	0.552
1.89 (1.54-2.31)	0.0001*	1.90 (1.06-3.40)	0.005*	0.99 (0.95-1.04)	0.684
Ref		Ref		Ref	
1.84 (1.74-1.95)	<0.001*	2.16 (1.82-2.57)	<0.001*	1.16 (1.4-1.17)	<0.001*
Ref		Ref		Ref	
1.04 (0.96-1.13)	0.333	0.98(0.76-1.25)	0.845	1.07 (1.06-1.08)	<0.001*
1.48 (1.29-1.70)	<0.001*	2.80 (1.92-4.08)	<0.001*	1.06 (1.03-1.09)	<0.001*
1.07 (0.95-1.20)	0.142	1.30 (0.91-1.85)	0.057	1.00 (0.98-1.02)	0.685
Ref		Ref		Ref	
1.01 (0.92-1.11)	0.756	0.93 (0.67-1.29)	0.588	0.98 (0.96-0.99)	0.001*
1.19 (1.09-1.31)	<0.001*	1.03 (0.76-1.39)	0.798	0.96 (0.95-0.98)	<0.001*
Ref		Ref		Ref	
1.33 (1.26-1.40)	<0.001*	0.86 (0.70-1.04)	0.121	1.03 (1.02-1.04)	<0.001**
1.15 (0.89-1.48)	0.194	0.90 (0.48-1.72)	0.708	0.97 (0.93-1.03)	0.225
Ref		Ref		Ref	
0.84 (0.65-1.08)	0.090	0.78 (0.45-1.33)	0.263	0.93 (0.87-0.98)	0.002*
Ref		Ref		Ref	
1.37 (1.19-1.59)	<0.001*	0.90 (0.65-1.24)	0.509	1.13 (1.10-1.17)	<0.001*

Supplemental Material: Table 5S. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC 30 days	Unadjusted OR (CI)	p-value
TWA-AUC $ETCO_2$<35 mmHg (CI 95%)				
No value <35 mmHg	474	31	Ref	
Any value <35 mmHg	11,649	925	1.09 (0.75-1.59)	0.642
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	3,213	283	1.18 (0.92-1.51)	0.080
31-33 mmHg	2,793	227	1.07 (0.83-1.38)	0.507
33-35 mmHg	2,984	227	Ref	
35-37 mmHg	1,980	139	0.90 (0.67-1.20)	0.345
37-45 mmHg	1,153	80	0.98 (0.69-1.40)	0.909
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	10,078	753	Ref	
Any value >45 mmHg	2,045	203	1.09 (1.17-1.63)	<0.001*
Laparoscopic & Robotic	9,221	318		
Median $ETCO_2$ (CI 98.8%, p <0.013)ǂ				
<35 mmHg	4,135	161	1.38 (1.01-1.89)	0.010*
35-40 mmHg	4,032	123	Ref	
40-45 mmHg	855	27	1.05 (0.61-1.81)	0.815
>45 mmHg	199	7	1.19 (0.44-3.20)	0.663
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,901	199	Ref	
Any value <28 mmHg	2,320	119	1.61 (1.28-2.06)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,004	25	Ref	
Any value <35 mmHg	8,217	293	1.33 (0.87-2.02)	0.190
TWA-AUC $ETCO_2$ <45 mmHg (CI 98.8%, p <0.013)ǂ				
<33 mmHg	996	49	1.38 (0.87-2.21)	0.082
33-35 mmHg	2,067	82	Ref	
35-37 mmHg	2,596	77	0.72 (0.48-1.08)	0.041
37-45 mmHg	3,562	110	0.74 (0.50-1.08)	0.045
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	6,292	193	Ref	
Any value >45 mmHg	2,929	125	1.24 (0.98-1.56)	0.074

PPCs - 7 days		Mortality		Length of stay ǂ	
Unadjusted OR (CI)	p-value	Unadjusted OR (CI)	p-value	% Change (CI)	p-value
Ref		Ref		Ref	
1.05 (0.70-1.57)	0.825	0.89 (0.42-1.91)	0.772	1.10 (1.03-1.18)	0.004*
1.27 (0.97-1.66)	0.020	1.01 (0.56-1.81)	0.970	1.07 (1.01-1.13)	0.003*
1.08 (0.82-1.42)	0.492	1.20 (0.68-2.11)	0.411	1.04 (0.99-1.10)	0.043
Ref		Ref		Ref	
0.92 (0.67-1.27)	0.498	0.83 (0.42-1.67)	0.496	0.99 (0.93-1.04)	0.528
1.02 (0.69-1.50)	0.904	0.86 (0.37-1.99)	0.638	0.99 (0.93-1.06)	0.716
Ref		Ref		Ref	
1.10 (1.17-1.68)	<0.001*	1.28 (0.51-1.35)	0.456	1.01 (1.03-1.11)	0.001*
1.46 (1.05-2.02)	0.004*	0.77 (0.22-2.72)	0.612	1.08 (1.04-1.12)	<0.001*
Ref		Ref		Ref	
1.08 (0.61-1.92)	0.728	0.51 (0.04-7.12)	0.525	0.95 (0.89-1.00)	0.020
0.77 (0.21-2.79)	0.619	4.44 (0.62-31.52)	0.058	0.88 (0.78-0.98)	0.003*
Ref		Ref		Ref	
1.77 (1.37-2.27)	<0.001*	1.03 (0.37-2.86)	0.956	1.08 (1.05-1.12)	<0.001*
Ref		Ref		Ref	
1.67 (1.02-2.72)	<0.001*	1.03 (0.24-4.42)	0.973	1.13 (1.08-1.18)	<0.001*
1.35 (0.83-2.20)	0.119	0.98 (0.11-8.46)	0.977	1.06 (0.99-1.13)	0.034
Ref		Ref		Ref	
0.68 (0.44-1.04)	0.025	0.93 (0.17-4.95)	0.910	0.96 (0.92-1.01)	0.068
0.72 (0.48-1.06)	0.035	1.10 (0.24-5.10)	0.871	0.90 (0.86-0.95)	<0.001*
Ref		Ref		Ref	
1.26 (0.98-1.61)	0.069	1.52 (0.61-3.82)	0.370	0.95 (0.93-0.98)	0001*

Supplemental Material: Table 5S. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC 30 days	Unadjusted OR (CI)	p-value
Non-laparoscopic abdominal	15,190	1,706		
Median $ETCO_2$ (CI 99%, p <0.01)				
<28 mmHg	199	41	2.07 (1.28-3.35)	<0.001*
28-35 mmHg	10,309	1,076	0.90 (0.77-1.05)	0.077
35-40 mmHg	4,250	511	Ref	
40-45 mmHg	369	59	1.44 (0.97-2.14)	0.017
>45 mmHg	63	19	3.56 (1.71-7.41)	8.514
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	11,337	1,158	Ref	
Any value <28 mmHg	3,853	548	1.41 (1.26-1.58)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,065	160	Ref	
Any value <35 mmHg	14,125	1,546	0.66 (0.55-0.80)	<0.001*
TWA-AUC $ETCO_2$ <45 mmHg (99%, p <0.01)				
<31 mmHg	1,033	151	1.67 (1.28-2.19)	<0.001*
31-33 mmHg	2,953	337	1.25 (1.03-1.53)	<0.003*
33-35 mmHg	4,962	493	Ref	
35-37 mmHg	3,816	384	0.98 (0.82-1.19)	0.816
37-45 mmHg	2,426	341	1.44 (1.18-1.76)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	12,544	1,375	Ref	
Any value >45 mmHg	2,646	331	1.16 (1.01-1.32)	0.031*

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. OR: odds ratio. PPCs: postoperative pulmonary complications. Ref: reference category. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant. ǂ There was limited variation in $ETCO_2$ for patients presenting for intracranial & carotid artery surgery and (robot-assisted) laparoscopic procedures.

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Unadjusted OR (CI)	p-value	Unadjusted OR (CI)	p-value	% Change (CI)	p-value
2.14 (1.30-3.50)	<0.001*	6.40 (2.70-15.19)	<0.001*	1.20 (1.04-1.39)	0.001*
0.91 (0.77-1.07)	0.143	1.16 (0.71-1.92)	0.433	1.00 (0.96-1.03)	0.774
Ref		Ref		Ref	
1.40 (0.92-2.12)	0.037	1.65 (0.59-4.63)	0.211	1.08 (0.96-1.21)	0.097
3.74 (1.76-7.96)	<0.001*	1.83 (0.27-12.33)	0.417	1.16 (0.90-1.51)	0.137
Ref		Ref		Ref	
1.45 (1.29-1.64)	<0.001*	1.51 (1.10-2.06)	0.010*	1.05 (1.01-1.08)	0.005*
Ref		Ref		Ref	
0.66 (0.54-0.80)	<0.001*	0.66 (0.43-1.02)	0.064	0.94 (0.89-0.99)	0.018*
1.67 (1.26-2.20)	<0.001*	3.37 (1.77-6.41)	<0.001*	1.12 (1.03-1.21)	<0.001*
1.28 (1.04-1.58)	0.002*	1.36 (0.78-2.36)	0.153	1.03 (0.98-1.08)	0.132
Ref		Ref		Ref	
1.00 (0.82-1.21)	0.952	0.81 (0.46-1.43)	0.339	1.01 (0.97-1.06)	0.414
1.46 (1.18-1.81)	<0.001*	1.16 (0.66-2.06)	0.499	1.03 (0.98-1.08)	0.196
Ref		Ref		Ref	
1.17 (1.02-1.34)	0.028*	0.84 (0.57-1.24)	0.381	0.99 (0.96-1.03)	0.650

Therefore, the number of categories for median $ETCO_2$ and TWA-AUC <45 mmHg was reduced, compared to the general cohort and other subgroups. ǂ Length of stay was log transformed before analysis. The obtained b-coefficient was transformed using (exp(coefficient)-1)*100 to obtain a percentage of change in length of stay.

Supplemental Material: Table 6S. Sensitivity analysis with data from the largest contributing institution

	PPCs - 30 days	
Thresholds	Adjusted OR (CI)	p-value
General cohort		
Median $ETCO_2$ (CI 99%, p <0.010)		
<28 mmHg	1.37 (0.91-2.05)	0.045
28-35 mmHg	1.01 (0.91-1.12)	0.768
35-40 mmHg	Ref	
40-45 mmHg	1.17 (0.95-1.44)	0.050
>45 mmHg	1.87 (1.37-2.54)	<0.001*
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)		
No value <28 mmHg	Ref	
Any value <28 mmHg	1.44 (1.32-1.57)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)		
No value <35 mmHg	Ref	
Any value <35 mmHg	0.94 (0.83-1.06)	0.307
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)		
<31 mmHg	1.22 (0.95-1.57)	0.041
31-33 mmHg	1.06 (0.89-1.25)	0.423
33-35 mmHg	Ref	
35-37 mmHg	1.00 (0.88-1.14)	0.967
37-45 mmHg	1.14 (1.00-1.30)	0.012
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)		
No value >45 mmHg	Ref	
Any value >45 mmHg	1.21 (1.12-1.31)	<0.001*

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. OR: odds ratio. PPCs: postoperative pulmonary complications. Ref: reference category. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant. ǂ Length of stay was log transformed before analysis. The obtained b-coefficient was transformed using (exp(coefficient)-1)*100 to obtain a percentage of change in length of stay. In the multivariable analyses adjustments were made for age, male sex, body mass index, American Society of Anesthesiologist physical status, chronic obstructive pulmonary disease, obstructive sleep apnea, congestive heart failure, preoperative albumin, epidural analgesia, total amount of fluids administered in crystalloid equivalents, mean of the

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
1.27 (0.81-2.00)	0.168	2.09 (0.94-4.64)	0.017	7.25 (-0.72-15.87)	0.019
1.02 (0.91-1.15)	0.591	0.95 (0.67-1.34)	0.693	2.94 (1.36-4.55)	<0.001*
Ref		Ref		Ref	
1.33 (1.07-1.66)	0.001*	1.43 (0.76-2.67)	0.141	-2.96 (-6.15-0.35)	0.022
2.04 (1.47-2.83)	<0.001*	1.50 (0.56-4.04)	0.294	-3.63 (-9.18-2.25)	0.107
Ref		Ref		Ref	
1.44 (1.31-1.58)	<0.001*	1.63 (1.26-2.12)	<0.001*	8.44 (6.75-10.15)	<0.001*
Ref		Ref		Ref	
0.96 (0.84-1.09)	0.492	0.91 (0.64-1.30)	0.621	2.12 (0.14-4.14)	0.042
1.11 (0.84-1.47)	0.339	1.73 (0.96-3.14)	0.017	1.92 (-2.45-6.48)	0.286
1.03 (0.85-1.24)	0.692	1.26 (0.76-2.09)	0.247	-0.70 (-3.22-1.89)	0.467
Ref		Ref		Ref	
0.99 (0.86-1.14)	0.898	1.14 (0.73-1.77)	0.459	-1.69 (-3.69-0.36)	0.029
1.16 (1.01-1.34)	0.007*	1.17 (0.75-1.83)	0.355	-3.92 (-5.88- -1.92)	<0.001*
Ref		Ref		Ref	
1.29 (1.18-1.40)	<0.001*	1.32 (0.99-1.74)	0.054	-0.60 (-1.95-0.77)	0.410

mean arterial pressure, median tidal volume per predicted body weight, median positive end-expiratory pressure, median respiratory rate, median intraoperative saturation and duration of data collection as proxy for intraoperative duration. A random intercept was used for period. Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals (CI) are reported accordingly. For example, when five categories were made within a threshold, p <0.010 was considered statistically significant after a Bonferroni correction (0.05/5), with a corresponding CI of 99%. For TWA-AUC $ETCO_2$ <28 mmHg, <35 mmHg and >45 mmHg no correction was used, since the variable was binned into two categories only.

Supplemental Material: Table 7S. Sensitivity analysis: association between $ETCO_2$ and postoperative pulmonary complications obtained with a fixed-effect model

	Count		**PPCs - 30 days**	
Thresholds ǂ	Total	PPC at 30 days	Adjusted OR (CI)	p-value
General cohort	107,235	7,296		
Median $ETCO_2$ (CI 99%, p <0.010)				
<28 mmHg	2,123	260	1.15 (0.93-1.42)	0.088
28-35 mmHg	58,997	3,854	0.97 (0.90-1.05)	0.296
35-40 mmHg	37,161	2,463	Ref	
40-45 mmHg	6,717	500	1.16 (1.01-1.33)	0.008*
>45 mmHg	2,237	219	1.64 (1.33-2.02)	<0.001*
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	82,652	4,767	Ref	
Any value <28 mmHg	24,583	2,529	1.40 (1.32-1.49)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	13,146	809	Ref	
Any value <35 mmHg	94,089	6,487	0.96 (0.88-1.04)	0.334
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	6,373	608	1.12 (0.97-1.29)	0.043
31-33 mmHg	14,627	1,003	1.03 (0.92-1.15)	0.539
33-35 mmHg	27,945	1,758	Ref	
35-37 mmHg	27,256	1,745	1.04 (0.94-1.14)	0.323
37-45 mmHg	31,034	2,182	1.16 (1.05-1.27)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	76,358	4,897	Ref	
Any value >45 mmHg	30,877	2,399	1.24 (1.17-1.31)	<0.001*
Intracranial & carotid artery	12,123	956		
Median $ETCO_2$ (CI 98.3%, p < 0.017) ǂ				
<28 mmHg	1,612	131	0.88 (0.67-1.17)	0.279
28-35 mmHg	8,245	672	Ref	
>35 mmHg	2,266	153	0.91 (0.72-1.16)	0.370
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,794	467	Ref	
Any value <28 mmHg	5,329	489	1.13 (0.96-1.32)	0.144

PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
1.17 (0.94-1.46)	0.060	1.49 (0.83-2.68)	0.080	17.37 (-5.74-46.14)	0.060
0.97 (0.90-1.06)	0.419	0.99 (0.77-1.28)	0.953	-2.52 (-10.12-5.74)	0.419
Ref		Ref		Ref	
1.20 (1.03-1.39)	0.002*	0.93 (0.58-1.47)	0.667	19.90 (3.27-39.21)	0.002*
1.70 (1.36-2.12)	<0.001*	1.29 (0.69-2.39)	0.293	69.94 (36.27-111.93)	<0.001*
Ref		Ref		Ref	
1.43 (1.34-1.52)	<0.001*	1.51 (1.24-1.83)	<0.001*	42.68 (34.28-51.61)	<0.001*
Ref		Ref		Ref	
0.98 (0.90-1.07)	0.684	1.12 (0.85-1.46)	0.425	-1.86 (-10.36-7.44)	0.684
1.13 (0.97-1.31)	0.039	1.47 (0.97-2.22)	0.019	12.77 (-2.95-31.05)	0.039
1.01 (0.89-1.14)	0.874	1.08 (0.74-1.56)	0.615	0.74(-10.64-13.57)	0.874
Ref		Ref		Ref	
1.04 (0.94-1.15)	0.307	1.00 (0.71-1.40)	0.996	4.13 (-5.97-15.31)	0.307
1.17 (1.06-1.29)	<0.001*	0.96 (0.70-1.31)	0.706	16.81 (5.62-29.19)	<0.001*
Ref		Ref		Ref	
1.27 (1.20-1.35)	<0.001*	1.08 (0.87-1.34)	0.485	27.10 (17.46-37.53)	<0.001*
0.93 (0.70-1.25)	0.579	0.96 (0.48-1.92)	0.894	-7.31 (-12.38- -1.96)	0.002*
Ref		Ref		Ref	
0.91 (0.69-1.19)	0.385	0.86 (0.49-1.51)	0.511	-1.28 (-5.24-2.84)	0.450
Ref		Ref		Ref	
1.12 (0.94-1.32)	0.216	0.84 (0.57-1.24)	0.382	1.16 (-1.83-4.25)	0.452

Supplemental Material: Table 7S. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC at 30 days	Adjusted OR (CI)	p-value
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	474	31	Ref	
Any value <35 mmHg	11,649	925	0.99 (0.66-1.48)	0.959
TWA-AUC $ETCO_2$ <45 mmHg (CI 99%, p <0.010)				
<31 mmHg	3,213	283	1.03 (0.78-1.36)	0.790
31-33 mmHg	2,793	227	1.02 (0.78-1.34)	0.849
33-35 mmHg	2,984	227	Ref	
35-37 mmHg	1,980	139	0.91 (0.67-1.24)	0.425
37-45 mmHg	1,153	80	0.98 (0.67-1.42)	0.872
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	10,078	753	Ref	
Any value >45 mmHg	2,045	203	1.10 (1.05-1.51)	0.012*
Laparoscopic & Robotic	9,221	318		
Median $ETCO_2$ (CI 98.8%, p < 0.013) ǂ				
<35 mmHg	4,135	161	1.19 (0.85-1.67)	0.200
35-40 mmHg	4,032	123	Ref	
40-45 mmHg	855	27	0.97 (0.55-1.74)	0.909
>45 mmHg	199	7	0.95 (0.33-2.78)	0.907
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	6,901	199	Ref	
Any value <28 mmHg	2,320	119	1.38 (1.06-1.79)	0.016*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,004	25	Ref	
Any value <35 mmHg	8,217	293	1.09 (0.69-1.73)	0.700
TWA-AUC $ETCO_2$ <45 mmHg (CI 98.8%, p < 0.013)ǂ				
<33 mmHg	996	49	1.23 (0.75-2.01)	0.300
33-35 mmHg	2,067	82	Ref	
35-37 mmHg	2,596	77	0.82 (0.54-1.27)	0.262
37-45 mmHg	3,562	110	0.85 (0.56-1.29)	0.318
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	6,292	193	Ref	
Any value >45 mmHg	2,929	125	1.16 (0.90-1.50)	0.245

	PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
	Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
	Ref		Ref		Ref	
	0.90 (0.58-1.39)	0.637	0.88 (0.39-2.00)	0.763	-1.28 (-7.39-5.24)	0.693
	1.06 (0.79-1.43)	0.622	1.04 (0.54-1.99)	0.887	-3.38 (-9.06-2.66)	0.150
	1.01 (0.75-1.36)	0.910	1.13 (0.62-2.06)	0.592	0.97 (-3.96-6.16)	0.619
	Ref		Ref		Ref	
	0.94 (0.67-1.31)	0.612	0.82 (0.40-1.68)	0.484	0.09 (-5.09-5.56)	0.964
	1.02 (0.68-1.54)	0.886	0.85 (0.35-2.08)	0.647	1.71 (-4.35-8.16)	0.477
	Ref		Ref		Ref	
	1.10 (1.02-1.50)	0.034*	1.29 (0.51-1.37)	0.474	0.88 (-3.00-4.90)	0.664
	1.27 (0.89-1.82)	0.088	0.71 (0.17-2.91)	0.541	3.94 (0.11-7.91)	0.012*
	Ref		Ref		Ref	
	1.01 (0.55-1.85)	0.977	0.47 (0.03-7.67)	0.503	-4.38 (-9.62-1.15)	0.047
	0.63 (0.16-2.46)	0.399	2.64 (0.21-33.62)	0.342	-9.43 (-18.77-0.98)	0.024
	Ref		Ref		Ref	
	1.50 (1.14-1.96)	0.004*	1.10 (0.34-3.56)	0.871	2.02 (-1.16-5.30)	0.219
	Ref		Ref		Ref	
	1.38 (0.82-2.33)	0.230	1.50 (0.26-8.78)	0.650	3.33 (-1.11-7.97)	0.147
	1.20 (0.72-2.00)	0.369	0.58 (0.05-6.69)	0.575	2.71 (-3.46-9.28)	0.283
	Ref		Ref		Ref	
	0.78 (0.50-1.22)	0.160	1.08 (0.17-6.62)	0.921	-1.07 (-5.56-3.64)	0.564
	0.82 (0.53-1.27)	0.264	0.91 (0.15-5.34)	0.890	-4.43 (-8.94-0.30)	0.022
	Ref		Ref		Ref	
	1.18 (0.91-1.54)	0.211	1.44 (0.50-4.13)	0.501	-4.80 (-7.29- -2.23)	<0.001*

Supplemental Material: Table 7S. Continued

	Count		PPCs - 30 days	
Thresholds ǂ	Total	PPC at 30 days	Adjusted OR (CI)	p-value
Non-laparoscopic abdominal	15,190	1,706		
Median $ETCO_2$ (CI 99%, p < 0.01)				
<28 mmHg	199	41	1.22(0.71-2.11)	0.342
28-35 mmHg	10,309	1,076	0.88 (0.74-1.04)	0.043
35-40 mmHg	4,250	511	Ref	
40-45 mmHg	369	59	1.13 (0.73-1.76)	0.465
>45 mmHg	63	19	2.33 (0.98-5.55)	0.012
TWA-AUC $ETCO_2$ <28 mmHg (CI 95%)				
No value <28 mmHg	11,337	1,158	Ref	
Any value <28 mmHg	3,853	548	1.38 (1.21-1.56)	<0.001*
TWA-AUC $ETCO_2$ <35 mmHg (CI 95%)				
No value <35 mmHg	1,065	160	Ref	
Any value <35 mmHg	14,125	1,546	0.75 (0.61-0.93)	0.008*
TWA-AUC $ETCO_2$ <45 mmHg (99%, p < 0.01)				
<31 mmHg	1,033	151	1.28 (0.95-1.71)	0.031
31-33 mmHg	2,953	337	1.22 (0.98-1.50)	0.017
33-35 mmHg	4,962	493	Ref	
35-37 mmHg	3,816	384	1.00 (0.82-1.22)	0.992
37-45 mmHg	2,426	341	1.36 (1.09-1.70)	<0.001*
TWA-AUC $ETCO_2$ >45 mmHg (CI 95%)				
No value >45 mmHg	12,544	1,375	Ref	
Any value >45 mmHg	2,646	331	1.18 (1.02-1.36)	0.022*

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. OR: odds ratio. PPCs: postoperative pulmonary complications. Ref: reference category. TWA-AUC: time-weighted average area-under-the-curve. * Statistically significant. ǂ There was limited variation in $ETCO_2$ for patients presenting for intracranial & carotid artery surgery and (robot assisted) laparoscopic procedures. Therefore, the number of categories for median $ETCO_2$ and TWA-AUC <45 mmHg was reduced, compared to other groups. ǂ Length of stay was log transformed before analysis. The obtained b-coefficient was transformed using (exp(coefficient)-1)*100 to obtain a percentage of change in length of stay.

	PPCs - 7 days		**Mortality**		**Length of stay ǂ**	
	Adjusted OR (CI)	p-value	Adjusted OR (CI)	p-value	% Change (CI)	p-value
	1.25 (0.72-2.18)	0.291	2.99 (1.02-8.82)	0.010*	5.15 (-8.36-20.65)	0.348
	0.90 (0.75-1.07)	0.106	1.16 (0.66-2.04)	0.510	-2.06 (-5.38-1.39)	0.122
	Ref		Ref		Ref	
	1.08 (0.68-1.71)	0.668	1.11 (0.37-3.27)	0.812	5.52 (-5.37-17.66)	0.206
	2.39 (0.99-5.79)	0.011	0.48 (0.06-4.17)	0.384	8.78 (-14.86-38.97)	0.377
	Ref		Ref		Ref	
	1.43 (1.26-1.63)	<0.001*	1.66 (1.17-2.36)	0.005*	-1.00 (-3.98-2.06)	0.518
	Ref		Ref		Ref	
	0.77 (0.62-0.96)	0.019*	1.10 (0.65-1.85)	0.725	-10.25 (-14.75- -5.52)	<0.001*
	1.27 (0.94-1.71)	0.042	1.96 (0.93-4.12)	0.022	4.68 (-2.88-12.84)	0.120
	1.24 (1.00-1.55)	0.011	1.25 (0.69-2.26)	0.325	2.38 (-2.13-7.09)	0.180
	Ref		Ref		Ref	
	1.01 (0.82-1.25)	0.897	0.83 (0.45-1.55)	0.455	3.24 (-0.77-7.42)	0.039
	1.36 (1.08-1.72)	0.001*	0.93 (0.47-1.83)	0.781	4.92 (0.06-10.01)	0.009*
	Ref		Ref		Ref	
	1.20 (1.03-1.39)	0.019*	1.04 (0.67-1.60)	0.860	-2.33 (-5.59-1.04)	0.175

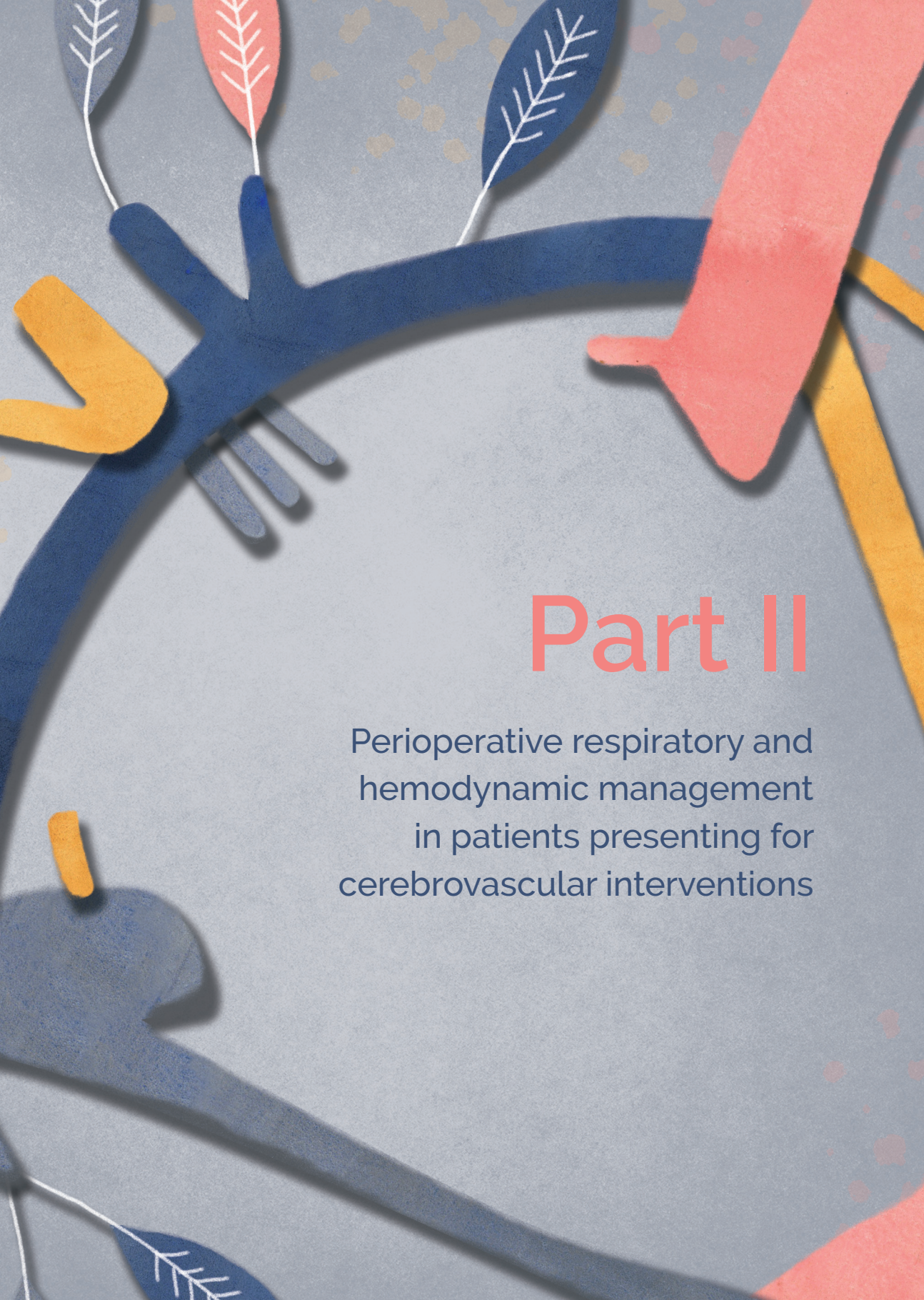
In the multivariable analyses adjustments were made for age, male sex, body mass index, American Society of Anesthesiologist physical status, chronic obstructive pulmonary disease, obstructive sleep apnea, congestive heart failure, preoperative albumin, epidural analgesia, total amount of fluids administered in crystalloid equivalents, mean of the mean arterial pressure, median tidal volume per predicted body weight, median positive end-expiratory pressure, median respiratory rate, median intraoperative saturation and duration of data collection as proxy for intraoperative duration. In the fixed model, period and institution were included as fixed effects. Bonferroni correction was used to correct for the number of categories within a threshold and p-values and CIs are reported accordingly. For example, when five categories were made within a threshold, p <0.010 was considered statistically significant after a Bonferroni correction (0.05/5), with a corresponding CI of 99%. For TWA-AUC <28 mmHg, <35 mmHg and >45 mmHg no correction was used, since the variable was binned into two categories only.

Supplemental Material: Table 8S. Intraclass correlation coefficients for the multivariable mixed-effect models

	PPCs - 30 days		**PPCs - 7 days**
Cohort & Category	ICC Institution	ICC period	ICC Institution
General cohort			
Median $ETCO_2$	0.11	0.01	0.11
TWA-AUC $ETCO_2$ <28 mmHg	0.11	0.01	0.11
TWA-AUC $ETCO_2$ <35 mmHg	0.11	0.01	0.11
TWA-AUC $ETCO_2$ <45 mmHg	0.11	0.01	0.11
TWA-AUC $ETCO_2$ >45 mmHg	0.11	0.01	0.11
Intracranial & carotid artery			
Median $ETCO_2$	0.12	0.001	0.12
TWA-AUC $ETCO_2$ <28 mmHg	0.12	0.001	0.12
TWA-AUC $ETCO_2$ <35 mmHg	0.12	0.001	0.12
TWA-AUC $ETCO_2$ <45 mmHg	0.12	0.001	0.12
TWA-AUC $ETCO_2$ >45 mmHg	0.12	0.001	0.12
Laparoscopic & Robotic			
Median $ETCO_2$	0.10	0.01	0.09
TWA-AUC $ETCO_2$ <28 mmHg	0.10	0.01	0.08
TWA-AUC $ETCO_2$ <35 mmHg	0.10	0.01	0.08
TWA-AUC $ETCO_2$ <45 mmHg	0.10	0.01	0.09
TWA-AUC $ETCO_2$ >45 mmHg	0.10	0.01	0.09
Non-laparoscopic abdominal			
Median $ETCO_2$	0.13	0.02	0.13
TWA-AUC $ETCO_2$ <28 mmHg	0.12	0.01	0.12
TWA-AUC $ETCO_2$ <35 mmHg	0.13	0.02	0.13
TWA-AUC $ETCO_2$ <45 mmHg	0.13	0.02	0.13
TWA-AUC $ETCO_2$ >45 mmHg	0.13	0.02	0.13

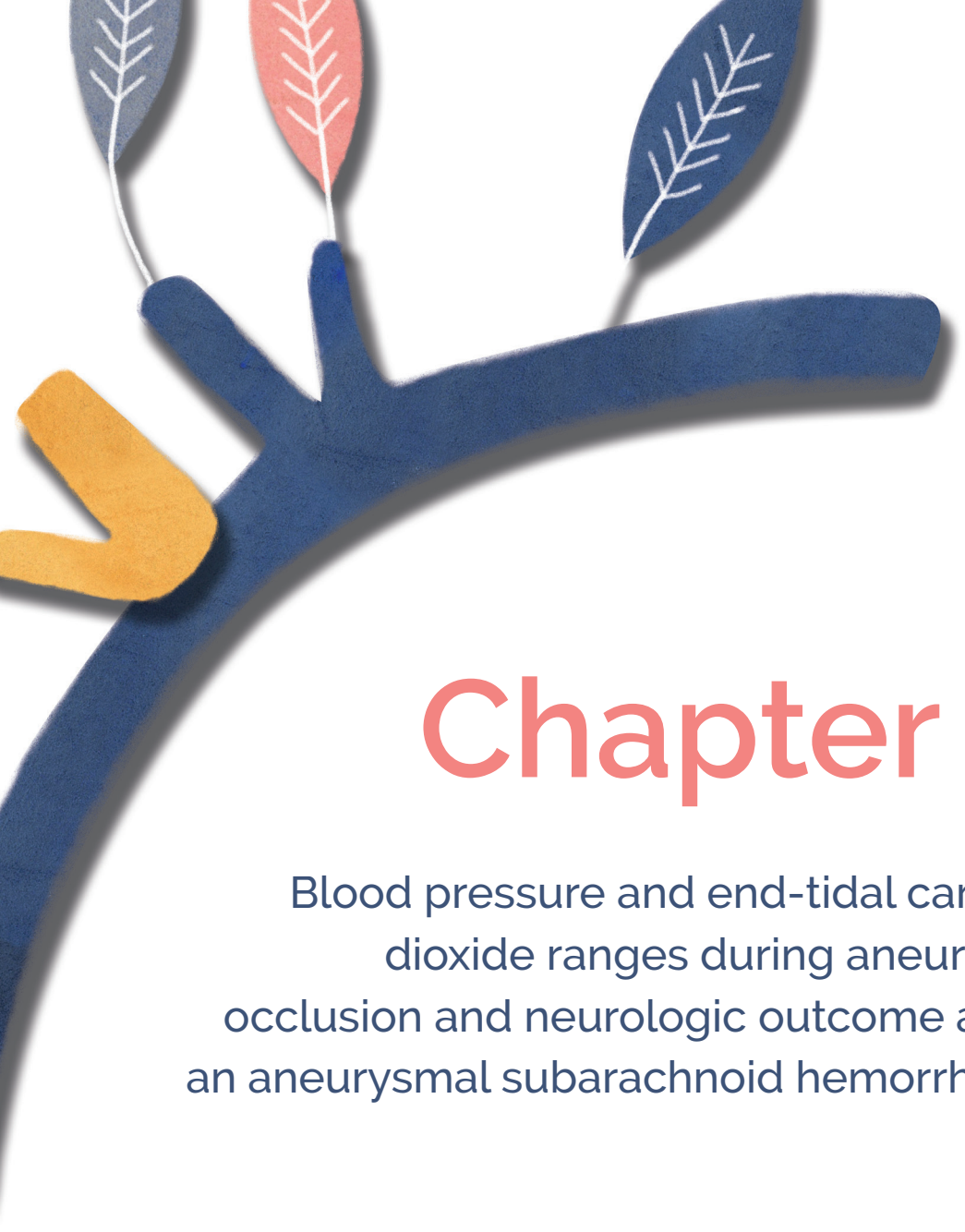
DNC: did not converge. $ETCO_2$: end-tidal carbon dioxide. ICC: intraclass correlation coefficient. PPCs: postoperative pulmonary complications. TWA-AUC: time-weighted average area-under-the-curve.

	Mortality		Length of stay	
ICC period	ICC Institution	ICC period	ICC Institution	ICC period
0.01	0.04	0.01	0.68	0.002
0.01	0.04	0.01	0.68	0.002
0.01	0.03	0.01	0.68	0.002
0.01	0.03	0.01	0.68	0.002
0.01	0.03	0.01	0.68	0.002
0.001	DNC	DNC	0.67	0.005
0.001	DNC	DNC	0.67	0.005
0.001	DNC	DNC	0.67	0.005
0.001	DNC	DNC	0.67	0.005
0.001	DNC	DNC	0.67	0.005
0.01	DNC	DNC	0.70	0.002
0.01	DNC	DNC	0.70	0.002
0.01	DNC	DNC	0.70	0.002
0.01	DNC	DNC	0.70	0.002
0.01	DNC	DNC	0.70	0.002
0.01	DNC	DNC	0.67	0.004
0.01	DNC	DNC	0.67	0.004
0.01	DNC	DNC	0.67	0.004
0.01	DNC	DNC	0.67	0.004
0.01	DNC	DNC	0.67	0.004



Part II

Perioperative respiratory and hemodynamic management in patients presenting for cerebrovascular interventions



Chapter 4

Blood pressure and end-tidal carbon dioxide ranges during aneurysm occlusion and neurologic outcome after an aneurysmal subarachnoid hemorrhage

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ABSTRACT

Background Hypocapnia, hypotension and hypertension during aneurysm occlusion in patients with an aneurysmal subarachnoid hemorrhage (ASAH) may lead to a poor prognosis, but evidence for end-tidal carbon dioxide ($ETCO_2$) and mean arterial pressure (MAP) targets is lacking. Within the ranges of standardized treatment, we aimed to study the association between hypocapnia (arterial carbon dioxide pressure <35mmHg), hypotension (MAP <80mmHg) and hypertension (MAP >100mmHg) during general anesthesia for aneurysm occlusion and neurologic outcome.

Methods This retrospective observational study included patients who underwent early aneurysm occlusion after ASAH under general anesthesia. $ETCO_2$ and MAP were summarized per patient as the mean and time-weighted average area-under-the-curve for various absolute ($ETCO_2$ <30, <35, <40, <45mmHg and MAP <60, <70, <80, >90, >100mmHg) and relative thresholds (MAP <70%, <60%, <50%). Clinical outcome was assessed with the Glasgow Outcome Scale at discharge and at three months, as primary and secondary outcome measure respectively.

Results Endovascular coiling was performed in 578 patients and 521 underwent neurosurgical clipping. Of these 1,099 patients, 447 (41%) had a poor neurologic outcome at discharge. None of the $ETCO_2$ and MAP ranges found within the current clinical setting were associated with a poor neurologic outcome at discharge, with an adjusted risk ratio (RR) for any $ETCO_2$ value <30mmHg of 0.95 (95% CI 0.81-1.10, p-value 0.496) and an adjusted RR for any MAP <60mmHg of 0.94 (95% CI 0.78-1.14, p-value 0.530). These results were not influenced by preoperative neurological condition, treatment modality and timing of the intervention. Comparable results were obtained for neurologic outcome at three months.

Conclusion Within a standardized intraoperative treatment strategy in accordance with current clinical consensus, hypocapnia, hypotension and hypertension during aneurysm occlusion were not found to be associated with a poor neurologic outcome at discharge in ASAH patients.

INTRODUCTION

Despite considerable treatment improvements over the past decades, case fatality and disability rates for patients with an aneurysmal subarachnoid hemorrhage (ASAH) remain high.[1–3] After ASAH, the cerebral autoregulation is disrupted and cerebral blood flow may become blood pressure dependent. Therefore, in patients undergoing general anesthesia for an intervention to obliterate the aneurysm, maintaining adequate blood pressure is considered important to avoid both hypertension-related re-bleeding as well as hypotension-related cerebral ischemia.[1,4] However, because only a few, relatively small studies have been performed in this specific population,[5–7] solid recommendations on peri-procedural blood pressure targets are lacking.[2]

In addition, arterial carbon dioxide pressure ($PaCO_2$) reactivity seems preserved or even increased in ASAH patients and therefore hypocapnia can aggravate secondary ischemia through cerebral vasoconstriction.[8] Hypocapnia has been shown to be associated with a poor neurologic outcome in patients with traumatic brain injury, an ischemic stroke or after a cardiac arrest.[9–11] While evidence for ASAH patients specifically is lacking, there is evidence supporting the benefit of hypercapnia for postoperative outcomes in the general surgery population.[12–14] Although PaCO2 is not monitored continuously, it is well reflected in end-tidal carbon dioxide ($ETCO_2$), which is routinely monitored during anesthesia.

Altogether, there is insufficient evidence to determine optimal target ranges for both $ETCO_2$ and mean arterial pressure (MAP) during anesthesia for interventions to treat cerebral aneurysms after ASAH. Therefore, this study sets out to explore the association between several intraoperative $ETCO_2$ and MAP thresholds and a poor neurologic outcome in a large cohort of ASAH patients who were treated according to a standardized institutional strategy based on current clinical consensus. The results may guide clinicians in setting peri-procedural target ranges in the future. Based on the above-mentioned literature, we hypothesized that prolonged (>10 minutes) intraoperative hypocapnia ($ETCO_2$ <35 mmHg), hypotension (MAP <80 mmHg) and hypertension (MAP >100 mmHg) are associated with a poor neurologic outcome in ASAH patients receiving general anesthesia for interventions to treat cerebral aneurysms.

METHODS

This study was conducted in adherence to the STROBE statement for observational research.[15] The local medical ethics committee approved the study protocol and the need for informed consent was waived (UMC Utrecht Medical Research Ethics Committee 16-194/C).

Patients

This retrospective, observational study included adult patients who received general anesthesia for neurosurgical clipping or endovascular coiling of a ruptured intracranial aneurysm at the University Medical Center Utrecht (UMC Utrecht) between January 2003 and December 2015. Patients who were treated within two weeks after the ictus were eligible for inclusion. Re-interventions in patients who had more than one episode of ASAH were included as a new patient if the time between these episodes was more than one year. Patients were excluded if they underwent bypass surgery for a giant aneurysm. Furthermore, patients were excluded if less than a total of 20 valid $ETCO_2$ and MAP measurements were available or when no MAP and $ETCO_2$ data were recorded for at least ten consecutive minutes during the procedure. When no $ETCO_2$ data were recorded, patients could still be included for blood pressure analyses and vice versa. Patients without a known baseline blood pressure were excluded from analyses for relative blood pressure thresholds only.

Patients were treated according to a local standardized protocol[5] and the preferred neurosurgical treatment modality was chosen on a multidisciplinary level and irrespective of the conduct of this study. Management of blood pressure and $ETCO_2$ were left to the judgment of the attending anesthesiologist. The protocol prescribed to maintain $ETCO_2$ between 35-45 mmHg and to keep the systolic blood pressure (SBP) <180 mmHg before treatment and <220 mmHg after securing the aneurysm, while maintaining a MAP >80 mmHg.

Outcomes

The primary outcome was the neurologic outcome at discharge, using the Glasgow Outcome Scale[16] (GOS, see Table 1S in the Supplemental Material). The GOS at three months was used as a secondary outcome. We defined a good outcome as a GOS score 4-5 and a poor outcome as a GOS score 1-3.

MAP and $ETCO_2$

To analyze the effect of $ETCO_2$ and blood pressure on a poor neurologic outcome we determined the mean $ETCO_2$ and the mean MAP for each patient. However, as those summary measures do not sufficiently take normal intraoperative variability into

account,[17] we further used a time-weighted average area-under-the-curve (TWA-AUC) for several absolute and relative thresholds. TWA-AUC represents the time spent under or above a certain threshold, adjusted for the total measurement time. For $ETCO_2$, we defined the following absolute thresholds: <30 mmHg, <35 mmHg, <40 mmHg and <45 mmHg, based on clinical relevance. For blood pressure, the following absolute and relative thresholds were defined: MAP < 60 mmHg, MAP <70 mmHg, MAP <80 mmHg, MAP >90 mmHg, MAP >100 mmHg and MAP <70%, MAP <60%, MAP <50% of the baseline MAP, based on reported thresholds in the literature.[18,19] In order to define the baseline MAP, we used the mean of all pre-induction MAPs per patient obtained at the operation room. Previous research in the general surgery population has shown that pre-induction blood pressure can be used as a baseline for research purposes.[20]

Data collection

Data on patient characteristics, comorbidities and chronic medication use were collected from electronic medical files. Data on preoperative neurologic condition, neurologic complications and postoperative neurologic outcomes were obtained from the local hospital ASAH registration database that contains data from admission until three months after the ictus. Intraoperative data were extracted from the electronic anesthesia record-keeping system (Anstat, Carepoint, Ede, Netherlands). Invasive blood pressure measurements, $ETCO_2$ values and respiratory minute volume (RMV) values were recorded as the median per minute; non-invasive blood pressure measurements were recorded every time a blood pressure was measured (i.e. at 1-3 minute intervals). RMV was calculated as tidal volume times respiratory rate. In order to avoid influences from induction and emergence from anesthesia on $ETCO_2$ and MAP values, extraction of intraoperative data started ten minutes after surgical incision and stopped ten minutes prior to the end of the procedure. The duration of surgery was defined as the time between surgical incision and end of the procedure. Data artifacts were excluded using criteria based on prior research (See Table 2S in the Supplemental Material).[21,22]

No statistical power calculation was conducted prior to start of the study. The sample size was based on the available data.

Missing data

As complete case analyses are known to lead to biased effect estimates, missing values were handled using multiple imputation.[23] We used the mice package in R, creating thirty imputation sets.[24] Analyses were conducted in each of these datasets; subsequently estimates were pooled using Rubin's rule.[25,26] Missing data for $ETCO_2$, MAP and RMV were not imputed.

Statistical analysis

Baseline characteristics were compared between patients with a good and poor outcome at discharge, and between patients presenting for endovascular coiling and neurosurgical clipping using a $\chi 2$ test, Fisher's exact test, independent *t* test or Mann-Whitney U test where appropriate. Continuous variables were checked for normality using the Kolmogorov-Smirnov test.

Association between MAP and $ETCO_2$

Since changes in blood pressure are known to affect $ETCO_2$ concentrations by influencing the $ETCO_2$-$PaCO_2$ gradient,[27] we first estimated the effect of changes in MAP on changes in $ETCO_2$. First, in each patient the median of all obtained $ETCO_2$, MAP and RMV values was calculated. Next, we determined the difference (Δ) between the median and every other value of $ETCO_2$, MAP and RMV, respectively. ΔMAP and ΔRMV were paired with $\Delta ETCO_2$ values that were obtained one minute later, to allow for a change in $ETCO_2$ to occur. Next, because a non-linear relationship between $\Delta ETCO_2$ and ΔMAP was expected, a univariable linear quantile mixed regression model was made with ten quantiles, using $\Delta ETCO_2$ as the dependent variable, ΔMAP as the independent variable and a random intercept per individual to take clustering within patients into account. Afterwards, a multivariable analysis was used to adjust for changes in RMV.

We considered that $ETCO_2$ values should be adjusted for MAP values in the subsequent analyses if there was a significant and clinically relevant association between $ETCO_2$ and MAP. In this, an effect estimate of 1.1 or higher for every 10 mmHg change in MAP was considered to be clinically relevant.

Association between $ETCO_2$ and MAP and neurologic outcomes

In line with previous studies,[10,28] we first calculated a mean MAP and mean $ETCO_2$ for each patient. Second, the AUC was calculated for each predefined threshold as mentioned above, for both MAP and $ETCO_2$. This AUC was adjusted for the total measurement time, resulting in a time-weighted average AUC (TWA-AUC, see Figure 1S in the Supplemental Material).

Next, univariable Poisson regression models were built using mean MAP, mean $ETCO_2$, TWA-AUC MAP or TWA-AUC $ETCO_2$ as the independent variable respectively and the dichotomized GOS score at discharge as the dependent variable. We used Poisson regression analyses with robust standard errors to present effect estimates as risk ratios (RR), since a poor neurologic outcome is relatively common and the rare disease assumption would not hold.[29] This means that an odds ratio, as found in a logistic regression analysis, would not approach the corresponding risk ratio, hampering the

interpretation of our results for clinical practice. Because we expected a non-linear relationship in these models based on previous research,[30] a restricted cubic spline function with three, four and five knots was tested for the best fit, using Akaike's Information Criterion.[31] Subsequently, a multivariable analysis was used to adjust for potential confounders. The variables shown in Table 1 were considered a potential confounder and were checked for collinearity using Pearson's correlation matrix. Variables with a correlation <0.6 were included in the model. In case of multicollinearity, the clinically most relevant variable was included. In addition, year of procedure was included as a potential confounder to account for possible changes in clinical practice over time.

To enhance clinical interpretation, the Poisson regression analyses were repeated using categorized versions of the independent variables, where categorization was based on distribution of the data and inspection of the spline plots. We used the following quantiles: 0, 0.1, 0.25, 0.5, 0.75, 0.9 and 1.0, with the 0.5-0.75 quantile as the reference category.

Finally, we explored the effect of extreme hypocapnia and hypotension further by repeating the analyses using 'having at least one $ETCO_2$ value <30 mmHg' and 'having at least one MAP value <60 mmHg' as the independent variable respectively.

To explore whether preoperative clinical condition, vulnerability to cerebral vasospasm and treatment modality modified the associations, we repeated all analyses for neurologic outcome at discharge with the following interaction terms: preoperative World Federation of Neurological Surgeons Grading System grade (WFNS, dichotomized in WFNS 4-5 and WFNS 1-3 (see Table 1S in the Supplemental Material)),[32] timing of intervention (dichotomized in early (≤ 2 days after the ictus) and late (>2 days after the ictus)) and treatment modality (clipping or coiling).

The aforementioned analyses were repeated for GOS score at three months as secondary outcome measure. Bonferroni correction was used to correct for the number of categories within a threshold, and p-values and confidence intervals (CI) were reported accordingly. For all other analyses a p-value of <0.05 was considered to be statistically significant. All statistical tests were two-tailed. The statistical analyses were performed with R (Version 3.3.1 – © 2016-06-21, R, Inc., for Macintosh).[33]

RESULTS

In the study period, 1,484 patients were admitted for ASAH and 1,099 (74.1%) were eligible for inclusion in our analyses (Figure 1). Of these patients, 447 (40.7%) had a poor neurologic outcome at discharge.

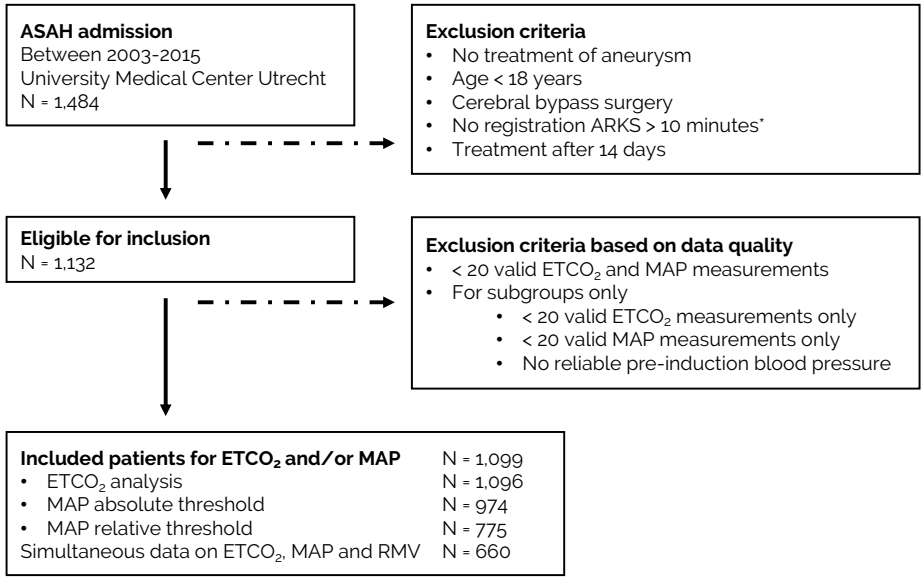


Figure 1. Flow chart

ASAH: Aneurysmal subarachnoid hemorrhage. ARKS: anesthesia record-keeping system. $ETCO_2$: End-tidal carbon dioxide. MAP: mean arterial pressure. RMV: respiratory minute volume. *No registration, largely due to (temporary) transfer to other institutions for intervention or failure to record for more than 10 consecutive minutes due to disconnection with the ARKS.

According to the local protocol for ASAH patients, general anesthesia was maintained with propofol (induction bolus 1-3 mg/kg, maintenance infusion 4-10 $mg \cdot kg^{-1} \cdot h^{-1}$), an opioid (either sufentanil or remifentanil) and a neuromuscular blocking agent (either rocuronium or atracurium). In all patients, non-invasive blood pressure measurements were used. Additionally, in all patients undergoing clipping, and by indication in some patients during coiling, blood pressure was measured continuously by using an intra-arterial catheter. Episodes of hypotension were treated with ephedrine, phenylephrine or norepinephrine (bolus and/or continuous infusion) and episodes of hypertension were generally treated with a mixed α- and β-adrenergic blocking drug (labetalol) or an α2-adrenergic agonist (clonidine).

Patient characteristics were compared for patients with a good and poor neurologic outcome at discharge and for patients presenting for endovascular coiling and neurosurgical clipping (Table 1). Most demographic factors, medical history and pre-admission medication, neurological and peri-procedural factors, and complications were associated with neurologic outcome. Patients with a poor neurologic outcome received more norepinephrine during the intervention. There was no significant difference in treatment modality or in procedure and anesthesia time between patients with a good and poor outcome. Patients treated with endovascular coiling were on average older and had a higher ASA class. During coiling, phenylephrine was frequently used as a vasopressor, whereas norepinephrine was primarily used during clipping. Patients treated with coiling suffered less from electrolyte imbalances, anemia, post-intervention neurological decline and cerebral edema. Additionally, they were treated less frequently with cerebral spinal fluid (CSF) drainage (defined as requiring an external ventricular drain, external lumbar drain or lumbar punctures).

Due to missing values in either $ETCO_2$ or MAP values, 1,096 patients (99.7%) could be included for analysis of $ETCO_2$ thresholds, 974 (88.6%) for analysis of absolute MAP thresholds and 775 (70.5%) for analysis of relative MAP thresholds, because pre-induction blood pressure measurements were missing in 199 patients. Data on the extent of missing data and the variables used for multiple imputation are provided in Table 3S and 4S of the Supplemental Material. Results from the univariable complete case analysis for neurologic outcome at discharge are presented in Table 5S of the Supplemental Material to show the impact of imputation on observed estimates.

The median of the mean $ETCO_2$ was 43 mmHg [IQR 41-45] in patients with a good neurologic outcome and 44 mmHg [IQR 42-46] in patients with a poor neurologic outcome ($p < 0.001$); the median was 43 mmHg [IQR 41-45] in patients treated with neurosurgical clipping, and 44 mmHg [IQR 42-46] in patients who received endovascular coiling ($p < 0.001$).

The median of the mean MAP was 80 mmHg [IQR 72-88] and 81 mmHg [IQR 74-88] in patients with good and poor neurologic outcome, respectively ($p = 0.021$). In patients treated with neurosurgical clipping, the median of the mean MAP was 82 [IQR 75-89], while the median was 79 [IQR 71-87] in patients receiving endovascular coiling ($p < 0.001$).

Table 1. Patient characteristics for good versus poor neurologic outcome at discharge and for clipping versus coiling

		GOS 4-5
		N = 652
Age (years, median [IQR])		55 [46-64]
Sex (%)	Male	186 (28.5)
BMI (median [IQR])		24.8 [22.4-28.2]
ASA class (%)	I	135 (20.7)
	II	478 (73.3)
	III	39 (6.0)
	IV	0 (0.0)
Myocardial infarction (%)		26 (4.0)
Congestive heart failure (%)		0 (0.0)
Cerebrovascular accident (%)		40 (6.1)
Diabetes mellitus (%)		26 (4.0)
Hypertension (%)		138 (21.2)
Vascular disease (%)		23 (3.5)
Pulmonary disorder (%)		58 (8.9)
History of smoking (%)	Past	72 (11.0)
	Current	355 (54.5)
Use of anticoagulants on admission (%)		81 (12.4)
Use of statins on admission (%)		71 (10.9)
Use of antihypertensive drugs on admission (%)		141 (21.6)
WFNS on admission (%)	1	393 (60.3)
	2	162 (24.9)
	3	32 (4.9)
	4	48 (7.4)
	5	17 (2.6)
Type of intervention (%)	Clipping	303 (46.5)
	Coiling	349 (53.5)
Day of intervention (days, median [IQR])		2 [1-4]

GOS 1-3	**p-value**	**Clipping**	**Coiling**	**p-value**
N = 447		N = 521	N = 578	
60 [49-70]	<0.001*	55 [47-64]	58 [48-68]	0.006*
119 (26.6)	0.532	140 (26.9)	165 (28.6)	0.581
25.1 [22.0-28.5]	0.702	25.0 [22.3-28.1]	24.9 [22.2-28.5]	0.864
90 (19.9)	0.003*	128 (24.6)	97 (16.8)	0.006*
304 (68.2)		355 (68.1)	427 (73.9)	
52 (11.6)		38 (7.3)	53 (9.2)	
1 (0.2)		0 (0.0)	1 (0.2)	
33 (7.4)	0.021*	23 (4.4)	36 (6.2)	0.231
1 (0.2)	0.407	1 (0.2)	0 (0.0)	0.474
32 (7.2)	0.583	34 (6.5)	38 (6.6)	1.000
23 (5.2)	0.444	20 (3.8)	29 (5.0)	0.424
146 (32.4)	<0.001*	117 (22.5)	167 (28.9)	0.018*
28 (6.3)	0.049*	24 (4.6)	27 (4.7)	1.000
37 (8.3)	0.803	38 (7.3)	57 (9.9)	0.160
71 (15.9	0.007*	73 (14.0)	70 (12.1)	0.029*
204 (45.9)		243 (46.8)	316 (54.7)	
86 (19.2)	0.003*	74 (14.2)	93 (16.1)	0.432
73 (16.3)	0.011*	64 (12.5)	80 (13.8)	0.500
144 (32.2)	<0.001*	117 (22.5)	168 (29.1)	0.015*
113 (25.3)	<0.001*	251 (48.4)	255 (44.1)	0.187
92 (20.6)		110 (21.1)	144 (24.9)	
38 (8.5)		31 (6.0)	39 (6.8)	
108 (24.2)		82 (15.6)	74 (12.8)	
96 (21.5)		47 (9.0)	66 (11.4)	
218 (48.8)	0.492	521 (100)	0 (0)	NA
229 (51.2)		0 (0)	578 (100)	
1 [1-3]	<0.001*	2 [1-4]	1 [1-3]	<0.001*

Table 1. Continued

		GOS 4-5
		N = 652
Pre-intervention WFNS (%)	1	421 (64.6)
	2	139 (21.3)
	3	28 (4.3)
	4	47 (7.2)
	5	17 (2.6)
Pre-intervention intubation (%)		41 (6.3)
Number of GA before intervention (%)	1	43 (6.6)
	2	1 (0.2)
Number of GA after intervention (%)	1	31 (4.8)
	2	1 (0.2)
	3	0 (0.0)
Cerebral spinal fluid drainage (%)		110 (16.9)
Coiling attempt prior to clipping (%)		16 (2.5)
Pre-induction mean MAP (mmHg, median [IQR])		103 [94-114]
Mean MAP during intervention (mmHg, median [IQR])		80 [72-88]
Mean $ETCO_2$ during intervention (mmHg, median [IQR])		43 [41-45]
Pre-induction oxygenation (%, median [IQR])		97 [95-98]
Duration of intervention (min; median [IQR])		129 [88-174]
Duration of anesthesia (min, median [IQR])		177 [123-253]
Ephedrine (mg/hour; median [IQR]) ǂ		0.0 [0.0-0.0]
Phenylephrine (µg/hour; median [IQR]) ǂ		0.0 [0.0-690.5]
Norepinephrine (µg/hour; median [IQR]) ǂ		0.0 [0.0-0.0]
Dopamine (%)		5 (0.8)
Dobutamine (%)		1 (0.2)
Post-intervention neurological decline (%)		142 (21.8)

GOS 1-3	**p-value**	**Clipping**	**Coiling**	**p-value**
N = 447		N = 521	N = 578	
121 (27.1)	<0.001*	264 (50.7)	278 (48.1)	0.516
91 (20.4)		101 (19.4)	129 (22.3)	
36 (8.29)		28 (5.4)	36 (6.2)	
102 (22.6)		77 (14.8)	72 (12.5)	
97 (21.7)		51 (9.8)	63 (10.9)	
152 (34.0)	<0.001*	87 (16.7)	106 (18.3)	0.526
93 (20.8)	<0.001*	63 (12.1)	73 (12.6)	0.132
6 (1.3)		6 (1.2)	1 (0.2)	
81 (18.1)	<0.001*	58 (11.1)	54 (9.3)	0.160
6 (1.3)		1 (0.2)	6 (1.0)	
4 (0.9)		3 (0.6)	1 (0.2)	
173 (38.9)	<0.001*	181 (34.7)	102 (17.7)	<0.001*
15 (3.4)	0.483	31 (6.0)	0 (0.0)	<0.001*
102 [91-113]	0.055	103 [94-115]	102 [92-112]	0.056
81 [74-88]	0.021*	82 [75-89]	79 [71-87]	<0.001*
44 [42-46]	<0.001*	43 [41-45]	44 [42-46]	<0.001*
97 [95-99]	0.926	97 [95-98]	97 [95-98]	0.005*
122 [90-187]	0.110	174 [146-218]	91 [71-121]	<0.001*
185 [125-262]	0.133	256 [221-309]	126 [108-153]	<0.001*
0.00 [0.0-0.0]	0.751	0.0 [0.0-0.0]	0.0 [0.0-0.0]	0.077
0.0 [0.0-734.7]	0.539	0.0 [0.0-173.6]	66.7 [0.0-1,026.7]	<0.001*
0.0 [0.0-88.0]	<0.001*	0.0 [0.0-88.0]	0.0 [0.0-0.0]	<0.001*
7 (1.6)	0.339	9 (1.7)	3 (0.5)	0.079
1(0.2)	1.000	1 (0.2)	1 (0.2)	1.000
195 (43.6)	<0.001*	189 (36.1)	148 (25.6)	<0.001*

Table 1. Continued

		GOS 4-5
		N = 652
Complications (%)‡	Re-bleed	48 (7.4)
	Cerebral ischemia	113 (17.3)
	Hydrocephalus	123 (18.9)
	Cerebral edema	23 (3.5)
	Convulsion	15 (2.3)
	Other intracranial complications	70 (10.7)
	Extracranial complications	188 (28.8)
	Hypernatremia	47 (7.2)
	Hyponatremia	470 (72.1)
	Anemia	95 (14.6)
	Hypomagnesemia	132 (20.3)
	Hyperglycemia	154 (23.6)
	Hypoglycemia	61 (9.4)
Length of stay (days, median[IQR])		18 [14-22]

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: end-tidal carbon dioxide. GA: general anesthesia. GOS: Glasgow Outcome Scale (good neurologic outcome (GOS 4,5), poor neurologic outcome (GOS 1,2,3). IQR: interquartile range. MAP: mean arterial pressure. NA: not applicable. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage (1 = optimal score, 5 = worst score).

Association between MAP and $ETCO_2$

In 660 patients (60.1%), paired data for $ETCO_2$, MAP and RMV were available, meaning that one minute before an $ETCO_2$ value was measured, a MAP and RMV value were registered, to be used to estimate the association between $ETCO_2$ and MAP. After adjustment for RMV, the results from the linear quantile mixed regression analysis showed a significant but not clinically relevant association between MAP and $ETCO_2$: for most quantiles of $ETCO_2$, $ETCO_2$ increased with factor 1.05 (95%CI 1.04-1.06, p-value <0.001) per 10 mmHg increase in MAP (Figure 2).

Association between $ETCO_2$, MAP and neurologic outcome

A restricted cubic spline regression analysis with three knots (at the 10^{th}, 50^{th} and 90^{th} percentile) resulted in the best fit. Based on distribution of the data and inspection of the spline plots, the independent variables could be grouped into 2-7 categories. Effect estimates for mean $ETCO_2$ and mean MAP are presented in Table 2. None of the categories of mean $ETCO_2$ and mean MAP were associated with neurologic outcome.

GOS 1-3	p-value	Clipping	Coiling	p-value
N = 447		N = 521	N = 578	
82 (18.3)	<0.001*	65 (12.5)	65 (11.3)	0.591
205 (45.9)	<0.001*	164 (31.5)	154 (26.7)	0.089
228 (51.0)	<0.001*	155 (29.8)	196 (33.9)	0.158
54 (12.1)	<0.001*	53 (10.2)	24 (4.2)	<0.001*
28 (6.3)	0.002*	23 (4.4)	20 (3.5)	0.510
93 (20.8)	<0.001*	97 (18.6)	66 (11.4)	0.001*
202 (45.2)	<0.001*	167 (32.1)	223 (38.6)	0.028*
131 (29.5)	<0.001*	102 (19.6)	76 (13.2)	0.005*
351 (78.5)	0.019*	392 (75.2)	429 (74.1)	0.750
170 (38.0)	<0.001*	175 (33.6)	90 (15.6)	<0.001*
151 (33.8)	<0.001*	151 (29.0)	132 (22.8)	0.024*
283 (63.3)	<0.001*	219 (42.0)	218 (37.7)	0.162
134 (30.0)	<0.001*	99 (19.0)	96 (16.6)	0.338
21 [14-31]	<0.001*	21 [16-27]	16 [14-21]	<0.001*

* Statistically significant at a level of significance of p <0.05. ǂ Strongly skewed distribution. ǂ Hypoglycemia: glucose <4 mmol/L (72 mg/dL). Hyperglycemia: glucose >10 mmol/L (180 mg/dL). Hyponatremia: sodium <136 mmol/L (136 mEq/L). Hypernatremia: sodium >146 mmol/L (146 mEq/L). Hypomagnesemia: magnesium <0.70 mmol/L (1.7 mg/dL). Anemia: hemoglobin <6 mmol/L (<9.7 g/dL).

The results from the multivariable analysis using TWA-AUC thresholds are shown in Figure 3 (see Table 6S of the Supplemental Material for both univariable and multivariable effect estimates for all TWA-AUC thresholds). After adjustment for potential confounders there was no association between any of the TWA-AUC thresholds of $ETCO_2$ or MAP and neurologic outcome.

The occurrence of extreme values of $ETCO_2$ (i.e. at least one $ETCO_2$ value <30 mmHg) or MAP (i.e. at least one MAP value <60 mmHg) was also not associated with neurologic outcome (Table 2). There was no clinically relevant modification of the results by preoperative WFNS grade, timing of the intervention (as proxy for vulnerability to cerebral vasospasm) and treatment modality (see Table 7S and 8S in the Supplemental Material, for the results from the multivariable analyses for all three interaction terms).

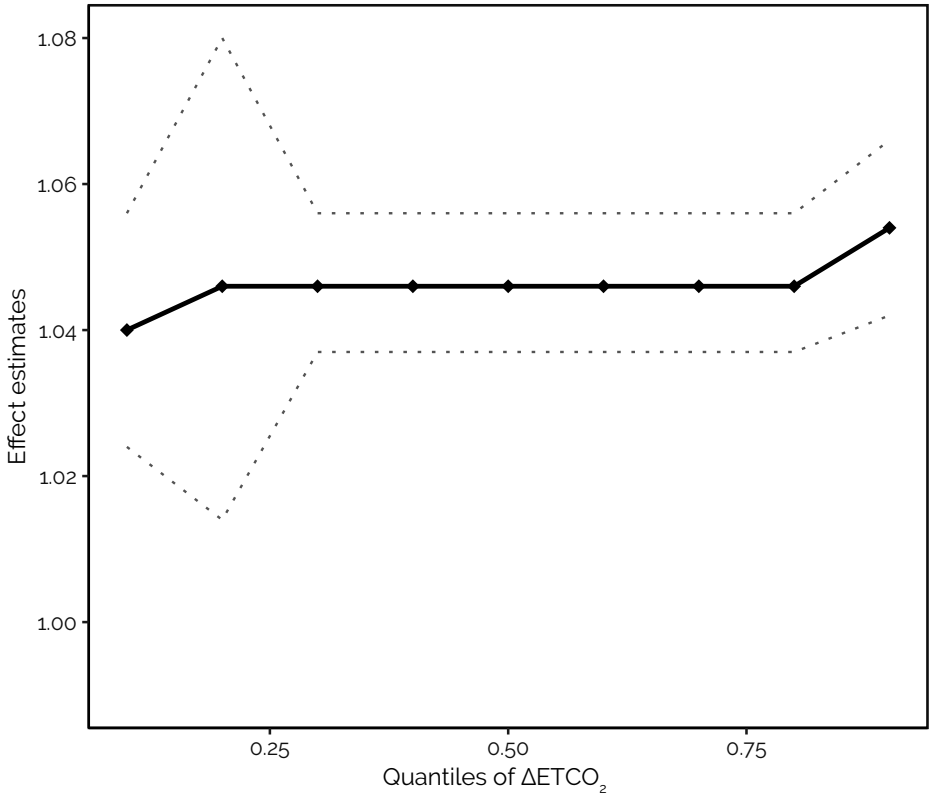


Figure 2. Association between $ETCO_2$ and MAP

The effect of changes in mean arterial pressure (MAP) on changes in end-tidal carbon dioxide concentrations ($ETCO_2$) was studied, using a mixed regression model taking clustering into account. The effect estimates found in the linear quantile mixed regression model were plotted per quantile $\Delta ETCO_2$, with their corresponding 95% confidence interval (dotted lines). Within the first quartiles we saw some extreme outliers, explaining the relatively broad confidence interval.

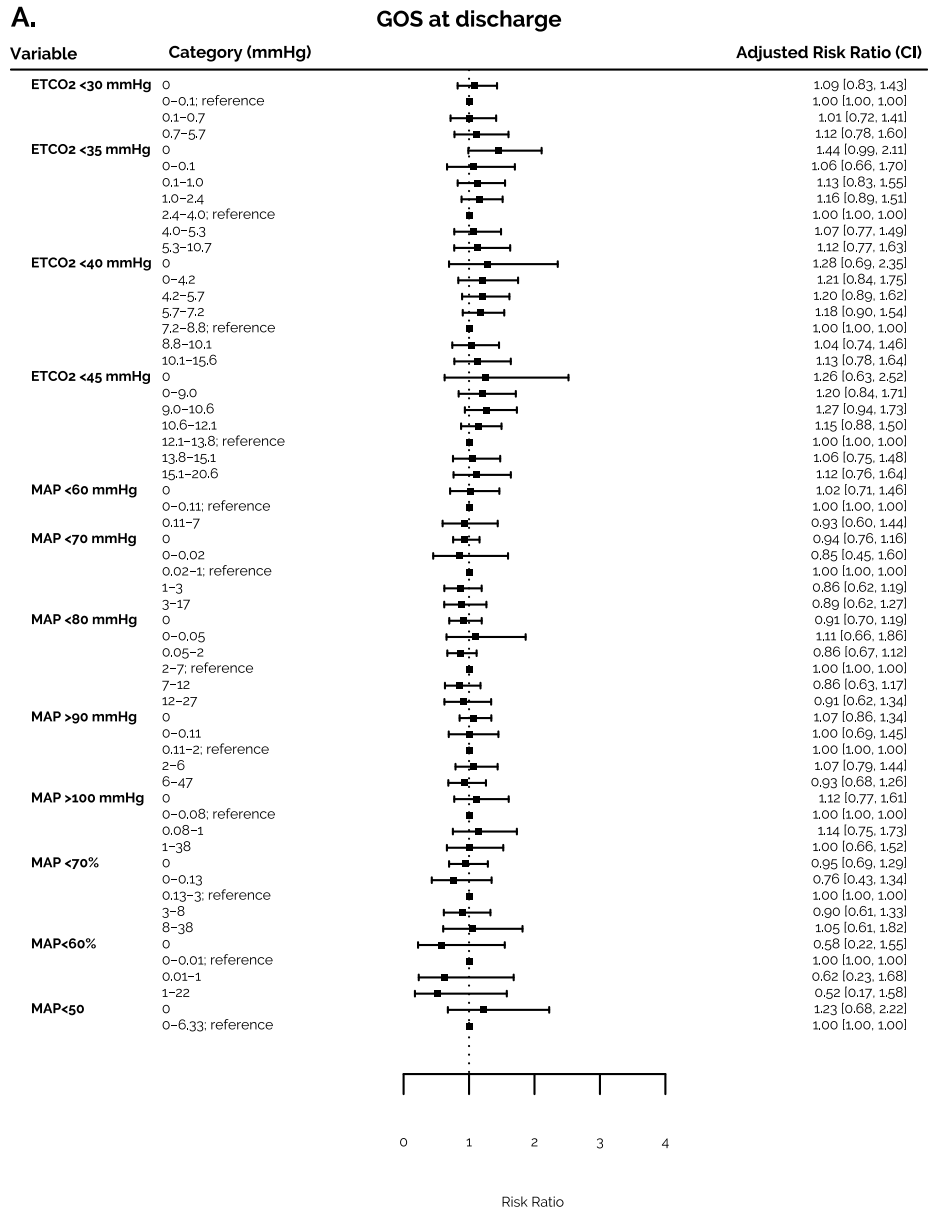
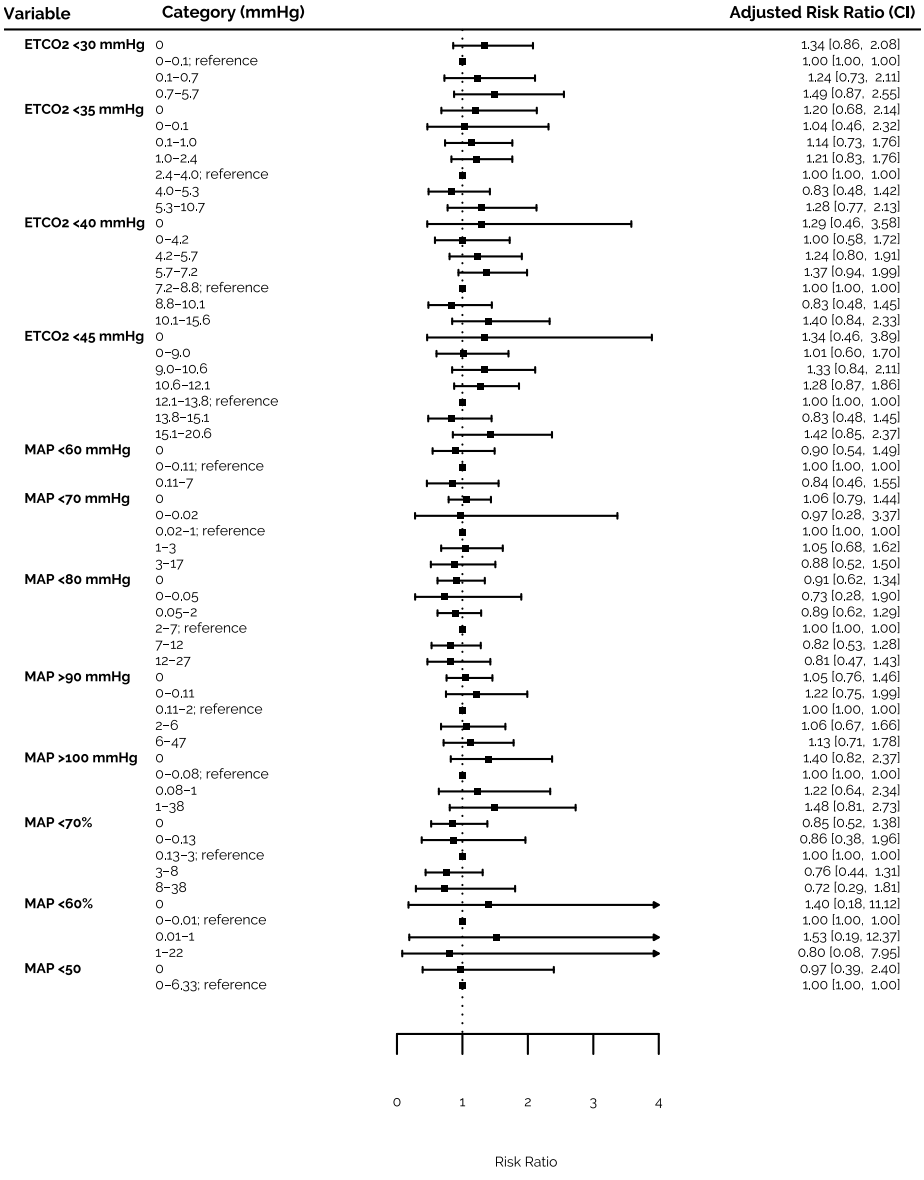


Figure 3. Adjusted risk ratios for all time-weighted average area-under-the-curve thresholds for $ETCO_2$ and MAP

B. **GOS at three months**



◂ **Figure 3.** Continued

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. GOS: Glasgow Outcome Scale, dichotomized into a good outcome (GOS score 4-5) and a poor outcome (GOS score 1-3). MAP: mean arterial pressure. Reference: reference category. Figure 3A shows the results from models using GOS at discharge, whereas Figure 3B shows the results from models using GOS at three months. All reference categories are shown in the plot with an effect estimate of 1.00. Bonferroni correction was used to correct for the number of categories within an independent variable and confidence intervals are reported accordingly. For example: when four categories were made within an independent variable, a p-value of <0.0125 was considered statistically significant after a Bonferroni correction (0.05/4) with a corresponding confidence interval of 98.8%. The models were adjusted for age, sex, history of myocardial infarction, cerebrovascular disease, diabetes mellitus, hypertension, vascular disorders (central and peripheral), (history of) smoking, World Federation of Neurological Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia prior to and after the intervention, cerebral spinal fluid drainage, postoperative neurological decline, re-bleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline administered per hour, preoperative oxygenation level and year of procedure. Additionally, the results for $ETCO_2$ thresholds were adjusted for mean MAP per case, whereas the results for MAP thresholds were adjusted for mean $ETCO_2$ per case.

Table 2. Association between $ETCO_2$, MAP and poor neurologic outcome

Threshold and categories ǂ	**Poor outcome at discharge**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value
Mean MAP (N = 974; 99.2% CI; sign. p <0.008)		
Q 0-0.1 (53-67.8 mmHg)	0.64 (0.33-1.25)	0.077
Q 0.1-0.25 (67.8-73.2 mmHg)	0.80 (0.45-1.41)	0.305
Q 0.25-0.5 (73.2-80.6 mmHg)	0.96 (0.59-1.56)	0.838
Q 0.5-0.75 (80.6-88.3 mmHg)	ref =1	
Q 0.75-0.9 (88.3-95.5 mmHg)	1.22 (0.70-2.15)	0.348
Q 0.9-1.0 (95.5-138 mmHg)	0.92 (0.48-1.74)	0.732
Mean $ETCO_2$ (N = 1,096; 99.2% CI, sign. p <0.008)		
Q 0-0.1 (32-39.6mmHg)	0.70 (0.38-1.31)	0.133
Q 0.1-0.25 (39.6-41.3mmHg)	0.79 (0.46-1.35)	0.248
Q 0.25-0.5 (41.3-43.5mmHg)	0.78 (0.49-1.23)	0.150
Q 0.5-0.75 (43.5-45.6mmHg)	ref =1	
Q 0.75-0.9 (45.6-47.3mmHg)	0.95 (0.56-1.62)	0.807
Q 0.9-1.0 (47.3-56 mmHg)	1.50 (0.83-2.71)	0.073
Any $ETCO_2$ <30 mmHg (N = 405; 95% CI, sign. p <0.05)	0.89 (0.69-1.15)	0.381
Any MAP <60 mmHg (N = 166; 95% CI, sign. p <0.05)	0.99 (0.70-1.39)	0.954

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile.

* Statistically significant.

ǂ Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. For example: when four categories were made within a threshold, a p-value of <0.0125 was considered statistically significant after a Bonferroni correction (0.05/4) with a corresponding confidence interval of 98.8%. For "any $ETCO_2$ <30 mmHg" and "any MAP <60 mmHg", no categories were used and a p-value <0.05 was considered statistically significant. N = number of patients with TWA-AUC or Mean >0.

		Poor outcome at three months			
Adjusted RR (CI) ǂ	p-value	Unadjusted RR (CI)	p-value	Adjusted RR (CI) ǂ	p-value
0.94 (0.63-1.42)	0.725	0.60 (0.27-1.29)	0.076	0.87 (0.49-1.54)	0.529
1.06 (0.79-1.43)	0.626	0.65 (0.34-1.25)	0.081	0.90 (0.56-1.45)	0.582
1.05 (0.81-1.37)	0.600	0.91 (0.54-1.55)	0.665	0.98 (0.68-1.42)	0.912
ref =1		ref =1		ref =1	
1.16 (0.87-1.53)	0.169	1.20 (0.66-2.19)	0.430	1.13 (0.75-1.71)	0.439
0.90 (0.64-1.25)	0.390	1.03 (0.51-2.07)	0.911	0.98 (0.59-1.64)	0.932
0.93 (0.65-1.35)	0.637	0.70 (0.35-1.41)	0.181	0.97 (0.59-1.62)	0.897
0.92 (0.68-1.25)	0.492	0.53 (0.28-1.01)	0.009	0.62 (0.37-1.05)	0.016
0.83 (0.64-1.07)	0.049	0.79 (0.48-1.32)	0.228	0.77 (0.54-1.10)	0.055
ref =1		ref =1		ref =1	
0.95 (0.72-1.26)	0.656	0.85 (0.47-1.54)	0.484	0.87 (0.58-1.29)	0.354
1.11 (0.82-1.52)	0.362	0.98 (0.51-1.88)	0.954	0.83 (0.53-1.32)	0.300
0.95 (0.81-1.10)	0.496	0.88 (0.66-1.17)	0.386	0.89 (0.71-1.13)	0.348
0.94 (0.78-1.14)	0.530	1.16 (0.80-1.67)	0.444	1.00 (0.77-1.31)	0.973

ǂ The models were adjusted for age, sex, history of myocardial infarction, cerebrovascular disease, diabetes mellitus, hypertension, vascular disorders (central and peripheral), (history of) smoking, World Federation of Neurological Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia prior to and after the intervention, cerebral spinal fluid drainage, postoperative neurological decline, re-bleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline administered per hour, preoperative oxygenation level and year of procedure. Additionally, the results for $ETCO_2$ thresholds were adjusted for mean MAP per case, whereas the results for MAP thresholds were adjusted for mean $ETCO_2$ per case. Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1-3.

DISCUSSION

Within the ranges of current clinical practice, i.e. consensus translated into a protocolized institutional strategy, none of the studied $ETCO_2$ and MAP ranges were associated with neurologic outcome at discharge, irrespective of the duration below or above the threshold and irrespective of preoperative clinical condition, timing of treatment or treatment modality. Even extreme hypotension and hypocapnia, still occurring although short of duration, were not associated with poor neurologic outcome.

Several studies described the effect of hyper- and hypocapnia on neurologic outcome after acute cerebral injury, primarily in an intensive care setting. Unfortunately, ASAH patients are underrepresented. In patients undergoing endovascular treatment after an acute ischemic stroke, a higher mean $ETCO_2$ (mean from values collected every 30 minutes) during general anesthesia was associated with a better neurologic outcome.[10] Additionally, postcardiac arrest $PaCO_2$ disturbances were associated with a poor neurologic outcome[11] and prolonged hyperventilation had deleterious effects on the neurologic outcome after traumatic brain injury.[9] Two small studies in poor-grade ASAH patients studied the association between carbon dioxide concentrations and neurologic outcome and found that the cerebral perfusion increased when the $PaCO_2$ increased.[34,35] Hypercapnia was well tolerated in the presence of continuous CSF drainage (thus eliminating the potential effect of an increased intracranial pressure), while increasing the cerebral perfusion and possibly preventing secondary cerebral ischemia.[34,35] To our knowledge, no studies reported on induced hypercapnia and neurologic outcome in ASAH patients without CSF drainage. In contrast to studies reporting a benefit for higher carbon dioxide concentrations, a large retrospective cohort study in patients with acute cerebral injury found that hypercapnia (mean $PaCO_2$ 52.2 mmHg, mean pH 7.39) was not associated with a better survival to discharge for all patients combined or for subgroups based on diagnosis (traumatic brain injury, stroke (hemorrhagic and ischemic stroke combined) and cardiac arrest). In fact, hypercapnic acidosis (mean $PaCO_2$ 56.7 mmHg, mean pH 7.19) was associated with an increased risk of in-hospital mortality.[28] Other studies found that spontaneous hyperventilation was associated with a poor neurologic outcome after ASAH.[36,37] In contrast to most other studies in the field of acute cerebral injury, we were not able to demonstrate an association between hyper- or hypocapnia and neurologic outcome in ASAH patients specifically.

Several studies described the effects of hypotension on neurologic outcome in ASAH patients treated with neurosurgical clipping. To our knowledge, no such studies were conducted in ASAH patients undergoing endovascular coiling. One retrospective study in 164 ASAH patients receiving neurosurgical clipping suggested that a decrease in

blood pressure of >50% was associated with a poor outcome. After adjusting for age and WFNS grade, these results were no longer significant.[5] Another retrospective study in 398 ASAH patients receiving neurosurgical clipping, defined intraoperative hypotension as a reduction of 30 mmHg or at least 20% of the initial SBP, for at least 15 minutes. Intraoperative hypotension was an independent risk factor for the development of a postoperative cerebral infarction (OR 3.02; 95% CI 1.29-7.08).[6] A study in 84 patients found a comparable association for intraoperative hypotension defined as a SBP <90 mmHg for more than 15 minutes.[7] Other studies found an association between deliberately induced hypotension in ASAH patients undergoing neurosurgical clipping and a poor neurologic outcome.[38,39] The current study did not look into the effects of relatively mild hypotension (decrease of 20% from the baseline) or SBP, but did not find any association for slightly more severe hypotension (MAP <30% from baseline or more) and neurologic outcome, nor did it find an association for any of the absolute MAP thresholds and neurologic outcome. Previous studies have found an association between pre-induction and intraoperative hypertension and a poor neurologic outcome.[38,39] Initiation of hypertension to prevent delayed cerebral ischemia in ASAH patients admitted at the Intensive Care Unit was not supported by any evidence.[40] The present study found no association between intraoperative hypertension and neurologic outcome after clipping or coiling of a ruptured aneurysm.

Strengths and limitations

This study has several strengths. First, it is one of the larger studies relating intraoperative blood pressure and carbon dioxide ranges in ASAH patients to neurologic outcome thus far, enabling us to find relatively small effects when present. Second, in contrast to previous studies, patients undergoing endovascular coiling were also included, making the results applicable to a larger group of ASAH patients, especially since endovascular treatment has become the recommended treatment entity when technically amendable.[2] Third, we used TWA-AUC as a measure to summarize the course of $ETCO_2$ and MAP in an elaborate manner, containing not only the distance from, but also the duration below (or above) the threshold. Fourth, the results of this study are adjusted for many potential confounders including comorbidities and postoperative complications. This may explain why we did not find an association between MAP and $ETCO_2$ ranges and neurologic outcome, while some of the previous studies did. All the previously conducted studies were smaller in sample size and were not able to include as many confounders, and therefore results may have been influenced by residual confounding.

Nevertheless, this study has some obvious limitations. First, $PaCO_2$ and pH rather than $ETCO_2$ influence the cerebral perfusion.[8,28] Unfortunately, we were unable to calibrate $ETCO_2$ concentrations with $PaCO_2$ (and pH) values, since the time points of

blood sampling could not be linked to the corresponding $ETCO_2$ values. In patients presenting for elective craniotomies, small $PaCO_2$-$ETCO_2$ gradients around 4 mmHg were reported,[41] meaning that in the present study, $PaCO_2$ concentrations may be slightly higher than the reported $ETCO_2$ values. We might therefore overestimate the effect of hypercapnia, while underestimating the effect of hypocapnia. However, with the reported small gradient of 4mmHg, we believe this is of limited effect. Second, we used GOS at discharge as our primary outcome measure. As improvement of functional outcome can continue even after the first year of ASAH,[42] the results of this study may not apply to long-term neurologic outcome. Third, the TWA-AUC is not easily applicable and interpretable in clinical practice. However, cohort studies in patients presenting for non-cardiac surgery have shown that a (TWA-)AUC can successfully be used to summarize intraoperative blood pressure levels for research purposes.[19,30,43] Fourth, despite the relatively large sample size, some of the $ETCO_2$ and MAP categories contained a relatively small number of patients, which may have resulted in a lack of power to detect differences. Fifth, although we adjusted the results for a large set of potential confounders, residual confounding might be present due to the retrospective nature of this study. In addition, we were not able to collect data on the presence of cerebral vasospasm during the intervention. Sixth, we had to deal with missing data. We imputed all variables except for the independent variables, because for these variables we already had extrapolated values from the median value per minute to obtain a TWA-AUC. The imputation had little effect on the effect estimates (see Table 5S of the Supplemental Material showing results of the univariable Poisson regression analyses for neurologic outcome at discharge for the complete cases and the imputed data). Finally, potential reasons for anesthesiologists to aim for certain MAP and $ETCO_2$ ranges were not documented. However, anesthesiologists were also not influenced by the conduct of this study.

Clinical implications

Despite sparse evidence, international guidelines currently recommend a SBP below 160-180 mmHg until the aneurysm is obliterated.[2,44] Once the aneurysm is secured, higher blood pressures are allowed, but it is unknown what exact thresholds should be aimed for.[2] A survey among European neuro-anesthesiologists and neurocritical care physicians showed that there is no agreement on that point.[45] Currently, there are no guidelines on $ETCO_2$ management in ASAH patients.

The present study did not demonstrate an association between any of the $ETCO_2$ or MAP ranges observed in current clinical practice and neurologic outcome at discharge. We therefore may conclude that a low $ETCO_2$, and a low or high MAP might not be as bad as expected. However, this needs some nuance. Anesthesiologists most likely

worked in adherence to current guidelines and standard clinical practice, focusing on $ETCO_2$ concentrations of 35-45 mmHg with MAP levels > 80 mmHg and SBP <180 mmHg before and <220 mmHg after securing the aneurysm. As a result, extreme values were relatively rare (e.g. only 166 patients had at least one MAP value <60 mmHg, see Table 2). This study therefore does not show that we can abandon strict $ETCO_2$ and blood pressure regulation; it merely shows that in the context of current clinical practice, no further subgroups of $ETCO_2$ and MAP values increased the chance of a good neurologic outcome at discharge. Larger, multicenter and especially prospective studies are required to further study the effect of $ETCO_2$ and MAP on short- and long-term neurologic outcome. In addition, intraoperative $ETCO_2$ concentrations and MAP levels might only be a minor part of a very large and complex puzzle, determining neurologic outcome after a subarachnoid hemorrhage.

Conclusion

Intraoperative hypocapnia, hypotension and hypertension as they occur in clinical practice during cerebral aneurysm clipping or coiling, are not associated with a poor neurologic outcome. However, there is insufficient evidence available to abandon currently used target ranges for $ETCO_2$ and blood pressure.

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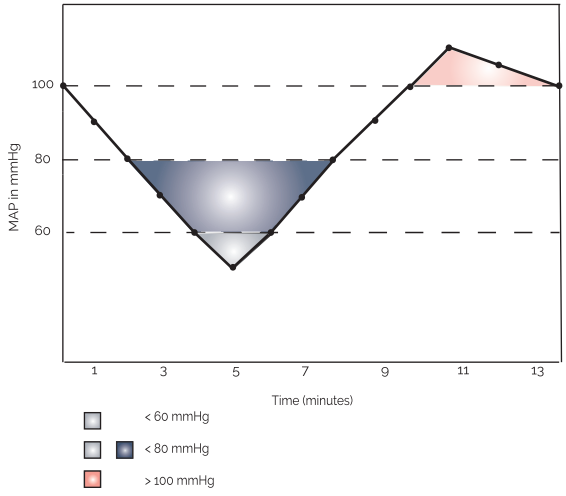
SUPPLEMENTAL MATERIAL



Supplemental Material: Figure 1S. Estimation of the area-under-the-curve per threshold

MAP: mean arterial pressure. This figure shows how the area-under-the-curve was estimated for an absolute threshold of a MAP <60 mmHg, MAP <80 mmHg and MAP >100 mmHg.

Supplemental Material: Table 1S. Classifications

Classification	Description
GOS 1	Death
GOS 2	Persistent vegetative state
GOS 3	Severe disability
GOS 4	Moderate disability
GOS 5	Low disability
WFNS grade 1	GCS 15, no motor deficit
WFNS grade 2	GCS 13-14, no motor deficit
WFNS grade 3	GCS 13-14, with motor deficit
WFNS grade 4	GCS 7-12, with or without motor deficit
WFNS grade 5	GCS 3-6, with or without motor deficit

GCS: Glasgow Coma Scale. GOS: Glasgow Outcome Scale. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage.

Supplemental Material: Table 2S. Artifact filter

Artifact criteria	
General criteria	• User entered values: invalid. • Two measurements had to be below the threshold, before it was classified as an episode. Within one episode, one measurement was allowed to reach the threshold without ending it, when the next measurement was again below the threshold. • Intraoperative data collection started ten minutes after incision (or 20 minutes after induction end when not available) and stopped ten minutes prior to procedure end (or 20 minutes prior to anesthesia end when not available).
Blood pressure	• At least 20 valid MAP measurements (not consecutive) • Exclusion if no recorded MAP >10 minutes uninterrupted • SBP had to be between 50 and 250 mmHg • DBP had to be between 20 and 200 mmHg • MAP had to be between 50 and 150 mmHg • MAP had to be between SBP and DBP • Pulse pressure was higher than 20 + (DBP/90)*10 • Pulse pressure was higher than 10 + (MAP/150)*10 • Non-invasive blood pressure was used unless an arterial blood pressure was measured at the same time or within 6 minutes before or after the non-invasive blood pressure measurement.
$ETCO_2$	• At least 20 valid $ETCO_2$ measurements (not consecutive) • Exclusion if no recorded $ETCO_2$ >10 minutes uninterrupted • $ETCO_2$ had to be between 10 and 65 mmHg • Invalid when abrupt changes in $ETCO_2$ values were seen, defined as ≥ 5mmHg change in either direction with a consecutive value changing back with at least 5 mmHg.
RMV	• Calculated measure: tidal volume * respiratory rate • Tidal volume had to be between 100 ml and 1,000ml • Respiratory rate had to be between 4 and 25/minute • RMV had to be between 500 and 25,000 ml/min

DBP: diastolic blood pressure. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. RMV: respiratory minute volume. SBP: systolic blood pressure.

Supplemental Material: Table 3S. Distribution of missing data

Variable	N	Variable	N
Age	0	Mean $ETCO_2$ during intervention	3
Sex	0	Pre-induction oxygenation	119
BMI	545	Duration of intervention	224
ASA class	18	Duration of anesthesia	0
Myocardial infarction	4	Ephedrine	0
Congestive heart failure	29	Phenylephrine	0
Cerebrovascular accident	5	Norepinephrine	0
Diabetes mellitus	15	Dopamine	0
Hypertension	6	Dobutamine	0
Vascular disease	15	Post-intervention neurological decline	110
Pulmonary disorder	15	Complications	
History of smoking	129	Re-bleed	0
Use of anticoagulants on admission	98	Cerebral ischemia	0
Use of statins on admission	98	Hydrocephalus	0
Use of antihypertensive drugs on admission	28	Cerebral edema	0
WFNS on admission	9	Convulsion	0
WFNS preoperative	314	Other intracranial complication	0
Type of intervention	0	Extracranial complication	0
Day of intervention	0	Hypernatremia	18
Pre-intervention WFNS	134	Hyponatremia	41
Pre-intervention intubation	7	Anemia	61
Number of GA before intervention	3	Hypomagnesemia	290
Number of GA after intervention	2	Hyperglycemia	77
CSF drainage	9	Hypoglycemia	68
Coiling attempt prior to clipping	3	Length of stay	30
Pre-induction mean MAP	216	GOS at discharge	12
Mean MAP during intervention	0	GOS at three months	261

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. CSF: cerebral spinal fluid. $ETCO_2$: end-tidal carbon dioxide. GA: general anesthesia. GOS: Glasgow Outcome Scale. MAP: mean arterial pressure. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage (1 = optimal score, 5 = worst score).

Supplemental Material: Table 4S. List of variables used for imputation

All observed information, except information on the independent variables (TWA-AUC, $ETCO_2$ and MAP) was used for multiple imputation.	
Baseline characteristics	Age; height; weight; sex; ASA class; history of myocardial infarction, congestive heart failure, cerebrovascular accident, diabetes mellitus, hypertension, vascular disease, pulmonary disorder, polycystic kidney disease, arrhythmia , pacemaker or implantable cardioverter defibrillator, smoking; use of anticoagulants, statins, antihypertensive drugs on admission
ASAH specific	WFNS on admission and prior to the intervention; location of aneurysm; type and day of intervention; cerebral spinal fluid drainage
Perioperative characteristics	Number of times of general anesthesia during admission (prior to and after occlusion of the aneurysm); intubation prior to the intervention; coiling attempt prior to clipping; pre-induction mean MAP; pre-induction oxygenation; duration of intervention and general anesthesia; amount of ephedrine, phenylephrine, norepinephrine, dopamine, dobutamine administered during the intervention; postoperative neurological decline
Complications	Re-bleed, cerebral ischemia, hydrocephalus, cerebral edema, convulsions, other intracranial complications, hypernatremia, hyponatremia, anemia, hypomagnesemia, hyperglycemia, hypoglycemia, other extracranial complications
Outcome	Length of stay; GOS at discharge and at three months

ASA: American Society of Anesthesiologists physical status. ASAH: aneurysmal subarachnoid hemorrhage. $ETCO_2$: end-tidal carbon dioxide. GOS: Glasgow Outcome Scale. MAP: mean arterial pressure. TWA-AUC: time-weighted average area-under-the-curve. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage (1 = optimal score, 5 = worst score).

Supplemental Material: Table 5S. Results from the complete case analyses versus analyses on the imputed data for the association between time-weighted average area-under-the-curve thresholds and neurologic outcome at discharge

Threshold and categories	**Poor outcome at discharge Complete cases**		**Poor outcome at discharge Multiple imputation**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value	Unadjusted RR (CI)	p-value
$ETCO_2$ <30 mmHg (N = 405; CI 98.8%; sign. p <0.013)				
Q 0 (0 mmHg)	1.01 (0.62 - 1.63)	0.980	0.99 (0.61 - 1.61)	0.965
Q 0-0.75 (0-0.1 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (0.1-0.7 mmHg)	0.84 (0.46 - 1.53)	0.467	0.82 (0.45 - 1.49)	0.407
Q 0.9-1.0 (0.7-5.7 mmHg)	0.88 (0.45 - 1.71)	0.650	0.86 (0.44 - 1.67)	0.576
$ETCO_2$ <35 mmHg (N = 1,022; CI 99.3%; sign. p <0.007)				
Q 0 (0 mmHg)	2.42 (1.17 - 5.01)	0.001*	2.39 (1.15 - 4.96)	0.001*
Q 0-0.1 (0-0.1 mmHg)	1.22 (0.47 - 3.16)	0.593	1.21 (0.46 - 3.21)	0.612
Q 0.1-0.25 (0.1-1.0 mmHg)	1.15 (0.67 - 1.99)	0.487	1.15 (0.67 - 1.98)	0.507
Q 0.25-0.5 (1.0-2.4 mmHg)	1.13 (0.71 - 1.82)	0.492	1.13 (0.71 - 1.81)	0.493
Q 0.5-0.75 (2.4-4.0 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (4.0-5.3 mmHg)	0.90 (0.52 - 1.56)	0.608	0.89 (0.51 - 1.55)	0.590
Q 0.9-1.0 (5.3-10.7 mmHg)	0.87 (0.46 - 1.64)	0.557	0.85 (0.45 - 1.62)	0.517
$ETCO_2$ <40 mmHg (N = 1,072; CI 99.3%; sign. p <0.007)				
Q 0 (0 mmHg)	2.23 (0.68 - 7.25)	0.068	2.17 (0.65 - 7.23)	0.083
Q 0-0.1 (0-4.2 mmHg)	1.71 (0.88 - 3.35)	0.031	1.70 (0.86 - 3.34)	0.035
Q 0.1-0.25 (4.2-5.7 mmHg)	1.36 (0.79 - 2.33)	0.131	1.34 (0.78 - 2.30)	0.148
Q 0.25-0.5 (5.7-7.2 mmHg)	1.33 (0.83 - 2.13)	0.107	1.31 (0.82 - 2.10)	0.122
Q 0.5-0.75 (7.2-8.8 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (8.8-10.1 mmHg)	0.95 (0.54 - 1.66)	0.808	0.94 (0.54 - 1.64)	0.771
Q 0.9-1.0 (10.1-15.6 mmHg)	0.90 (0.48 - 1.71)	0.683	0.89 (0.47 - 1.68)	0.626
$ETCO_2$ <45 mmHg (N= 1,074; CI 99.3%; sign. p <0.007)				
Q 0 (0 mmHg)	1.90 (0.56 - 6.44)	0.160	1.87 (0.54 - 6.54)	0.178
Q 0-0.1 (0-9.0 mmHg)	1.89 (0.97 - 3.67)	0.010	1.88 (0.96 - 3.69)	0.011
Q 0.1-0.25 (9.0-10.6 mmHg)	1.36 (0.79 - 2.34)	0.124	1.36 (0.79 - 2.34)	0.129
Q 0.25-0.5 (10.6-12.1 mmHg)	1.31 (0.82 - 2.11)	0.123	1.32 (0.82 - 2.11)	0.115
Q 0.5-0.75 (12.1-13.8 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (13.8-15.1 mmHg)	0.98 (0.56 - 1.70)	0.918	0.98 (0.56 - 1.70)	0.912
Q 0.9-1.0 (15.1-20.6 mmHg)	0.90 (0.47 - 1.70)	0.664	0.89 (0.47 - 1.69)	0.634

Supplemental Material: Table 5S. Continued

Threshold and categories	**Poor outcome at discharge Complete cases**		**Poor outcome at discharge Multiple imputation**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value	Unadjusted RR (CI)	p-value
MAP <60 mmHg (N = 166; CI 98.3%; sign. p <0.017)				
Q 0 (0 mmHg)	0.84 (0.45 - 1.56)	0.516	0.92 (0.50 - 1.71)	0.767
Q 0-0.9 (0-0.11 mmHg)	ref = 1		ref = 1	
Q 0.9-1.0 (0.11-7 mmHg)	0.85 (0.39 - 1.85)	0.628	0.86 (0.39 - 1.85)	0.641
MAP <70 mmHg (N = 503; CI 99.0%; sign. p <0.010)				
Q 0 (0 mmHg)	0.71 (0.48 - 1.06)	0.026	0.81 (0.53 - 1.22)	0.181
Q 0-0.5 (0-0.02 mmHg)	0.72 (0.21 - 2.44)	0.497	0.71 (0.20 - 2.58)	0.510
Q 0.5-0.75 (0.02-1 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (1-3 mmHg)	0.58 (0.33 - 1.04)	0.016	0.57 (0.32 - 1.02)	0.013
Q 0.9-1.0 (3-17 mmHg)	0.63 (0.34 - 1.16)	0.052	0.61 (0.33 - 1.13)	0.038
MAP <80 mmHg (N = 761; 99.2%; sign. p <0.008)				
Q 0 (0 mmHg)	0.68 (0.43 - 1.06)	0.023	0.87 (0.53 - 1.43)	0.464
Q 0-0.25 (0-0.05 mmHg)	1.08 (0.38 - 3.06)	0.849	1.08 (0.37 - 3.16)	0.854
Q 0.25-0.5 (0.05-2 mmHg)	0.92 (0.57 - 1.49)	0.654	0.91 (0.56 - 1.47)	0.607
Q 0.5-0.75 (2-7 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (7-12 mmHg)	0.63 (0.35 - 1.11)	0.032	0.62 (0.35 - 1.11)	0.030
Q 0.9-1.0 (12-27 mmHg)	0.69 (0.36 - 1.32)	0.133	0.68 (0.36 - 1.30)	0.116
MAP >90 mmHg (N= 580; CI 99.0%; sign. p <0.010)				
Q 0 (0 mmHg)	0.80 (0.53 - 1.20)	0.157	0.91 (0.60 - 1.39)	0.597
Q 0-0.5 (0-0.11 mmHg)	0.95 (0.50 - 1.82)	0.861	0.93 (0.49 - 1.77)	0.779
Q 0.5-0.75 (0.11-2 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (2-6 mmHg)	1.02 (0.58 - 1.80)	0.925	1.02 (0.58 - 1.80)	0.930
Q 0.9-1.0 (6-47 mmHg)	1.01 (0.56 - 1.84)	0.960	1.03 (0.57 - 1.88)	0.904
MAP >100 mmHg (N = 319; CI 98.8%; sign. p <0.013)				
Q 0 (0 mmHg)	1.05 (0.57 - 1.95)	0.853	1.16 (0.62 - 2.18)	0.556
Q 0-0.75 (0-0.08 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (0.08-1 mmHg)	1.26 (0.60 - 2.66)	0.440	1.27 (0.60 - 2.68)	0.441
Q 0.9-1.0 (1-38 mmHg)	1.23 (0.58 - 2.60)	0.510	1.26 (0.59 - 2.68)	0.459
MAP <70% (N = 446; CI 99.0%; sign. p <0.010)				
Q 0 (0 mmHg)	1.32 (0.86 - 2.03)	0.093	0.95 (0.59 - 1.54)	0.802
Q 0-0.5 (0-0.13 mmHg)	0.58 (0.25 - 1.38)	0.104	0.58 (0.24 - 1.40)	0.114

Supplemental Material: Table 5S. Continued

Threshold and categories	**Poor outcome at discharge Complete cases**		**Poor outcome at discharge Multiple imputation**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value	Unadjusted RR (CI)	p-value
Q 0.5-0.75 (0.13-3 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (3-8 mmHg)	0.83 (0.44 - 1.57)	0.471	0.86 (0.45 - 1.61)	0.535
Q 0.9-1.0 (8-38 mmHg)	0.80 (0.38 - 1.68)	0.440	0.80 (0.38 - 1.70)	0.459
MAP <60% (N =199; CI 98.8%; sign. p <0.013)				
Q 0 (0 mmHg)	0.10 (0.01 - 1.45)	0.031	0.08 (0.00 - 1.60)	0.034
Q 0-0.75 (0-0.01 mmHg)	ref = 1		ref = 1	
Q 0.75-0.9 (0.01-1 mmHg)	0.10 (0.01 - 1.56)	0.037	0.11 (0.00 - 2.31)	0.068
Q 0.9-1.0 (1-22 mmHg)	0.05 (0.00 - 0.79)	0.007*	0.05 (0.00 - 1.15)	0.017
MAP <50% (N= 43; CI 97.5%; sign. p <0.025)				
Q 0 (0 mmHg)	1.75 (0.80 - 3.82)	0.106	1.41 (0.63 - 3.14)	0.346
Q 0-1 (0-0.633) mmHg)	ref = 1		ref = 1	

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile.

* Significant difference. ǂ Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. For example: when four categories were made within a threshold, a p-value of <0.0125 was considered statistically significant after a Bonferroni correction (0.05/4) with a corresponding confidence interval of 98.8%. N = number of patients with TWA-AUC >0. Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1-3.

Supplemental Material: Table 6S. The association between time-weighted average area-under-the-curve thresholds for $ETCO_2$ and MAP and neurologic outcome

Threshold and categories ǂ	**Poor outcome at discharge**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value
$ETCO_2$ <30 mmHg (N = 405; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	0.99 (0.61 - 1.61)	0.965
Q 0-0.75 (0-0.1 mmHg)	ref = 1	
Q 0.75-0.9 (0.1-0.7 mmHg)	0.82 (0.45 - 1.49)	0.407
Q 0.9-1.0 (0.7-5.7 mmHg)	0.86 (0.44 - 1.67)	0.576
$ETCO_2$ <35 mmHg (N = 1,022; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	2.39 (1.15 - 4.96)	0.001*
Q 0-0.1 (0-0.1 mmHg)	1.21 (0.46 - 3.21)	0.612
Q 0.1-0.25 (0.1-1.0 mmHg)	1.15 (0.67 - 1.98)	0.507
Q 0.25-0.5 (1.0-2.4 mmHg)	1.13 (0.71 - 1.81)	0.493
Q 0.5-0.75 (2.4-4.0 mmHg)	ref = 1	
Q 0.75-0.9 (4.0-5.3 mmHg)	0.89 (0.51 - 1.55)	0.590
Q 0.9-1.0 (5.3-10.7 mmHg)	0.85 (0.45 - 1.62)	0.517
$ETCO_2$ <40 mmHg (N = 1,072; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	2.17 (0.65 - 7.23)	0.083
Q 0-0.1 (0-4.2 mmHg)	1.70 (0.86 - 3.34)	0.035
Q 0.1-0.25 (4.2-5.7 mmHg)	1.34 (0.78 - 2.30)	0.148
Q 0.25-0.5 (5.7-7.2 mmHg)	1.31 (0.82 - 2.10)	0.122
Q 0.5-0.75 (7.2-8.8 mmHg)	ref = 1	
Q 0.75-0.9 (8.8-10.1 mmHg)	0.94 (0.54 - 1.64)	0.771
Q 0.9-1.0 (10.1-15.6 mmHg)	0.89 (0.47 - 1.68)	0.626
$ETCO_2$ <45 mmHg (N= 1,074; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	1.87 (0.54 - 6.54)	0.178
Q 0-0.1 (0-9.0 mmHg)	1.88 (0.96 - 3.69)	0.011
Q 0.1-0.25 (9.0-10.6 mmHg)	1.36 (0.79 - 2.34)	0.129
Q 0.25-0.5 (10.6-12.1 mmHg)	1.32 (0.82 - 2.11)	0.115
Q 0.5-0.75 (12.1-13.8 mmHg)	ref = 1	
Q 0.75-0.9 (13.8-15.1 mmHg)	0.98 (0.56 - 1.70)	0.912
Q 0.9-1.0 (15.1-20.6 mmHg)	0.89 (0.47 - 1.69)	0.634
MAP <60 mmHg (N = 166; CI 98.3%; sign. p <0.017)		
Q 0 (0 mmHg)	0.92 (0.50 - 1.71)	0.767

			Poor outcome at three months			
	Adjusted RR (CI) ǂ	p-value	Unadjusted RR (CI)	p-value	Adjusted RR (CI) ǂ	p-value
	1.09 (0.83 - 1.43)	0.463	1.15 (0.66 - 2.02)	0.533	1.34 (0.86 - 2.08)	0.101
	ref = 1		ref = 1		ref = 1	
	1.01 (0.72 - 1.41)	0.961	0.99 (0.49 - 1.97)	0.965	1.24 (0.73 - 2.11)	0.325
	1.12 (0.78 - 1.60)	0.457	1.08 (0.51 - 2.29)	0.820	1.49 (0.87 - 2.55)	0.062
	1.44 (0.99 - 2.11)	0.009	1.60 (0.75 - 3.42)	0.093	1.20 (0.68 - 2.14)	0.390
	1.06 (0.66 - 1.70)	0.741	0.98 (0.32 - 2.95)	0.962	1.04 (0.46 - 2.32)	0.911
	1.13 (0.83 - 1.55)	0.293	1.04 (0.57 - 1.91)	0.868	1.14 (0.73 - 1.76)	0.434
	1.16 (0.89 - 1.51)	0.141	1.05 (0.63 - 1.78)	0.797	1.21 (0.83 - 1.76)	0.171
	ref = 1		ref = 1		ref = 1	
	1.07 (0.77 - 1.49)	0.570	0.60 (0.31 - 1.17)	0.040	0.83 (0.48 - 1.42)	0.352
	1.12 (0.77 - 1.63)	0.412	0.86 (0.42 - 1.76)	0.589	1.28 (0.77 - 2.13)	0.186
	1.28 (0.69 - 2.35)	0.282	2.04 (0.59 - 7.07)	0.121	1.29 (0.46 - 3.58)	0.518
	1.21 (0.84 - 1.75)	0.167	1.25 (0.58 - 2.67)	0.437	1.00 (0.58 - 1.72)	0.999
	1.20 (0.89 - 1.62)	0.094	1.20 (0.65 - 2.22)	0.421	1.24 (0.80 - 1.91)	0.185
	1.18 (0.90 - 1.54)	0.095	1.47 (0.87 - 2.47)	0.048	1.37 (0.94 - 1.99)	0.025
	ref = 1		ref = 1		ref = 1	
	1.04 (0.74 - 1.46)	0.757	0.69 (0.35 - 1.36)	0.143	0.83 (0.48 - 1.45)	0.384
	1.13 (0.78 - 1.64)	0.396	1.00 (0.49 - 2.06)	0.988	1.40 (0.84 - 2.33)	0.073
	1.26 (0.63 - 2.52)	0.383	1.95 (0.53 - 7.19)	0.167	1.34 (0.46 - 3.89)	0.470
	1.20 (0.84 - 1.71)	0.167	1.42 (0.68 - 2.98)	0.200	1.01 (0.60 - 1.70)	0.946
	1.27 (0.94 - 1.73)	0.034	1.20 (0.65 - 2.21)	0.432	1.33 (0.84 - 2.11)	0.091
	1.15 (0.88 - 1.50)	0.168	1.41 (0.84 - 2.39)	0.074	1.28 (0.87 - 1.86)	0.083
	ref = 1		ref = 1		ref = 1	
	1.06 (0.75 - 1.48)	0.677	0.69 (0.35 - 1.36)	0.145	0.83 (0.48 - 1.45)	0.375
	1.12 (0.76 - 1.64)	0.439	1.03 (0.50 - 2.11)	0.923	1.42 (0.85 - 2.37)	0.063
	1.02 (0.71 - 1.46)	0.906	0.79 (0.41 - 1.54)	0.407	0.90 (0.54 - 1.49)	0.635

Supplemental Material: Table 6S. Continued

Threshold and categories ǂ	**Poor outcome at discharge**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value
Q 0-0.9 (0-0.11 mmHg)	ref = 1	
Q 0.9-1.0 (0.11-7 mmHg)	0.86 (0.39 - 1.85)	0.641
MAP <70 mmHg (N = 503; CI 99.0%; sign. p<0.010)		
Q 0 (0 mmHg)	0.81 (0.53 - 1.22)	0.181
Q 0-0.5 (0-0.02 mmHg)	0.71 (0.20 - 2.58)	0.510
Q 0.5-0.75 (0.02-1 mmHg)	ref = 1	
Q 0.75-0.9 (1-3 mmHg)	0.57 (0.32 - 1.02)	0.013
Q 0.9-1.0 (3-17 mmHg)	0.61 (0.33 - 1.13)	0.038
MAP <80 mmHg (N = 761; 99.2%; sign. p <0.008)		
Q 0 (0 mmHg)	0.87 (0.53 - 1.43)	0.464
Q 0-0.25 (0-0.05 mmHg)	1.08 (0.37 - 3.16)	0.854
Q 0.25-0.5 (0.05-2 mmHg)	0.91 (0.56 - 1.47)	0.607
Q 0.5-0.75 (2-7 mmHg)	ref = 1	
Q 0.75-0.9 (7-12 mmHg)	0.62 (0.35 - 1.11)	0.030
Q 0.9-1.0 (12-27 mmHg)	0.68 (0.36 - 1.30)	0.116
MAP >90 mmHg (N= 580; CI 99.0%; sign. p <0.010)		
Q 0 (0 mmHg)	0.91 (0.60 - 1.39)	0.597
Q 0-0.5 (0-0.11 mmHg)	0.93 (0.49 - 1.77)	0.779
Q 0.5-0.75 (0.11-2 mmHg)	ref = 1	
Q 0.75-0.9 (2-6 mmHg)	1.02 (0.58 - 1.80)	0.930
Q 0.9-1.0 (6-47 mmHg)	1.03 (0.57 - 1.88)	0.904
MAP >100 mmHg (N = 319; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	1.16 (0.62 - 2.18)	0.556
Q 0-0.75 (0-0.08 mmHg)	ref = 1	
Q 0.75-0.9 (0.08-1 mmHg)	1.27 (0.60 - 2.68)	0.441
Q 0.9-1.0 (1-38 mmHg)	1.26 (0.59 - 2.68)	0.459
MAP <70% (N = 446; CI 99.0%; sign. p <0.010)		
Q 0 (0 mmHg)	0.95 (0.59 - 1.54)	0.802
Q 0-0.5 (0-0.13 mmHg)	0.58 (0.24 - 1.40)	0.114
Q 0.5-0.75 (0.13-3 mmHg)	ref = 1	

		Poor outcome at three months			
Adjusted RR (CI) ǂ	p-value	Unadjusted RR (CI)	p-value	Adjusted RR (CI) ǂ	p-value
ref = 1		ref = 1		ref = 1	
0.93 (0.60 - 1.44)	0.689	0.86 (0.37 - 1.98)	0.683	0.84 (0.46 - 1.55)	0.512
0.94 (0.76 - 1.16)	0.441	0.93 (0.59 - 1.45)	0.678	1.06 (0.79 - 1.44)	0.603
0.85 (0.45 - 1.60)	0.516	0.80 (0.19 - 3.37)	0.702	0.97 (0.28 - 3.37)	0.947
ref = 1		ref = 1		ref = 1	
0.86 (0.62 - 1.19)	0.241	0.75 (0.40 - 1.43)	0.257	1.05 (0.68 - 1.62)	0.807
0.89 (0.62 - 1.27)	0.390	0.59 (0.29 - 1.21)	0.059	0.88 (0.52 - 1.50)	0.556
0.91 (0.70 - 1.19)	0.375	0.88 (0.51 - 1.52)	0.548	0.91 (0.62 - 1.34)	0.540
1.11 (0.66 - 1.86)	0.624	0.57 (0.15 - 2.14)	0.264	0.73 (0.28 - 1.90)	0.387
0.86 (0.67 - 1.12)	0.130	0.97 (0.57 - 1.63)	0.879	0.89 (0.62 - 1.29)	0.420
ref = 1		ref = 1		ref = 1	
0.86 (0.63 - 1.17)	0.207	0.61 (0.32 - 1.18)	0.048	0.82 (0.53 - 1.28)	0.246
0.91 (0.62 - 1.34)	0.542	0.59 (0.28 - 1.25)	0.063	0.81 (0.47 - 1.43)	0.340
1.07 (0.86 - 1.34)	0.438	0.84 (0.52 - 1.34)	0.339	1.05 (0.76 - 1.46)	0.708
1.00 (0.69 - 1.45)	0.999	1.04 (0.52 - 2.11)	0.890	1.22 (0.75 - 1.99)	0.297
ref = 1		ref = 1		ref = 1	
1.07 (0.79 - 1.44)	0.583	0.93 (0.50 - 1.75)	0.793	1.06 (0.67 - 1.66)	0.768
0.93 (0.68 - 1.26)	0.535	1.23 (0.65 - 2.34)	0.407	1.13 (0.71 - 1.78)	0.512
1.12 (0.77 - 1.61)	0.465	1.33 (0.64 - 2.77)	0.339	1.40 (0.82 - 2.37)	0.116
ref = 1		ref = 1		ref = 1	
1.14 (0.75 - 1.73)	0.435	1.17 (0.49 - 2.80)	0.669	1.22 (0.64 - 2.34)	0.446
1.00 (0.66 - 1.52)	0.983	1.86 (0.79 - 4.37)	0.070	1.48 (0.81 - 2.73)	0.106
0.95 (0.69 - 1.29)	0.655	0.81 (0.46 - 1.41)	0.326	0.85 (0.52 - 1.38)	0.394
0.76 (0.43 - 1.34)	0.218	0.62 (0.22 - 1.75)	0.241	0.86 (0.38 - 1.96)	0.654
ref = 1		ref = 1		ref = 1	

Supplemental Material: Table 6S. Continued

Threshold and categories ǂ	**Poor outcome at discharge**	
CI and sign. level for p-value; reported per threshold	Unadjusted RR (CI)	p-value
Q 0.75-0.9 (3-8 mmHg)	0.86 (0.45 - 1.61)	0.535
Q 0.9-1.0 (8-38 mmHg)	0.80 (0.38 - 1.70)	0.459
MAP <60% (N =199; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	0.08 (0.00 - 1.60)	0.034
Q 0-0.75 (0-0.01 mmHg)	ref = 1	
Q 0.75-0.9 (0.01-1 mmHg)	0.11 (0.00 - 2.31)	0.068
Q 0.9-1.0 (1-22 mmHg)	0.05 (0.00 - 1.15)	0.017
MAP <50% (N= 43; CI 97.5%; sign. p <0.025)		
Q 0 (0 mmHg)	1.41 (0.63 - 3.14)	0.346
Q 0-1 (0-0.633) mmHg)	ref = 1	

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile.

* Significant difference. ǂ Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. N = number of patients with TWA-AUC >0. ǂ The models were adjusted for age, sex, history of myocardial infarction, cerebrovascular disease, diabetes mellitus, hypertension, vascular disorders (central and peripheral), (history of) smoking, World Federation of Neurological Surgeons Grading System Score on admission, intervention modality (clipping or coiling), day of intervention, number of times receiving general anesthesia prior to and after the intervention, cerebral spinal fluid drainage, postoperative neurological decline, re-bleed, edema, cerebral ischemia, hydrocephalus, anemia, extracranial complications, preoperative MAP, amount of ephedrine, phenylephrine and noradrenaline administered per hour, preoperative oxygenation level and year of procedure. Additionally, the results for $ETCO_2$ thresholds were adjusted for mean MAP per case, whereas the results for MAP thresholds were adjusted for mean $ETCO_2$ per case. Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1-3.

			Poor outcome at three months			
	Adjusted RR (CI) ǂ	p-value	Unadjusted RR (CI)	p-value	Adjusted RR (CI) ǂ	p-value
	0.90 (0.61 - 1.33)	0.505	0.82 (0.39 - 1.72)	0.503	0.76 (0.44 - 1.31)	0.191
	1.05 (0.61 - 1.82)	0.835	0.64 (0.25 - 1.62)	0.217	0.72 (0.29 - 1.81)	0.367
	0.58 (0.22 - 1.55)	0.169	0.57 (0.06 - 5.34)	0.538	1.40 (0.18 - 11.12)	0.698
	ref = 1		ref = 1		ref = 1	
	0.62 (0.23 - 1.68)	0.237	0.94 (0.10 - 9.21)	0.949	1.53 (0.19 - 12.37)	0.627
	0.52 (0.17 - 1.58)	0.143	0.33 (0.03 - 3.67)	0.252	0.80 (0.08 - 7.95)	0.821
	1.23 (0.68 - 2.22)	0.450	0.76 (0.33 - 1.76)	0.470	0.97 (0.39 - 2.40)	0.944
	ref = 1		ref = 1		ref = 1	

Supplemental Material: Table 7S. Results for interaction in the association between time-weighted average area-under-the-curve thresholds for $ETCO_2$ and MAP and neurologic outcome at discharge

Threshold and categories ǂ	**Interaction**	
	Treatment modality	
CI and sign. level for p-value; reported per threshold	Adjusted RR (CI)	p-value
$ETCO_2$ <30 mmHg (N = 405; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	0.87 (0.51 - 1.49)	0.526
Q 0-0.75 (0-0.1 mmHg)	ref = 1	
Q 0.75-0.9 (0.1-0.7 mmHg)	0.82 (0.42 - 1.59)	0.454
Q 0.9-1.0 (0.7-5.7 mmHg)	0.91 (0.42 - 1.97)	0.767
$ETCO_2$ <35 mmHg (N = 1,022; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	1.94 (0.54 - 6.96)	0.166
Q 0-0.1 (0-0.1 mmHg)	1.36 (0.47 - 3.92)	0.441
Q 0.1-0.25 (0.1-1.0 mmHg)	1.36 (0.71 - 2.60)	0.200
Q 0.25-0.5 (1.0-2.4 mmHg)	1.05 (0.61 - 1.79)	0.830
Q 0.5-0.75 (2.4-4.0 mmHg)	ref = 1	
Q 0.75-0.9 (4.0-5.3 mmHg)	1.25 (0.66 - 2.37)	0.361
Q 0.9-1.0 (5.3-10.7 mmHg)	1.38 (0.65 - 2.94)	0.257
$ETCO_2$ <40 mmHg (N = 1,072; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	1.21 (0.27 - 5.49)	0.751
Q 0-0.1 (0-4.2 mmHg)	3.17 (1.17 - 8.59)	0.002*
Q 0.1-0.25 (4.2-5.7 mmHg)	1.09 (0.60 - 1.99)	0.717
Q 0.25-0.5 (5.7-7.2 mmHg)	1.06 (0.62 - 1.80)	0.796
Q 0.5-0.75 (7.2-8.8 mmHg)	ref = 1	
Q 0.75-0.9 (8.8-10.1 mmHg)	1.30 (0.67 - 2.52)	0.282
Q 0.9-1.0 (10.1-15.6 mmHg)	1.38 (0.65 - 2.95)	0.255
$ETCO_2$ <45 mmHg (N= 1,074; CI 99.3%; sign. p <0.007)		
Q 0 (0 mmHg)	1.08 (0.22 - 5.26)	0.900
Q 0-0.1 (0-9.0 mmHg)	2.91 (1.15 - 7.33)	0.002*
Q 0.1-0.25 (9.0-10.6 mmHg)	0.93 (0.50 - 1.75)	0.784
Q 0.25-0.5 (10.6-12.1 mmHg)	0.96 (0.56 - 1.63)	0.834
Q 0.5-0.75 (12.1-13.8 mmHg)	ref = 1	
Q 0.75-0.9 (13.8-15.1 mmHg)	1.21 (0.63 - 2.32)	0.452
Q 0.9-1.0 (15.1-20.6 mmHg)	1.27 (0.58 - 2.76)	0.423

Interaction Preoperative WFNS		**Interaction Timing of intervention**	
Adjusted RR (CI)	p-value	Adjusted RR (CI)	p-value
1.11 (0.67 - 1.87)	0.613	1.09 (0.59 - 2.00)	0.737
ref = 1		ref = 1	
1.19 (0.61 - 2.29)	0.530	1.56 (0.74 - 3.29)	0.137
1.75 (0.87 - 3.54)	0.046	0.95 (0.42 - 2.15)	0.884
0.79 (0.39 - 1.60)	0.382	0.70 (0.27 - 1.80)	0.318
1.52 (0.58 - 3.99)	0.245	0.47 (0.14 - 1.56)	0.090
1.10 (0.61 - 1.98)	0.688	0.55 (0.24 - 1.24)	0.046
1.36 (0.81 - 2.27)	0.111	0.71 (0.39 - 1.30)	0.132
ref = 1		ref = 1	
1.07 (0.58 - 1.95)	0.789	1.08 (0.55 - 2.13)	0.762
2.00 (0.99 - 4.03)	0.008	0.61 (0.25 - 1.48)	0.132
0.69 (0.17 - 2.76)	0.476	0.66 (0.08 - 5.26)	0.602
0.89 (0.45 - 1.78)	0.665	0.61 (0.24 - 1.53)	0.147
1.26 (0.72 - 2.21)	0.278	0.78 (0.36 - 1.67)	0.388
1.19 (0.72 - 1.98)	0.361	0.75 (0.41 - 1.38)	0.205
ref = 1		ref = 1	
0.97 (0.52 - 1.80)	0.901	1.11 (0.55 - 2.25)	0.700
1.90 (0.95 - 3.82)	0.013	0.70 (0.29 - 1.68)	0.278
0.67 (0.10 - 4.53)	0.590	0.73 (0.09 - 5.94)	0.697
0.93 (0.47 - 1.81)	0.771	0.63 (0.25 - 1.60)	0.181
1.21 (0.68 - 2.15)	0.376	0.92 (0.44 - 1.94)	0.783
1.27 (0.76 - 2.13)	0.220	0.85 (0.45 - 1.59)	0.485
ref = 1		ref = 1	
0.99 (0.53 - 1.84)	0.972	1.14 (0.56 - 2.31)	0.636
1.89 (0.93 - 3.84)	0.016	0.76 (0.31 - 1.84)	0.410

Supplemental Material: Table 7S. Continued

Threshold and categories ǂ	**Interaction**	
	Treatment modality	
CI and sign. level for p-value; reported per threshold	Adjusted RR (CI)	p-value
MAP<60 mmHg (N = 166; CI 98.3%; sign. p <0.017)		
Q 0 (0 mmHg)	2.36 (0.57 - 9.69)	0.146
Q 0-0.9 (0-0.11 mmHg)	ref = 1	
Q 0.9-1.0 (0.11-7 mmHg)	2.58 (0.58 - 11.43)	0.128
MAP <70 mmHg (N = 503; CI 99.0%; sign. p<0.010)		
Q 0 (0 mmHg)	0.86 (0.56 - 1.32)	0.379
Q 0-0.5 (0-0.02 mmHg)	1.26 (0.06 - 25.09)	0.855
Q 0.5-0.75 (0.02-1 mmHg)	ref = 1	
Q 0.75-0.9 (1-3 mmHg)	0.62 (0.33 - 1.18)	0.056
Q 0.9-1.0 (3-17 mmHg)	0.85 (0.42 - 1.73)	0.573
MAP <80 mmHg (N = 761; CI 99.2%; sign. p <0.008)		
Q 0 (0 mmHg)	1.21 (0.72 - 2.03)	0.343
Q 0-0.25 (0-0.05 mmHg)	0.64 (0.10 - 4.26)	0.543
Q 0.25-0.5 (0.05-2 mmHg)	1.38 (0.84 - 2.26)	0.087
Q 0.5-0.75 (2-7 mmHg)	ref = 1	
Q 0.75-0.9 (7-12 mmHg)	0.98 (0.53 - 1.80)	0.931
Q 0.9-1.0 (12-27 mmHg)	1.14 (0.53 - 2.45)	0.657
MAP >90 mmHg (N= 580; CI 99.0%; sign. p <0.010)		
Q 0 (0 mmHg)	1.04 (0.66 - 1.64)	0.845
Q 0-0.5 (0-0.11 mmHg)	1.37 (0.66 - 2.88)	0.272
Q 0.5-0.75 (0.11-2 mmHg)	ref = 1	
Q 0.75-0.9 (2-6 mmHg)	1.69 (0.93 - 3.08)	0.024
Q 0.9-1.0 (6-47 mmHg)	1.08 (0.57 - 2.04)	0.770
MAP >100 mmHg (N = 319; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	0.83 (0.35 - 1.96)	0.597
Q 0-0.75 (0-0.08 mmHg)	ref = 1	
Q 0.75-0.9 (0.08-1 mmHg)	1.35 (0.49 - 3.77)	0.469
Q 0.9-1.0 (1-38 mmHg)	1.17 (0.44 - 3.13)	0.695
MAP <70% (N = 446; CI 99.0%; sign. p <0.010)		
Q 0 (0 mmHg)	1.14 (0.62-2.08)	0.587
Q 0-0.5 (0-0.13 mmHg)	1.23 (0.36-4.23)	0.678

Interaction		**Interaction**	
Preoperative WFNS		**Timing of intervention**	
Adjusted RR (CI)	p-value	Adjusted RR (CI)	p-value
1.61 (0.82 - 3.17)	0.091	0.73 (0.34 - 1.57)	0.330
ref = 1		ref = 1	
1.69 (0.71 - 4.01)	0.149	0.65 (0.22 - 1.91)	0.349
1.03 (0.68 - 1.55)	0.885	1.02 (0.60 - 1.72)	0.927
1.64 (0.36 - 7.50)	0.412	0.53 (0.09 - 3.16)	0.369
ref = 1		ref = 1	
1.04 (0.56 - 1.94)	0.880	1.28 (0.59 - 2.79)	0.423
0.88 (0.44 - 1.74)	0.633	1.23 (0.52 - 2.95)	0.547
1.02 (0.62 - 1.68)	0.925	0.98 (0.52 - 1.84)	0.924
0.95 (0.34 - 2.65)	0.897	1.25 (0.39 - 4.03)	0.625
1.23 (0.76 - 2.00)	0.264	0.95 (0.50 - 1.79)	0.827
ref = 1		ref = 1	
1.39 (0.74 - 2.60)	0.171	1.26 (0.58 - 2.76)	0.437
0.89 (0.43 - 1.83)	0.673	1.26 (0.49 - 3.21)	0.531
0.96 (0.63 - 1.48)	0.836	1.17 (0.66 - 2.06)	0.497
0.79 (0.39 - 1.61)	0.398	0.77 (0.32 - 1.82)	0.435
ref = 1		ref = 1	
0.92 (0.51 - 1.68)	0.746	0.80 (0.40 - 1.61)	0.419
0.92 (0.48 - 1.77)	0.757	1.04 (0.50 - 2.16)	0.895
1.19 (0.59 - 2.38)	0.553	1.58 (0.62 - 3.99)	0.221
ref = 1		ref = 1	
1.06 (0.47 - 2.42)	0.861	1.50 (0.52 - 4.32)	0.344
1.16 (0.49 - 2.75)	0.685	1.42 (0.50 - 4.03)	0.408
0.85 (0.48-1.53)	0.496	0.84 (0.42-1.66)	0.513
1.17 (0.28-4.85)	0.791	0.83 (0.22-3.12)	0.726

Supplemental Material: Table 7S. Continued

Threshold and categories ǂ	**Interaction**	
	Treatment modality	
CI and sign. level for p-value; reported per threshold	Adjusted RR (CI)	p-value
Q 0.5 -0.75 (0.13-3 mmHg)	ref = 1	
Q 0.75-0.9 (3-8 mmHg)	0.84 (0.37-1.93)	0.609
Q 0.9-1.0 (8-38 mmHg)	1.28 (0.45-3.64)	0.553
MAP <60% (N = 199; CI 98.8%; sign. p <0.013)		
Q 0 (0 mmHg)	0.55 (0.03-11.22)	0.637
Q 0-0.75 (0-0.01 mmHg)	ref = 1	
Q 0.75-0.9 (0.01-1 mmHg)	0.48 (0.02-10.12)	0.556
Q 0.9-1.0 (1-22 mmHg)	0.74 (0.03-17.80)	0.822
MAP <50% (N = 43; CI 97.5%; sign. p <0.025)		
Q 0 (0 mmHg)	0.51 (0.09-2.86)	0.391
Q 0-1 (0-0.633) mmHg)	ref = 1	

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage.

Interaction Preoperative WFNS		**Interaction Timing of intervention**	
Adjusted RR (CI)	p-value	Adjusted RR (CI)	p-value
ref = 1		ref = 1	
0.83 (0.37-1.84)	0.559	0.83 (0.37-1.82)	0.543
0.74 (0.23-2.38)	0.520	0.83 (0.28-2.49)	0.678
2.20 (0.32-15.28)	0.313	1.25 (0.12-13.18)	0.823
ref = 1		ref = 1	
1.85 (0.26-13.11)	0.442	1.21 (0.11-13.72)	0.853
1.89 (0.16-22.20)	0.530	1.03 (0.08-13.56)	0.980
0.80 (0.22-2.93)	0.710	1.79 (0.62-5.15)	0.216
ref = 1		ref = 1	

* Significant difference. ǂ Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. N = number of patients with TWA-AUC >0. Only results obtained from the adjusted models are reported (see Supplemental Material Table 6s for a list of included confounders). Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1-3. Treatment modality was defined as clipping or coiling. Preoperative WFNS was dichotomized into "4,5" versus "1,2,3". Timing of intervention was dichotomized into "within 2 days after the ictus" and "after two days after the ictus".

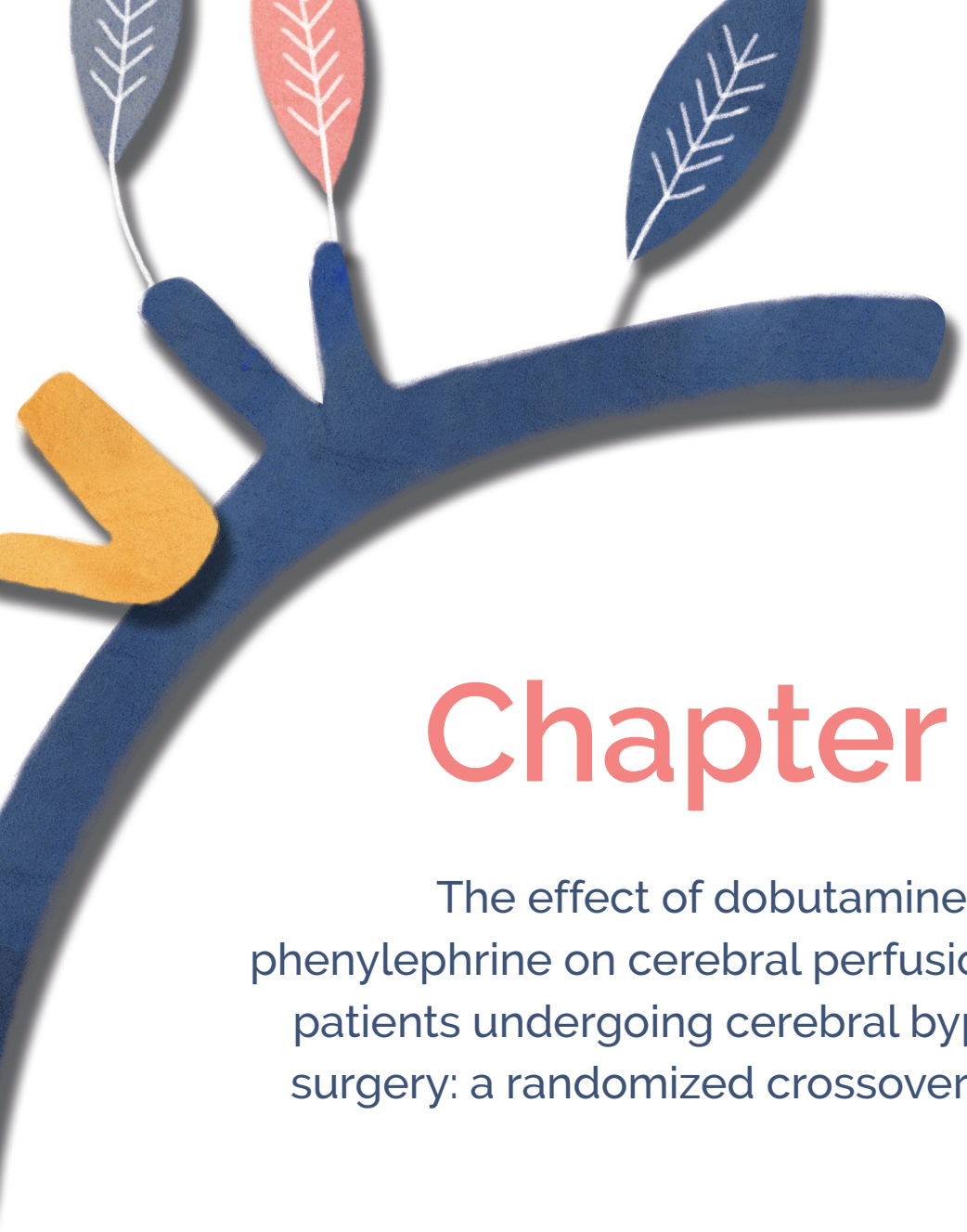
Supplemental Material: Table 8S. Results for interaction in the association between mean MAP, mean $ETCO_2$, any $ETCO_2$ <30 mmHg and any MAP <60 mmHg and neurologic outcome at discharge

Threshold and categories ǂ	**Interaction**	
	Treatment modality	
CI and sign. level for p-value are reported per threshold	Adjusted RR (CI)	p-value
Mean MAP (N = 974; 99.2% CI; sign. p <0.008)		
Q 0-0.1 (53-67.8 mmHg)	0.96 (0.43-2.14)	0.898
Q 0.1-0.25 (67.8-73.2 mmHg)	0.77 (0.43-1.38)	0.238
Q 0.25-0.5 (73.2-80.6 mmHg)	0.92 (0.55-1.54)	0.679
Q 0.5-0.75 (80.6-88.3 mmHg)	ref = 1	
Q 0.75-0.9 (88.3-95.5 mmHg)	1.03 (0.60-1.76)	0.907
Q 0.9-1.0 (95.5-138 mmHg)	0.94 (0.47-1.97)	0.812
Mean $ETCO_2$ (N = 1,096; 99.2% CI, sign. p <0.008)		
Q 0-0.1 (32-39.6mmHg)	1.20 (0.58-2.51)	0.519
Q 0.1-0.25 (39.6-41.3mmHg)	1.04 (0.57-1.92)	0.860
Q 0.25-0.5 (41.3-43.5mmHg)	0.97 (0.58-1.62)	0.869
Q 0.5-0.75 (43.5-45.6mmHg)	ref = 1	
Q 0.75-0.9 (45.6-47.3mmHg)	1.14 (0.64-2.04)	0.552
Q 0.9-1.0 (47.3-56 mmHg)	1.42 (0.66-3.06)	0.234
Any $ETCO_2$ <30 mmHg (N = 405; 95% CI, sign. p <0.05)	0.98 (0.73-1.30)	0.877
Any MAP <60 mmHg (N = 166, 95% CI, sign. p <0.05)	0.85 (0.56-1.27)	0.428

CI: confidence interval. $ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. Ref: reference category. RR: risk ratio. Sign.: significant. Q: quantile. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage

Interaction Preoperative WFNS		**Interaction Timing of intervention**	
Adjusted RR (CI)	p-value	Adjusted RR (CI)	p-value
0.75 (0.35-1.61)	0.321	1.34 (0.54-3.34)	0.402
1.05 (0.57-1.91)	0.852	1.29 (0.61-2.69)	0.375
0.72 (0.44-1.18)	0.080	1.23 (0.64-2.37)	0.405
ref =1		ref = 1	
0.79 (0.46-1.36)	0.257	1.13 (0.60-2.14)	0.623
0.81 (0.40-1.66)	0.452	1.12 (0.51-2.43)	0.720
1.67 (0.86-3.23)	0.040	0.91 (0.39-2.12)	0.776
0.79 (0.45-1.39)	0.276	1.68 (0.89-3.18)	0.031
0.87 (0.53-1.43)	0.463	1.13 (0.61-2.10)	0.607
ref =1		ref = 1	
1.11 (0.64-1.94)	0.630	0.96 (0.44-2.09)	0.888
0.71 (0.41-1.24)	0.110	0.83 (0.37-1.85)	0.549
1.10 (0.84-1.43)	0.497	1.04 (0.75-1.45)	0.805
0.84 (0.59-1.20)	0.347	1.09 (0.70-1.71)	0.718

* Significant difference. ǂ Bonferroni correction was used to correct for the number of categories within a threshold and p-values and confidence intervals are reported accordingly. N = number of patients with TWA-AUC or mean >0. Only results obtained from the adjusted models are reported (see Supplemental Material Table 6s for a list of included confounders). Poor neurologic outcome was defined as a Glasgow Outcome Scale of 1-3. Treatment modality was defined as clipping or coiling. Preoperative WFNS was dichotomized into "4,5" versus "1,2,3". Timing of intervention was dichotomized into "within 2 days after the ictus" and "after two days after the ictus".



Chapter 5

The effect of dobutamine and phenylephrine on cerebral perfusion in patients undergoing cerebral bypass surgery: a randomized crossover trial

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ABSTRACT

Background Patients undergoing cerebral bypass surgery are prone for cerebral hypoperfusion. Currently, blood pressure is often increased with vasopressors to prevent ischemia. However, this might cause vasoconstriction of the graft and cerebral vasculature and decrease perfusion. We hypothesized that cardiac output rather than blood pressure is essential for adequate perfusion and aimed to determine whether dobutamine administration resulted in higher graft perfusion than phenylephrine administration.

Methods This randomized crossover study included ten adult patients undergoing cerebral bypass surgery. Intraoperatively, patients randomly and sequentially received dobutamine to increase cardiac index and phenylephrine to increase mean arterial pressure (MAP). An increase of >10% in cardiac index and >10% in MAP was targeted, respectively. Before both interventions, a reference phase was implemented. Primary outcome was the absolute difference in graft flow between the reference and intervention phase. We compared the absolute flow difference between both interventions (Wilcoxon signed rank test) and constructed a random-effect linear regression model to explore treatment and carry-over effect.

Results Graft flow increased with a median of 4.1 ml/min [IQR 1.7-12.0] after dobutamine administration and 3.6 ml/min [IQR 1.3-7.8] after phenylephrine administration (difference -0.6 ml/min; 95% CI -14.5–5.3, p-value 0.441). There was no treatment effect (0.9 ml/min; 95% CI 0.0-20.1, p-value 0.944) and no relevant carry-over effect.

Conclusion Both dobutamine and phenylephrine increase graft flow during cerebral bypass surgery, without a preference for one method over the other.

INTRODUCTION

Preservation of adequate cerebral perfusion during cerebral bypass procedures is a challenge for both neurosurgeons and anesthesiologists.[1] Cerebral bypass surgery can be used as a revascularization technique for flow augmentation in steno-occlusive vascular disease such as moyamoya disease, or flow preservation when a major artery has to be sacrificed to treat an underlying disease such as a complex intracranial aneurysm.[1] Graft patency rates are generally well above 90%.[2] However, graft patency itself does not guarantee adequate cerebral perfusion and conventional cerebral bypass surgery carries a risk of intraoperative ischemic stroke.[1] Therefore, it has been suggested to maintain a normal blood pressure during general anesthesia or to even increase the blood pressure with 10-20% from the preoperative baseline.[3] In order to achieve this goal, administration of vasopressors is often required.[3] Interestingly, systolic blood pressure (SBP) levels were not associated with graft flow in the postoperative setting.[4] Concurrent administration of vasopressors might partly explain this observation, as vasoconstriction can actually decrease blood flow. An increase in blood pressure with vasopressors might surpass the effect of vasoconstriction and eventually increase the cerebral perfusion, but at the cost of systemic hypertension. However, as systemic blood pressure is determined by cardiac output and total peripheral resistance, it can be argued that an increase in graft flow can also be accomplished by an increase in cardiac output with the use of inotropes, without the side effects of vasoconstriction and systemic hypertension.[5] While according to Ohm's law, augmenting cardiac output should not increase cerebral blood flow when the blood pressure remains unchanged, this axiom assumes that we know the pressure at the level of small cerebral arteries. However, in a hypovolemic patient, vasopressors can increase 'central' blood pressure to normal levels while at the same time there is considerable impaired organ perfusion.[6,7] Unfortunately, the differential effect of blood pressure and cardiac output augmentation on cerebral blood flow during neurosurgery has hardly been studied.[8–12]

We hypothesized that inotropes – to increase cardiac output – rather than vasopressors – to increase blood pressure – are a key element for adequate graft flow and cerebral perfusion. Thus, we aimed to study the effect of dobutamine administration versus the effect of phenylephrine administration on graft perfusion in patients undergoing cerebral bypass surgery.

METHODS

Study design

This randomized crossover study was conducted between September 2018 and July 2019 at the University Medical Center (UMC) Utrecht in adherence to the CONSORT statement: extension to randomized crossover trials.[13] The local medical ethics committee, the national competent authority and the European Medicines Agency approved the study protocol (UMC Utrecht Medical Research Ethics Committee 18/321, Protocol number NL65095.041.18 and EudraCT number 2018-002008-15). This trial was registered at the Netherlands Trial Register (NL7077; Principal Investigator: W.A. van Klei; Registration date June 21st, 2018). The full study protocol is available upon request.

Adult patients (≥18 years) presenting for an extracranial-intracranial or intracranial-intracranial cerebral bypass were eligible for inclusion after written informed consent, irrespective of the indication or type of graft. Exclusion criteria were an emergency procedure, pregnancy, a contra-indication for either dobutamine or phenylephrine, and a mean arterial pressure (MAP) <60 mmHg or SBP >180 mmHg under general anesthesia before start of the interventions (Figure 1). Patients could be included a second time when undergoing surgery on the contralateral side.

The interventions took place after construction of the bypass. Patients were randomized to sequentially receive dobutamine and phenylephrine via a central venous catheter (Figure 1). Randomization to determine which drug was to be given first was performed using sealed opaque envelopes in a 1:1 allocation ratio. The attending anesthesiologist opened the envelope at the end of the cerebral bypass procedure. After a first reference phase to record baseline graft flow, the first intervention (administration of dobutamine or phenylephrine) was applied. After a wash-out period of twenty minutes and a second reference phase, the alternative intervention was applied (Figure 1). The dosages of dobutamine (2-15 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and phenylephrine (0.15-1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) varied depending on their effect on cardiac index and blood pressure, respectively. For dobutamine, the infusion rate was targeted at an increase in cardiac index of at least 10%, as compared to the mean cardiac index in the reference phase. For phenylephrine, the infusion rate was adjusted to target a 10% increase in MAP as compared to the reference phase. During the reference and the intervention phases SBP, MAP, heart rate, stroke volume, cardiac index and graft flow were measured every minute once a steady state was reached for at least two minutes.

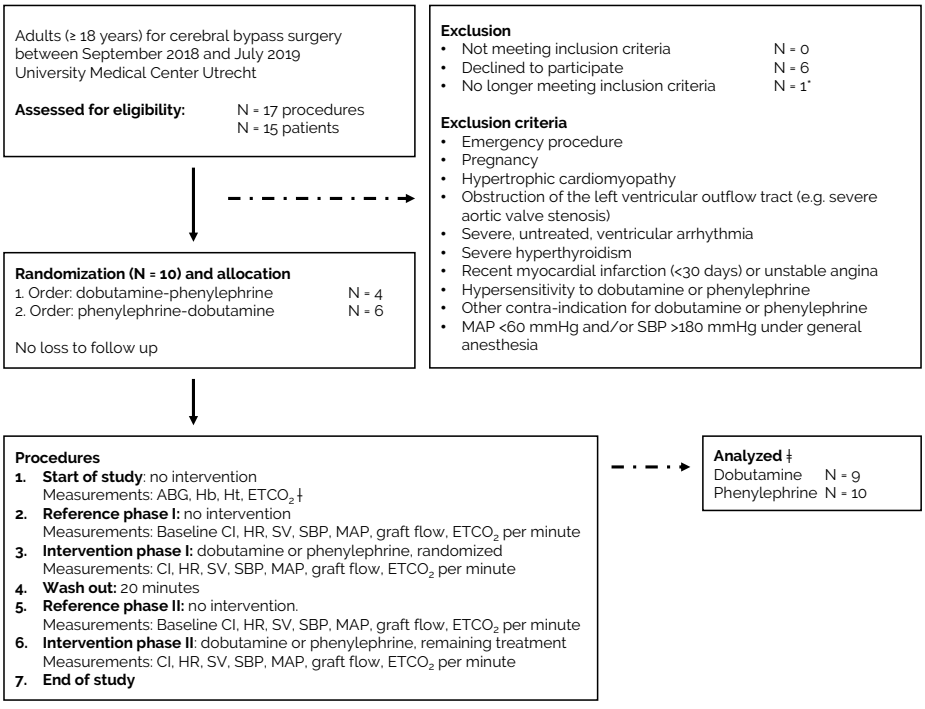

Figure 1. Study design and Flow Chart

ABG: arterial blood gas. CI: cardiac index. $ETCO_2$: end-tidal carbon dioxide. Hb: hemoglobin. HR: heart rate. Ht: hematocrit. MAP: mean arterial pressure. SBP: systolic blood pressure. SV: stroke volume. * Drop-out before randomization: one patient signed informed consent, but during the procedure primary clipping of the giant cerebral aneurysm was possible and an intracranial-intracranial cerebral bypass was no longer necessary. ǂ $ETCO_2$ value that corresponds to $PaCO_2$ (arterial carbon dioxide pressure) from arterial blood gas sampling. ≠ One patient developed arrhythmia after dobutamine administration. We did not exclude this patient entirely, but only excluded data obtained during the dobutamine intervention from our analyses.

Infusion of fluids and administration of other medications was kept constant throughout the study period. To maintain a constant arterial carbon dioxide pressure ($PaCO_2$), no adjustments to ventilator settings were allowed and end-tidal carbon dioxide ($ETCO_2$) values were documented throughout the study period. To prevent vasoconstriction, topical application of papaverine at the intracranial part of the bypass was allowed throughout the measurement period and at the discretion of the neurosurgeon. SBP, MAP and heart rate were continuously measured via an arterial catheter using a 4th generation FloTrac® transducer placed in the radial artery and an EV1000 monitor (Edwards Lifesciences, Irvine, California, USA) and uncalibrated arterial pressure waveform analysis was used to measure stroke volume and cardiac index.[14] Graft flow

was measured with an ultrasonographic flow meter (Transonic Systems Inc., Ithaca, New York, USA), with a probe encircling the bypass in close proximity to the anastomosis with the intracranial artery. The anesthesiologist was blinded for graft flow, whereas the neurosurgeon, who measured graft flow, was blinded for medication given and blood pressure and cardiac index data.

Conduct of general anesthesia

General anesthesia was maintained with propofol (induction bolus 1-3 mg/kg, maintenance infusion 4-10 $mg \cdot kg^{-1} \cdot h^{-1}$), remifentanil (0.25-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and atracurium (induction bolus 0.5 mg/kg, maintenance infusion 5-10 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Management of blood pressure and $ETCO_2$ outside the study period were left to the judgment of the attending anesthesiologist, except that our local protocol prescribed to maintain SBP <180 mmHg and to keep $ETCO_2$ between 35-45 mmHg. During anesthesia but outside the study period, episodes of hypotension were treated with ephedrine (5 mg/ml, bolus 2.5-10 mg) or phenylephrine (100 µg/ml, bolus 100 µg, infusion 0.15-1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). When phenylephrine infusion was started prior to start of the study, this was continued at a constant infusion rate during the study period. The intervention drug, either dobutamine or phenylephrine, was given in addition to this maintenance infusion. Only during the wash-out period, a bolus or change in maintenance infusion of phenylephrine was allowed and this was left to the judgement of the attending anesthesiologist.

Outcome measures

The primary outcome measure was the absolute change in graft flow during dobutamine and phenylephrine administration as compared to the reference phase. Secondary outcome measures were the change in MAP, SBP, heart rate, stroke volume and cardiac index.

Additional data collection

Data on patient, procedure and graft characteristics were collected from electronic medical files. Variables were selected based on their possible influence on graft patency or flow. Variables on patient and procedure characteristics included age, sex, body mass index, American Society of Anesthesiologists (ASA) physical status,[15] indication and duration of the procedure, bypass technique, graft type (venous or arterial),[4] donor vessel and recipient vessel.[4,16] Additionally, data on comorbidities, use of cardiovascular medication, and intraoperative data were collected. Baseline MAP was defined as mean MAP from all values obtained within five minutes prior to induction, measured with an arterial catheter.

Prior to the first reference phase, an arterial blood gas sample was obtained and the corresponding $ETCO_2$ level was documented to determine the gradient between $PaCO_2$ and $ETCO_2$. Also, hemoglobin and hematocrit were determined. This blood gas sampling was used to determine whether any deviations in $PaCO_2$, hemoglobin or hematocrit were present that could possible influence graft flow. Finally, the amount of dobutamine and phenylephrine administered was collected, as well as the duration of the administration.

Sample size

Since no data were available on the effect of an increase in cardiac index on graft perfusion in cerebral bypass surgery, we were not able to perform a proper sample size calculation. However, the crossover design enabled us to limit the sample size. With around 20 cerebral bypass procedures in adults in our institution each year, we aimed to include ten patients.

Statistical analysis

All analyses were performed with use of R (Version 3.6.1 – © (2019-07-05), for Macintosh, R. Inc., Vienna, Austria).[17] Descriptive statistics were done using frequencies, percentages and either means with standard deviation (SD) or medians with 25th and 75th percentiles (IQR, interquartile range) as appropriate.

The mean graft flow was estimated for each reference and intervention phase and was plotted over time for each patient. The change in graft flow between intervention phase I and the corresponding reference phase I, and between intervention phase II and reference phase II was calculated. Afterwards, a two-sided Wilcoxon signed rank test was used to assess the difference in flow, after confirmation that the data was not normally distributed. A pseudomedian was reported since differences between paired samples were not fully symmetrically distributed around the median. The same method was applied to assess differences in MAP, SBP, heart rate, stroke volume and cardiac index.

In order to study the treatment effect (i.e. dobutamine versus phenylephrine), the sequence effect (i.e. randomization order) and a potential carry-over effect (i.e. the duration of the wash-out period), a random effect multivariable linear regression model was constructed, with graft flow as the dependent variable and treatment (dobutamine versus phenylephrine) as a fixed effect. Subject ID was included as random effect to account for within-subject variance. As graft flow may increase between opening of the bypass and the end of surgery,[16] we incorporated two reference phases in our study design. To account for any additional effect of timing of graft flow measurement, time was also included as random effect. We included an interaction term for treatment and randomization order as fixed effect to adjust for any incomplete wash-out.

P-values <0.05 were considered to be statistically significant and 95% confidence intervals (CI) were reported. There was no need to account for multiplicity.

RESULTS

Within the study period, 15 patients presented for cerebral bypass surgery for a total of 17 procedures. Of these, eight patients were enrolled and randomized to either receive first dobutamine and thereafter phenylephrine or vice-versa (Figure 1). Two patients were enrolled for a second time when they underwent surgery contralateral to the side of the first bypass. One patient developed a short episode of atrial arrhythmia when dobutamine was administered, which converted to sinus rhythm after discontinuation of dobutamine. Although there were no hemodynamic consequences, the validity of arterial wave form analysis might be compromised.[14] Data obtained during dobutamine administration in this patient were removed from our analyses. There were no additional missing data. All patients received an extracranial-intracranial bypass, all with the superficial temporal artery as donor vessel and the middle cerebral artery as recipient vessel. Five patients (63%) were diagnosed with moyamoya disease of whom two were included twice, and three patients (38%) had atherosclerotic carotid artery occlusion. Additional baseline characteristics are presented in Table 1. There were no important deviations in $PaCO_2$, hemoglobin or hematocrit.

Table 1. Baseline characteristics

Preoperative characteristics		**Patients (N=8)***
Sex (%)	Female	5 (62.5)
Age (years, median [IQR])		48 [41-53]
BMI (kg/m², median [IQR])		29 [26-35]
ASA class (%)	I	0 (0.0)
	II	2 (25.0)
	III	5 (62.5)
	IV	1 (12.5)
Ischemic heart disease (%)		0 (0.0)
Heart failure (%)		0 (0.0)
Cerebrovascular accident (%)	Ischemic	8 (100.0)
	Hemorrhagic	0 (0.0)

Table 1. Continued

Preoperative characteristics		**Patients (N=8)***	
Diabetes Mellitus (%)	No	7 (87.5)	
	Non-insulin dependent	0 (0.0)	
	Insulin dependent	1 (12.5)	
Hypertension (%)		4 (50.0)	
Vascular Disease (%)	No	5 (62.5)	
	Peripheral	0 (0.0)	
	Central	3 (32.5)	
Elevated creatinine level (%)		0 (0.0)	
Anticoagulants (%)		8 (100.0)	
Beta Blocking agents (%)		1 (12.5)	
Renin-Angiotensin-Aldosteron-System Inhibitors (%)		2 (25.0)	
Calcium antagonist (%)		1 (12.5)	
Diuretics (%)		0 (0.0)	
Statins (%)		5 (62.5)	
Indication for cerebral bypass (%)	Moyamoya disease	5 (62.5)	
	Carotid occlusion	3 (37.5)	
Intraoperative characteristics		**Patients (N=8)***	**Cases (N=10) ǂ**
Duration of surgery (min, median [IQR])		299 [260-357]	297 [260-342]
pH prior to start study (median [IQR])		7.39 [7.38-7.40]	7.39 [7.38-7.40]
$PaCO_2$ prior to start study (mmHg, median [IQR])		39 [36-39]	39 [36-39]
$ETCO_2$ prior to start study (mmHg, median [IQR])		36 [34-37]	36 [34-37]
Hemoglobin prior to start study (mmol/L, median [IQR])		7.1 [6.1-7.5]	7.1 [6.2-7.4]
Hematocrit prior to start study (%, median [IQR])		34 [29-35]	34 [30-35]
Baseline MAP prior to induction of anesthesia (mmHg, median [IQR])		98 [96-101]	98 [93-105]

ASA: American Society of Anesthesiologists physical status. BMI: body mass index. $ETCO_2$: End-tidal carbon dioxide. IQR: interquartile range. MAP: mean arterial pressure. $PaCO_2$: Arterial carbon dioxide pressure. * Only the first case per patient was included in this part of the table. ǂ This includes all ten cases, including the two patients who presented twice for cerebral bypass surgery.

Table 2. Change in hemodynamic parameters

Hemodynamic parameters	**Phenylephrine (median [IQR])**		
Cases (N = 10)	**Reference**	**Intervention**	**Difference**
Graft flow (ml/min)	15.5 [6.4–20.9]	20.8 [7.5–32.5]	3.6 [1.3–7.8]
MAP (mmHg)	91 [88–101]	108 [104–118]	16 [14–19]
SBP (mmHg)	139 [123–155]	169 [154–185]	32 [26–33]
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	3.0 [2.6–3.5]	3.0 [2.6–4.0]	0.1 [-0.2–0.3]
Heart rate (/min)	53 [50–59]	51 [47–59]	-1 [-2– -1]
Stroke volume (ml)	57 [49–63]	60 [55–68]	4 [-0.5–7]

CI: confidence interval. IQR: interquartile range. MAP: mean arterial pressure. SBP: systolic blood pressure. * Statistically significant at a level of significance of p <0.05. ǂ Differences were estimated using a Wilcoxon signed rank test comparing the effects of dobutamine with phenylephrine and reporting a pseudomedian since differences between paired samples were

A median of 4.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [IQR 2.9-5.1] dobutamine for a duration of 14 minutes [IQR 13-18] and 0.31 $\mu g \cdot kg^{-1} \cdot min^{-1}$ [IQR 0.26-0.41] phenylephrine for 12 minutes [10-14] were administered. Graft flow increased with a median of 4.1 ml/min [IQR 1.7-12.0] after administration of dobutamine and with 3.6 ml/min [IQR 1.3-7.8] after administration of phenylephrine (Table 2). The pseudomedian difference in increase in graft flow of dobutamine versus phenylephrine was -0.6 ml/min (95% CI -14.5–5.3). Cardiac index increased with a median of 1.1 $L \cdot min^{-1} \cdot m^{-2}$ [IQR 0.8-1.5] during dobutamine administration, while MAP decreased with a median of -7 mmHg [IQR -7–0]. MAP increased with a median of 16 mmHg [IQR 14-19] during phenylephrine administration, which was not accompanied by a change in cardiac index (median 0.1 $L \cdot min^{-1} \cdot m^{-2}$ [IQR -0.2–0.3]). In all patients, $ETCO_2$ was kept constant (see Table 1S in the Supplemental Material). The change in graft flow, MAP and cardiac index during dobutamine and phenylephrine administration is presented for all patients separately in Figure 2.

After adjustment in the random effect multivariable linear regression model, type of treatment was not associated with graft flow (0.9 ml/min; 95% CI 0.0-20.1, p-value 0.944). There was no relevant carry-over effect for dobutamine (0.0 ml/min; 95% CI 0.0-0.2, p-value 0.004).

Dobutamine (median [IQR])			Between intervention	p-value
Reference	**Intervention**	**Difference**	**Difference (95% CI)** *ǂ*	
21.0 [6.4–27.5]	21.6 [10.0–38.2]	4.1 [1.7–12.0]	- 0.6 (-14.5–5.3)	0.441
99 [93–103]	96 [90–104]	-7 [-7–0]	21 (12–31)	0.004*
146 [135–153]	151 [135–167]	5 [-1–20]	24 (7–35)	0.013*
2.7 [2.4–3.1]	4.0 [3.4–5.2]	1.1 [0.8–1.5]	-1.0 (-1.4– -0.7)	0.009*
53 [50–57]	62 [57–64]	5 [2–6]	-7 (-12– -4)	0.004*
54 [44–63]	69 [62–80]	13 [11–22]	-10 (-19– -4)	0.004*

not fully symmetrically distributed around the median. Data from the dobutamine intervention in patient 6b were removed from the analyses, since arrhythmia occurred during dobutamine administration, making values obtained with the EV1000/FloTrac system less reliable.

In one patient, distinctive results were found. This patient was included twice as she presented for a second, contralateral bypass. During the second procedure we found a very low graft flow, with hardly any effect on graft flow during both an increase in MAP and cardiac index (see Table 1S in the Supplemental Material). A CT-angiography revealed a large collateral system surrounding the circle of Willis, shunting blood away from the bypass. In order to determine whether hypovolemia might also have affected the results found in this patient, we retrospectively collected data on pulse pressure variation from our anesthesia record-keeping system and found no clinically relevant change (see Table 2S in the Supplemental Material).

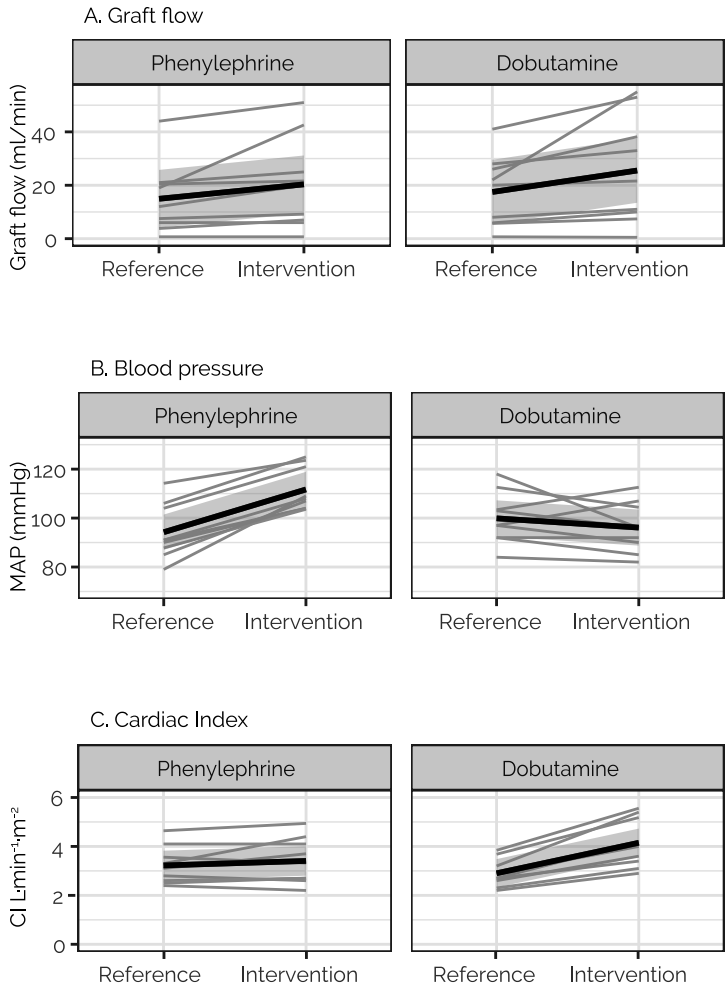

Figure 2. Spaghetti plot for change in graft flow, mean arterial pressure and cardiac index

The plots show the value for [A] graft flow, [B] mean arterial pressure (MAP), and [C] cardiac index (CI) for all patients. Two values were plotted per patient; i.e. the mean in the reference phase and the mean in the intervention phase. For visualization purposes, spaghetti plots were made. The graphs on the left represent the results for the phenylephrine stage, whereas the graphs on the right represent the results obtained in the dobutamine stage. The black line shows the mean change with in grey the standard deviation for all patients combined.

DISCUSSION

We administered dobutamine – to increase cardiac output – and phenylephrine – to increase blood pressure – during cerebral bypass surgery and observed similar increases in graft flow. This finding was consistent in most patients and except for a short episode of atrial arrhythmia in one patient, we did not encounter any adverse effects.

Blood pressure, cardiac output and cerebral perfusion

When assessing the effect of blood pressure and cardiac output on cerebral perfusion, studies have differentiated between awake and anesthetized patients and between healthy patients and patients with a disturbed cerebral autoregulation. A study in healthy patients under general anesthesia found that an increase in MAP with phenylephrine caused a decrease in cerebral oxygenation as measured with near-infrared spectroscopy (NIRS), while the cardiac output did not change.[9] A similar increase in MAP following ephedrine administration increased cardiac output and preserved cerebral oxygenation.[9] Although this finding suggests that cardiac output may be an important variable to maintain cerebral oxygenation, interpretation is complicated since NIRS was used to assess cerebral oxygenation.[8] The accuracy of NIRS is known to suffer from extracranial contamination and is influenced by vasopressors causing vasoconstriction of the scalp.[18] Studies using healthy, awake patients found that 1% change in cardiac output corresponded to a 0.35% change in cerebral blood flow velocity, as measured with transcranial Doppler.[10–12,19]

Results from studies in awake and healthy subjects may not always apply to the diseased population under general anesthesia. Anesthesia can potentially affect cerebral perfusion via a variety of pathways, including suppression of the sympathetic nervous system.[12] However, anesthesia does not seem to significantly affect cerebral autoregulation itself in patients with intact or disrupted cerebral autoregulation.[20–22] It appears that the cerebral vasculature also does not respond differently on vasoactive agents after initiation of general anesthesia.[22,23] Healthy subjects are likely to have good cerebral autoregulation, whereas the effects of adrenergic agents may be stronger in patients with disrupted cerebral autoregulation.[8] This is supported by a study in healthy patients where maintenance of MAP with phenylephrine after initiation of general anesthesia decreased cerebral oxygenation,[9] while a comparable study in patients with disrupted autoregulation found maintained cerebral oxygenation.[24]

The differential effects of blood pressure and cardiac output on cerebral blood flow in the neurosurgical population is insufficiently studied. Interestingly, cerebral dysregulation is a phenomenon also seen in cardiac surgery.[8,25] A randomized trial studying the effect of a low target MAP (40-50 mmHg) versus a high target MAP (70-80 mmHg) during cardiopulmonary bypass, with a fixed bypass flow, found no difference in new ischemic cerebral lesions on

MRI.[26] Another study in cardiac surgery patients found that cerebral oxygenation was lower with lower pump flow, regardless of arterial blood pressure.[27] Like the studies in cardiac patients, the present study found that an increase in cardiac output can increase cerebral blood flow, even when MAP remains unchanged.

Clinical implications

Although cerebral bypass surgery aims to prevent future ischemic strokes, patients are at risk for perioperative cerebral ischemia.[1] Currently, vasopressors are used to maintain blood pressure levels.[3,28] However, in patients with a disrupted autoregulation the cerebral perfusion may not solely depend on blood pressure, as demonstrated in studies conducted in the cardiac surgery population[12,26,27] and supported by findings in the present study. It should be noted that the effects of dobutamine and phenylephrine on cerebral blood flow – via cardiac output and blood pressure – cannot be interpreted separately from the direct effect of these agents on cerebral vessels and the close relation between cardiac output and blood pressure.

Both α-adrenergic and β-adrenergic receptors are suggested to play a role in cerebral autoregulation.[8,29,30] Vasopressors used to increase blood pressure, such as the α_1-receptor agonist phenylephrine, might actually cause cerebral vasoconstriction.[31] We propose that the increase in cardiac output by dobutamine caused the increase in graft flow found in this study, while only having a minimal α-adrenergic effect at best, thus preventing cerebral vasoconstriction. However, dobutamine can also decrease blood pressure to a varying extent, possibly explaining why not all patients did benefit from dobutamine administration. In addition, by increasing preload, administration of phenylephrine can also increase cardiac output when anesthesia-induced hypotension is the result of hypovolemia.[32] Interestingly, the present study found that phenylephrine did not change cardiac output. Additionally, others found a decrease in cardiac output after phenylephrine administration.[33] These differences might be explained by timing of phenylephrine administration (i.e. anesthesia-induced hypotension might be maximal immediately after initiation of anesthesia) and the method of cardiac output measurement.[32–35] Our study used a 4th generation FloTrac algorithm for arterial pressure waveform analysis, with good performance when reporting changes in cardiac output after phenylephrine administration.[33–35]

We cannot definitively conclude that dobutamine administration benefits all patients presenting for cerebral bypass surgery. Still, this study does show that dobutamine can increase cerebral perfusion and should be considered when targeted graft flows are not reached or only at the cost of (severe) systemic hypertension, when using phenylephrine. Inotropes such as dobutamine can cause arrhythmia and increased myocardial oxygen demand and should be used with caution in patients with cardiac comorbidities. Although

not tested in this study, norepinephrine, a combined α_1-, α_2- and β_1-receptor agonist, primarily causes vasoconstriction and an increase in blood pressure, but can also (slightly) increase cardiac output and may be a good alternative to phenylephrine.[36] Future studies should consider testing the effect of norepinephrine on cerebral blood flow and further explore the effect of an increase in cardiac output in all patients at risk of perioperative cerebral ischemia.

Strengths and limitations

This study has several strengths. First, cerebral bypass procedures provided us with the opportunity to measure cerebral perfusion invasively with an ultrasonographic flow meter in close proximity to the middle cerebral artery, providing reliable measurements.[37] In contrast, several other existing techniques, such as NIRS, each have their limitations, ranging from invasiveness to contamination by the extracranial circulation.[8] Doppler sonography assesses velocity (cm/s) rather than volume per time unit (ml/min), and is no longer reliable when the diameter of the vessel changes.[8] Second, as $PaCO_2$ levels are known to influence cerebral blood flow, it is important to keep these constant, which was confirmed by stable $ETCO_2$ levels throughout the conduct of the study. Third, due to the crossover design of this study we were able to eliminate substantial between-patient variability. Finally, a wash-out period was used between both interventions and there was no relevant carry-over effect.

Nevertheless, this study has several obvious limitations. First, most patients suffered from moyamoya disease, which limits generalizability. However, the results from this study might also be applicable to a broader population at risk for perioperative cerebral ischemia. Like in moyamoya disease, cardiac surgery patients, post ischemic stroke patients and patients after subarachnoid hemorrhages or traumatic brain injury all suffer from a disrupted autoregulation.[8,25,38,39] However, to confirm or refute such effects in other patient populations, targeted cerebral blood flow studies are needed, administering vasoactive drugs in a similar crossover design as used in the present study. Second, an increase in cardiac index and MAP of 10-20% was intended. The increase in cardiac index was much higher than intended. However, this further strengthens our observation that dobutamine was not superior to phenylephrine in improving cerebral perfusion. Third, we used an uncalibrated sensor to continuously measure cardiac index. The accuracy of the EV1000/FloTrac® system has been shown to be sufficient in the absence of large changes in vascular tone and can be used to follow trends in cardiac index over time.[14,35]

Conclusion

Both administration of dobutamine – by increasing cardiac output while decreasing MAP – and phenylephrine – by increasing MAP while maintaining cardiac output – increased graft flow in patients undergoing cerebral bypass surgery.

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SUPPLEMENTAL MATERIAL

Supplemental Material: Table 1S. Differences in hemodynamic parameters per individual patient

StudyID	Graft flow (ml/min)	MAP (mmHg)	SBP (mmHg)	Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)	Heart rate (/min)	Stroke volume (ml)	$ETCO_2$ (mmHg)
Phenylephrine							
1	3.2	17	34	1.1	2	16	0.1
2	23.6	9	20	0.3	-1	7	0.0
3	8.0	17	33	0.6	0	12	0.1
4a	1.6	16	25	-0.2	-1	-4	0.1
4b	0.0	22	32	0.0	-11	7	0.0
5	4.0	19	32	0.2	-2	4	0.1
6a	7.0	13	27	-0.2	-2	-1	0.0
6b	13.1	14	20	-0.1	-1	-1	0.0
7	0.0	14	32	0.1	-2	5	0.1
8	1.2	30	46	-0.2	-6	1	0.1
Dobutamine							
1	4.1	10	27	2.2	6	30	0.3
2	12.2	-8	20	1.5	12	11	0.3
3	5.0	-7	0	1.1	6	13	0.2
4a	1.7	9	21	1.7	2	28	0.2
4b	-0.2	-22	-11	1.5	1	22	0.1
5	33.0	-7	-3	0.8	3	11	0.2
6a	12.0	-2	-1	0.7	1	15	0.2
6b	NA	NA	NA	NA	NA	NA	NA
7	3.0	-7	5	1.0	5	13	0.3
8	1.6	0	11	0.7	12	3	0.2

$ETCO_2$: end-tidal carbon dioxide. MAP: mean arterial pressure. SBP: systolic blood pressure. Patient 4 and 6 were enrolled for a second time (4b and 6b) when they underwent surgery contralateral to the side of the first bypass. Data from the dobutamine intervention in patient 6b were recorded as missing, since arrhythmia occurred during dobutamine administration, making values obtained with the EV1000/FloTrac system less reliable.

Supplemental Material: Table 2S. Pulse pressure variation

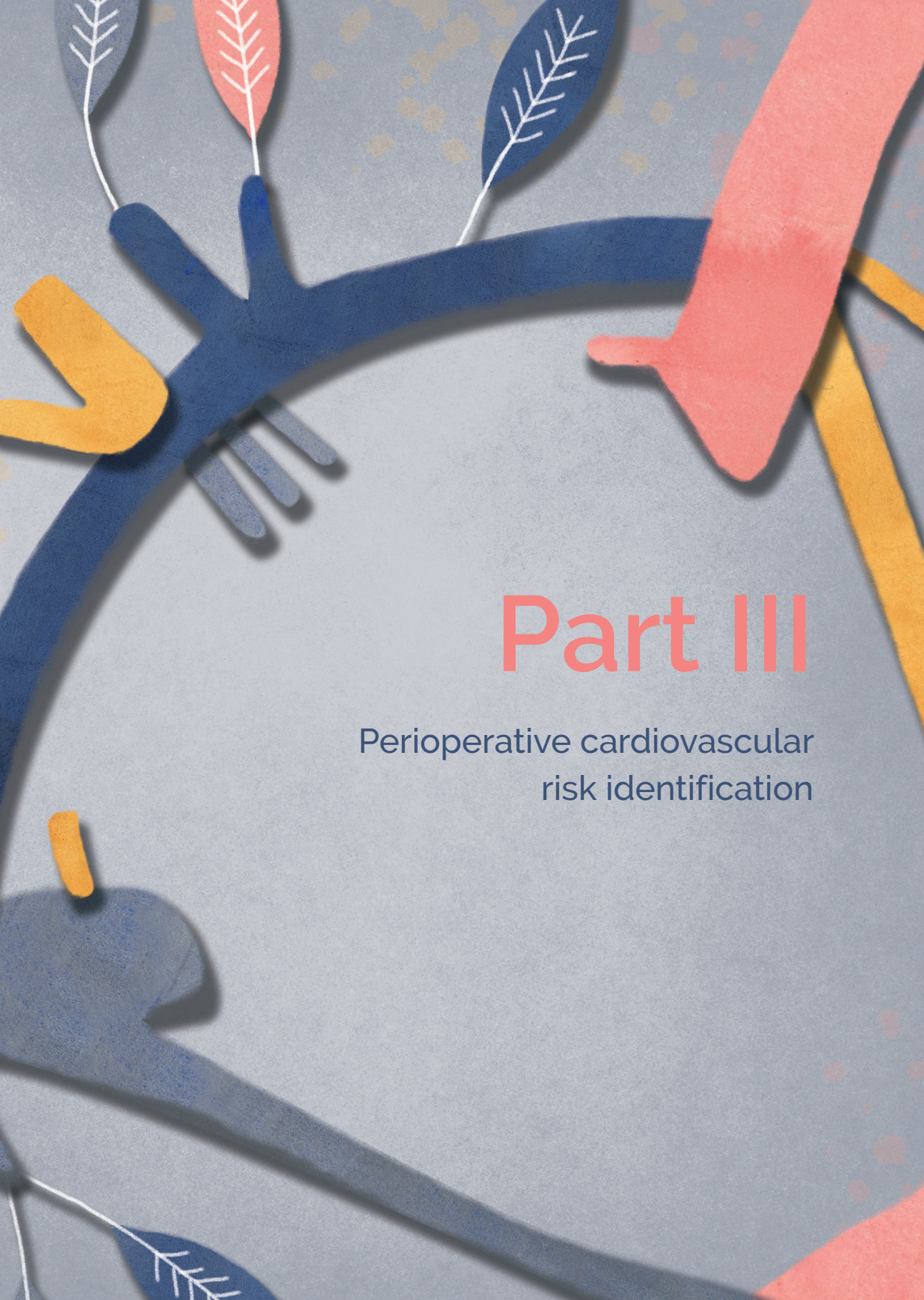
Patient	Prior to study ǂ	PPV Dobu-tamine	PPV Phenyl-ephrine	p-value[a]	p-value[b]	p-value[c]
Patient 4a (median [IQR])	12 [12-13]	15 [13-16]	16 [15-18]	0.005*	<0.001*	0.005*
Patient 4b (median [IQR])	17 [16-19]	20 [20-21]	23 [16-24]	0.005*	0.160	0.483

IQR: interquartile range. PPV: pulse pressure variation. * Statistically significant at a level of significance of p <0.05. ǂ Data on PPV were retrospectively collected for this patient during the first (patient 4a) and second procedure (patient 4b), as she presented a second time for a contralateral bypass. ǂ Data were collected between 30 and 15 minutes prior to start of the first study intervention.

[a]Wilcoxon signed rank test comparing PPV obtained prior to start of the study and during dobutamine administration.

[b]Wilcoxon signed rank test comparing PPV obtained prior to start of the study and during phenylephrine administration.

[c]Wilcoxon signed rank test comparing PPV obtained during dobutamine administration and during phenylephrine administration.



Part III

Perioperative cardiovascular risk identification

Chapter 6

Cardiac events within one year after a subarachnoid hemorrhage: the predictive value of troponin elevation after aneurysm occlusion

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ABSTRACT

Background Patients who survive after an aneurysmal subarachnoid hemorrhage (ASAH) have an increased incidence of cardiovascular events compared to the general population. We assessed whether troponin elevation after aneurysm occlusion, as marker of myocardial injury, can predict long-term cardiac events.

Methods We analyzed a prospectively collected cohort of 159 patients with ASAH and early aneurysm occlusion, in whom routine post-intervention troponin I (TnI) measurements were performed. With competing risk regression modeling we estimated the association between TnI elevation after aneurysm occlusion and major adverse cardiac events (MACE) within one year. Secondary outcome measures were all-cause mortality and neurologic condition within one year. The predictive value of post-intervention TnI was compared to the predictive value of pre-intervention characteristics using c-statistics and the Integrated Discrimination Improvement index (IDI).

Results Subdistribution hazard ratios (SHR) for TnI elevation and MACE at one year were 1.05 (95% CI 1.03-1.07) per 10 ng/L increase in TnI and 7.91 (95% CI 1.46-43.0) for any TnI elevation. After adjustment for pre-intervention variables, the SHR were 1.47 (95% CI 0.81-2.67) per 10ng/L and 9.00 (95% CI 1.62-50.1) for any elevation. The c-statistic was 0.71 for TnI elevation as a continuous measure and 0.69 for any TnI elevation. The IDI showed a minimum improvement in prediction of 0.08 [IQR 0.06-0.09] for TnI as a continuous measure and 0.003 [IQR -0.004-0.01] for any TnI elevation, when compared to pre-intervention characteristics.

Conclusion TnI elevation after occlusion of a ruptured intracranial aneurysm predicts the occurrence of MACE within one year after ASAH.

INTRODUCTION

Patients who have survived an episode of aneurysmal subarachnoid hemorrhage (ASAH) and in whom the aneurysm has been occluded, have an overall increased long-term mortality rate and an increased incidence of cardiovascular events compared to age- and sex-matched groups.[1,2]

In the hours to days after an ASAH, excessive sympathetic activation can cause neurogenic stress cardiomyopathy,[3] which is displayed by an increased cardiac troponin as a biomarker of cardiac injury.[4] In up to half of all ASAH patients, elevated troponins are reported[4] and several studies have shown the prognostic relevance of elevated troponin early after admission for poor neurologic outcome and mortality.[4–6] ASAH patients have lower peak troponin levels as compared to patients with acute coronary syndromes,[5] suggesting that most have so-called contraction band necrosis, instead of myocardial ischemia.[4,5] Interestingly, a second increase in troponin levels was observed on day three after the ictus,[5] which may reflect myocardial injury during interventions to occlude the aneurysm. Studies among patients undergoing non-cardiac surgery have suggested that perioperative myocardial injury is a predictor of future major adverse cardiac events (MACE).[7,8] Therefore, our aim was to assess the pattern of pre- and post-intervention troponin levels, to study the association between post-intervention troponin elevation and MACE and to investigate whether troponin elevation after early occlusion of the ruptured aneurysm would be a good predictor of MACE within the first year after an ASAH.

METHODS

Patients

For the current study we included patients who received general anesthesia for early neurosurgical clipping or endovascular coiling of a ruptured intracranial aneurysm and in whom routine troponin I (TnI) measurements were performed. The preferred treatment modality was chosen on a multidisciplinary level and irrespective of the research question of this study. Patients were retrospectively collected from two different prospective cohorts (see Figure 1S in the Supplemental Material). The first cohort consisted of patients who underwent early aneurysm occlusion with either clipping or coiling at our hospital between November 2005 and February 2008. TnI was measured daily until eight days after presentation.[9] The second part of our patients was retrieved from a database including patients aged 60 years or older who underwent non-cardiac surgery at our hospital and in whom TnI was measured routinely on post-intervention day one, two and three.[8] From this database we selected all patients who underwent early clipping

between March 2011 and November 2014; patients who underwent coiling were not part of this database. After selecting eligible patients from both cohorts, we excluded patients who underwent a re-operation within three days, to make sure the peak TnI value within three days could be assigned to the first procedure. In both cohorts, further follow-up of elevated TnI levels was left to the discretion of the treating physician.

The local medical ethics committee waived the need for informed consent. (Medical Research Ethics Committee, University Medical Center Utrecht, 16-441/C). This study was conducted in adherence to the STROBE statement for observational research.[10]

Troponin values

Different TnI assays were used over the years (see Figure 1S in the Supplemental Material). In our analyses, we used the clinical cutoff values as used at our institution within the respective time periods, instead of the 99th percentile upper reference limit,[11] since clinical decisions were based upon these cutoff values. TnI values were collected from the day of admission until post-intervention day three and the highest TnI value within three days after the intervention was selected. Two different definitions of troponin elevation were used: an absolute increase above the cutoff value (continuous measure) and presence of any post-intervention TnI elevation above the cutoff value (dichotomized measure).

Outcomes

The primary outcome was MACE at one year, defined as myocardial infarction, need for revascularization or cardiac death. All-cause mortality within one year was a secondary outcome measure, as was neurologic outcome at three months, defined by the Glasgow Outcome Scale.[12] Lastly, we included residence at one year to reflect neurologic outcome, defined as 1) residing at home, 2) residing in a nursing home or rehabilitation center or 3) deceased.

Other risk factors

Preoperative cardiac risk factors for the general non-cardiac surgery population were summarized in the Revised Cardiac Risk Index (RCRI) and included a history of ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative treatment with insulin and preoperative serum creatinine levels >177 µmol/L (>2mg/dL).[13] Furthermore, we included hypertension and a history of smoking (as they are major risk factors for ASAH and are associated with cardiovascular disease),[14] age and clinical condition on admission, assessed by means of the World Federation of Neurological Surgeons (WFNS) grading system for ASAH[15] and dichotomized into good (WFNS 1-3) and poor clinical condition (WFNS

4-5), as has been done before.[4,6] Additionally, we collected the American Society of Anesthesiologists (ASA) physical status to reflect physical condition prior to ASAH.[16] For an elaborate description of RCRI, WFNS and ASA class, we refer to Table 1S in the Supplemental Material.

Data were extracted from two databases: the ASAH registration database which contains data from admission until three months after the ictus and a separate database containing long-term follow up data, collected by means of annually distributed standardized surveys. Additional data on pre-intervention risk factors were derived from the hospital-wide data warehouse.

Missing values

As complete case analyses are known to lead to biased effect estimates, missing values were handled using multiple imputation after confirming that data was indeed missing at random.[17] For this, we compared baseline characteristics and outcomes for patients in whom a post-intervention TnI was measured, with those in whom it was not. We used the mice package in R, creating thirty-five imputation sets.[18,19] Analyses were conducted in each of these datasets; subsequently estimates were pooled using Rubin's rule.[20–22]

Statistical analysis

Routine TnI measurements prior to the intervention were only obtained between November 2005 and February 2008. Therefore, these values were only used to inspect the pattern of TnI elevation by using boxplots, including all values from the day of admission until three days after the intervention.

Descriptive statistics for baseline characteristics were obtained by stacking the imputation sets. Patients with and without any post-intervention TnI elevation were compared with respect to the baseline characteristics using a $\chi 2$ test, Fisher's exact test, independent *t* test or Mann-Whitney U test where appropriate.

To determine the association between post-intervention TnI values and MACE at one year and to adjust this association for the competing risk of all-cause death, a univariable competing risks regression analysis was done using the method of Fine & Gray.[23] From this analysis we extracted the subdistribution hazard ratio (SHR), where patients remain in the risk set after experiencing a competing event, which is most suitable for prediction research.[23] For all-cause mortality after one year a Cox proportional hazards regression analysis was conducted.

Subsequently, the regression analyses were repeated with adjustment for risk factors that had a known association with TnI elevation after ASAH in the literature, namely age and WFNS score on admission.[4,6] The proportional hazard assumption was tested by inspecting the Kaplan Meier curve and by plotting the scaled Schoenfeld Residuals of the included variables versus time and by testing the slopes.[23]

Cumulative incidences were calculated, taking competing risks into account. Finally, we compared the predictive value of the above defined pre-intervention risk factors with TnI alone. The predictive value was expressed using the c-statistic, again adjusted for competing risks.[24] Additionally, the Integrated Discrimination Improvement index (IDI) was used to further determine the predictive accuracy of TnI, by comparing the predictive value of TnI alone to that of several pre-intervention patient characteristics separately.[25,26] The IDI was expressed as the median and the interquartile range (IQR) of all indices obtained from the thirty-five imputed datasets. Separate analyses were done for TnI elevation as a continuous and as a dichotomous measure.

Throughout the analyses, a p-value <0.05 was considered to be significant and 95% confidence intervals (CI) or IQRs were reported were applicable. The statistical analyses were performed with R (Version 3.3.1 – © 2016-06-21, R, Inc., for Macintosh, Vienna, Austria).[22]

RESULTS

The study included 159 patients. In 30 patients (18.9%), no post-intervention TnI values were available, while in 41 patients (25.8%) no data were present on MACE within one year (see Table 2S in the Supplemental Material for an overview of missing data). To determine whether values were missing at random, patients in whom troponin was measured were compared with those in whom it was not. MACE occurred in 5 out of 129 patients (3.9%) with an available post-intervention TnI value and in 1 out of 30 patients (3.3%) without a post-intervention TnI value (p = 1.00). There were small differences in baseline characteristics in patients with and without available post-intervention TnI values (Table 1), indicating that missingness was not completely at random, thus supporting the need for multiple imputation.

Table 1. Comparison between patients with and without post-intervention troponin measurement

		Post-intervention TnI not measured	Post-intervention TnI measured	p-value
		N = 30	N = 129	
Age (year, mean (sd))		63.2 (12.3)	61.8 (11.8)	0.564
Weight (kg, mean (sd))		70.2 (17.0)	71.6 (15.2)	0.760
Sex (%)	Male	2 (6.7)	31 (24.0)	0.044*
WFNS on admission (%)	1	9 (34.6)	55 (46.2)	0.149
	2	5 (19.2)	31 (26.1)	
	3	2 (7.7)	7 (5.9)	
	4	5 (19.2)	20 (16.8)	
	5	5 (19.2)	6 (5.0)	
Intervention (%)	coiling	10 (33.3)	54 (41.9)	0.515
ASA class (%)	I	3 (12.5)	19 (15.4)	0.617
	II	19 (79.2)	84 (68.3)	
	III	2 (8.3)	20 (16.3)	
	IV-V	0 (0.0)	0 (0.0)	
RCRI factors				
Myocardial infarction (%)		1 (3.3)	7 (5.4)	1.000
Congestive heart failure (%)		0 (0.0)	0 (0.0)	NA
Cerebrovascular disease (%)		2 (6.7)	8 (6.2)	1.000
Insulin dependent diabetes mellitus (%)		1 (3.3)	0 (0.0)	0.189
Pre-intervention creatinine (median [IQR])		63.0 [52.0, 72.3]	63.0 [56.0, 72.8]	0.754
Other comorbidities				
Diabetes mellitus (%)		2 (6.7)	4 (3.1)	0.318
Hypertension (%)		6 (20.0)	40 (31.0)	0.316
Arrhythmia (%)		0 (0.0)	5 (3.9)	1.000
Central artery disease (%)		0 (0.0)	3 (2.3)	1.000
Peripheral artery disease (%)		2 (6.7)	6 (4.7)	0.646
Carotid artery disease (%)		0 (0.0)	3 (2.3)	1.000
Smoking (%)	Stopped	1 (4.2)	17 (14.5)	0.429
	Currently	13 (54.2)	52 (44.4)	

Table 1. Continued

		Post-intervention TnI not measured	Post-intervention TnI measured	p-value
		N = 30	N = 129	
Medication use prior to admission				
Anticoagulants (%)	Coumarin derivate	0 (0.0)	4 (3.1)	1.000
	Acetylsalicylic acid	3 (10.0)	15 (11.7)	
	Multiple anticoagulants	0 (0.0)	2 (1.6)	
Statins (%)		3 (10.0)	14 (11.4)	1.000
Antihypertensive medication (%)		5 (16.7)	45 (34.9)	0.086
	β-blocking agents	1 (3.3)	17 (14.0)	0.126
	Calcium antagonist	2 (6.7)	12 (9.9)	0.737
	RAAS inhibitor	4 (13.3)	22 (18.2)	0.787
	Diuretics	4 (13.3)	11 (9.1)	0.500

ASA: American Society of Anesthesiologists physical status. IQR: interquartile range. NA: not applicable. RAAS: Renin-Angiotensin-Aldosterone-System. RCRI: Revised Cardiac Risk Index. Sd: standard deviation. TnI: troponin I. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage. * Statistically significant at a level of significance of $p < 0.05$

During admission, eleven patients (6.9%) died after aneurysm occlusion and five (3.1%) experienced a MACE. Within the first year, 26 patients (16.4%) had died and seven patients (4.4%) had a MACE. After imputation (with an efficiency of 0.99), patient characteristics were compared for patients with and without TnI elevation (Table 2). Troponin elevation after aneurysm occlusion occurred in 43 patients (27.0%). These patients were on average older, more likely to have cerebrovascular diseases and had a worse clinical condition on admission. In the group with TnI elevation, five patients (11.6%) experienced MACE within the first year after an ASAH, as compared to two patients (1.7%) without TnI elevation. Ten patients (23.3%) died within one year in the group with TnI elevation versus 16 (13.8%) in the group without TnI elevation.

On group level, there seemed a renewed increase in median TnI starting at day four after admission, while, on average, the aneurysm was occluded at 2.5 days after admission (Figure 1). From 33 patients we had both pre-intervention and post-intervention TnI values. Twelve patients showed an increase in TnI after the intervention, but in only six patients this value passed the cutoff value for an elevated TnI. Only one of these patients was diagnosed with a myocardial infarction.

Table 2. Baseline characteristics

		Post-intervention TnI not elevated (n=116)	**Post-intervention TnI elevated (n=43)**	**p-value**
		N = 116	N = 43	
Age (years, mean (sd))		61.6 (11.8)	63.6 (11.7)	0.031*
Weight (kg, mean (sd))		72.3 (16.2)	72.7 (16.3)	0.764
Sex (%)	Male	25 (21.6)	8 (18.6)	0.852
WFNS on admission (%)	1	59 (50.9)	11 (25.6)	0.041*
	2	24 (20.7)	16 (37.2)	
	3	6 (5.2)	3 (7.0)	
	4	19 (16.4)	8 (18.6)	
	5	8 (6.9)	5 (11.6)	
Intervention (%)	Coiling	42 (36.2)	22 (51.2)	0.127
ASA class(%)	I	15 (12.9)	8 (18.6)	0.359
	II	85 (73.3)	26 (60.5)	
	III	16 (13.8)	8 (20.9)	
	IV-V	0 (0.0)	0 (0.0)	
RCRI factors				
Myocardial infarction (%)		6 (5.2)	2 (4.7)	1.000
Congestive heart failure (%)		0 (0.0)	0 (0.0)	NA
Cerebrovascular disease (%)		4 (3.4)	7 (16.3)	0.009*
Insulin dependent diabetes mellitus (%)		1 (0.9)	0 (0.0)	1.000
Pre-intervention creatinine (median [IQR])		62.0 [54.0, 72.0]	66.0 [57.0, 76.8]	<0.001*
Other comorbidities				
Diabetes mellitus (%)		6 (5.2)	0 (0.0)	0.192
Hypertension (%)		33 (28.4)	13 (30.2)	0.981
Arrhythmia (%)		2 (1.7)	3 (7.0)	0.123
Central artery disease (%)		2 (1.7)	1 (2.3)	1.000
Peripheral artery disease (%)		6 (5.2)	2 (4.7)	1.000
Carotid artery disease (%)		0 (0.0)	3 (7.0)	0.019*
Smoking (%)	Stopped	16 (13.7)	4 (9.3)	0.476
	Currently	56 (48.3)	18 (41.9)	

Table 2. Continued

		Post-intervention TnI not elevated (n=116)	Post-intervention TnI elevated (n=43)	p-value
		N = 116	N = 43	
Medication use prior to admission				
Anticoagulants (%)	Coumarin derivate	2 (1.7)	2 (4.7)	0.103
	Acetylsalicylic acid	10 (8.6)	8 (18.6)	
	Multiple anticoagulants	1 (0.9)	1 (2.3)	
Statins (%)		12 (10.3)	7 (16.3)	0.454
Antihypertensive medication (%)		36 (31.0)	14 (32.6)	1.000
	β-blocking agents	16 (13.8)	5 (11.6)	0.925
	Calcium antagonist	10 (8.6)	6 (14.0)	0.486
	RAAS inhibitor	22 (19.0)	7 (16.3)	0.874
	Diuretics	11 (9.5)	4 (9.3)	1.000

ASA: American Society of Anesthesiologists physical status. IQR: interquartile range. NA: not applicable. RAAS: Renin-Angiotensin-Aldosterone-System. RCRI: Revised Cardiac Risk Index. Sd: standard deviation. TnI: troponin I. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage. * Statistically significant at a level of significance of p <0.05

The effect estimates of the regression analyses are presented in Table 3. The proportional hazard assumption was confirmed. The cumulative incidence for MACE at one year was 1.63% (95% CI -0.71-3.97) for patients without TnI elevation and 12.52% (95% CI 2.34-22.71) for patients with any TnI elevation (relative risk 7.67; 95% CI 1.52-38.7). The absolute risk of MACE for a 60-year-old patient with WFNS score 1-3 and no post-intervention TnI elevation would be 2.18% versus 16.29% if there would be any TnI elevation. The model containing TnI as a continuous measure allows for more nuance, e.g. the risk for a similar patient, but with TnI being 100ng/L above the cutoff value, would be 5.61%.

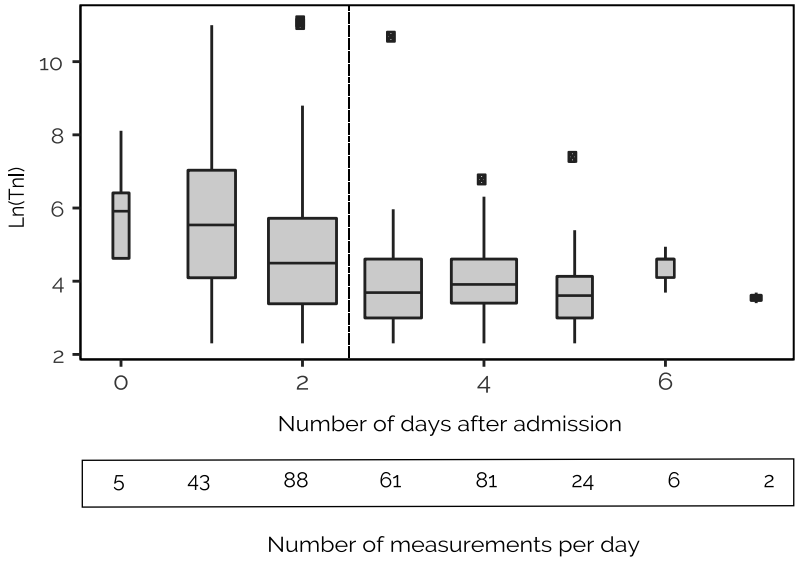

Figure 1. Boxplots showing the distribution of troponin I (TnI) levels per day after admission.

For visualization purposes we performed a log transformation of TnI. The width of the boxplots corresponds to the relative amount of values available. The absolute number of measurements per day is reported underneath the graph. The dashed line depicts the average day of aneurysm occlusion. There seemed to be a renewed increase in median TnI after aneurysm occlusion.

The c-statistic was 0.71 for TnI as a continuous measure and 0.69 for any TnI elevation (Table 4). The IDI revealed a higher predictive accuracy for TnI when compared to pre-intervention variables, with the smallest improvement found when compared to a history of smoking (Table 4).

Table 3. TnI elevation and clinical outcomes

		Unadjusted analysis		**Adjusted analysis** §	
		Effect estimate (CI)	p-value	Effect estimate (CI)	p-value
Elevated TnI, continuous †					
MACE ‡	SHR	1.05 (1.03-1.07)	<0.001*	1.47 (0.81-2.67)	0.213
All-cause mortality	HR	1.03 (1.01-1.04)	<0.001*	1.02 (0.997-1.05)	0.090
GOS	IRR	0.99 (0.97-1.01)	0.158	0.99 (0.97-1.01)	0.211
Residence	IRR	1.01 (0.997-1.02)	0.170	1.01 (0.99-1.02)	0.162
Elevated TnI, dichotomous					
MACE	SHR	7.91 (1.46-42.99)	0.016*	9.00 (1.62-50.14)	0.012*
All-cause mortality	HR	1.89 (0.69-5.18)	0.210	1.44 (0.54-3.82)	0.472
GOS	IRR	0.85 (0.70-1.05)	0.134	0.88 (0.72-1.08)	0.221
Residence	IRR	1.11 (0.81-1.53)	0.513	1.05 (0.77-1.42)	0.786

CI: confidence interval. GOS: Glasgow Outcome Scale. HR: hazard ratio. IRR: incidence rate ratio. MACE: major adverse cardiac event. SHR: subdistribution hazard ratio. TnI: troponin I. * Statistically significant at a level of significance of p <0.05. † Expressed per 10ng/L change in troponin from the cutoff. ‡ MACE, all-cause mortality and residence *at one year*. GOS *at three months*. § Adjusted for age and World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage.

Table 4. Predictive value of post-intervention TnI

	C-statistic	**IDI [IQR]** † **Elevated TnI, continous**	**IDI [IQR]** † **Elevated TnI, dichotomous**
Elevated TnI, continuous	0.71	-	-
Elevated TnI, dichotomous	0.69	-	-
Age	0.55	0.11 [0.10-0.13]	0.04 [0.03-0.04]
ASA class	0.52	0.11 [0.10-0.13]	0.03 [0.02-0.04]
Hypertension	0.55	0.11 [0.09-0.13]	0.04 [0.02-0.04]
RCRI	*	*	*
Smoking	0.73	0.08 [0.06-0.09]	0.003 [-0.004-0.01]
WFNS	0.55	0.11 [0.10-0.13]	0.04 [0.02-0.04]

ASA: American Society of Anesthesiologists physical status. IDI: Integrated Discrimination Improvement Index. IQR: interquartile range. RCRI: Revised Cardiac Risk Index. TnI: Troponin I. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage. * Variable could not be included because the model did not converge. † Predictive value of TnI compared to the predictive value of pre-intervention patient characteristics separately.

DISCUSSION

This study showed that troponin elevation after early occlusion of a ruptured intracranial aneurysm was an independent predictor for MACE within one year after an ASAH. After adjustment for age and WFNS score on admission, the association with MACE at one year was no longer statistically significant for troponin elevation on a continuous scale, but remained significant for troponin elevation as a dichotomized measure. There was no association between troponin elevation after aneurysm occlusion and neurologic outcome, nor with mortality in the multivariable analysis. The pattern in troponin levels during the initial days after admission suggested a second elevation corresponding to the average day of aneurysm treatment, as was found previously.[5] This renewed increase in troponin might very well reflect perioperative myocardial injury.

Clinical implications

To our knowledge, neither the predictive value of post-intervention troponin elevation, nor the association of post-intervention troponin values with MACE in the long-term has been investigated before in ASAH patients. The 2016 European Guidelines on cardiovascular disease prevention states that patients with a history of cardiovascular disease, including any kind of stroke, have a high cardiovascular risk profile. Implementation of prevention strategies such as lifestyle changes and management of risk factors before hospital discharge is recommended.[27] We believe that post-intervention troponin elevation may be helpful in identifying patients with the highest cardiovascular risk. The predictive value of post-intervention troponin levels has been more extensively studied in the general non-cardiac surgery population,[7,8] where the vast majority of patients with elevated troponin levels was asymptomatic, despite frequent perioperative exposure to physiological and emotional stress.[8] This implicates that postoperative TnI elevation reflects myocardial injury rather than myocardial ischemia, as well as that routine postoperative TnI surveillance can be utilized for postoperative risk stratification to direct secondary prevention. It has been shown in the non-cardiac surgery population that this can not only improve outcomes, but it is also cost-effective.[28] For ASAH patients, the (cost-)effectiveness of secondary prevention for cardiac events remains unclear and needs further investigation.[27]

Limitations

Strength of this study is the use of routinely obtained troponin values and data from clinical care, thus representing daily practice instead of a controlled research setting. Nevertheless, this study has some obvious limitations. First, although we found that a post-intervention increase in TnI is an independent predictor of MACE, the sample size was too small to create an extensive prediction model. Second, due to a limited amount

of routine pre-intervention TnI measurements, pre-intervention values were used for the boxplot, but were excluded from further analyses. To explore the underlying etiology of perioperative myocardial injury and MACE, these values should be incorporated in future studies. Third, although we did not find a relevant difference in baseline characteristics (see Table 3S in the Supplemental Material), our study cohort was created using two different cohorts. We used the cutoff values set by our laboratory, since clinical decision making and diagnosis was based upon these values. Therefore, we believe that the use of different TnI assays did not influence our results. Fourth, this study does not differentiate between intervention types, since surgical and endovascular therapies are known to be associated with similar risks of cardiac injury in patients with ASAH.[29] Finally, we used a survey to collect data after discharge, which can cause (non-) response bias. Although the response rate of the survey was reasonable (65%, see Table 4S in the Supplemental Material), myocardial infarction might be underreported in our study, possibly underestimating the effect estimates.

Conclusions

Patients with TnI elevation after occlusion of a ruptured intracranial aneurysm have a higher risk of MACE within one year than patients without TnI elevation. Although post-intervention troponin elevation was a predictor of these events, further research is required to explore the utility of troponin monitoring in directing secondary prevention in ASAH patients.

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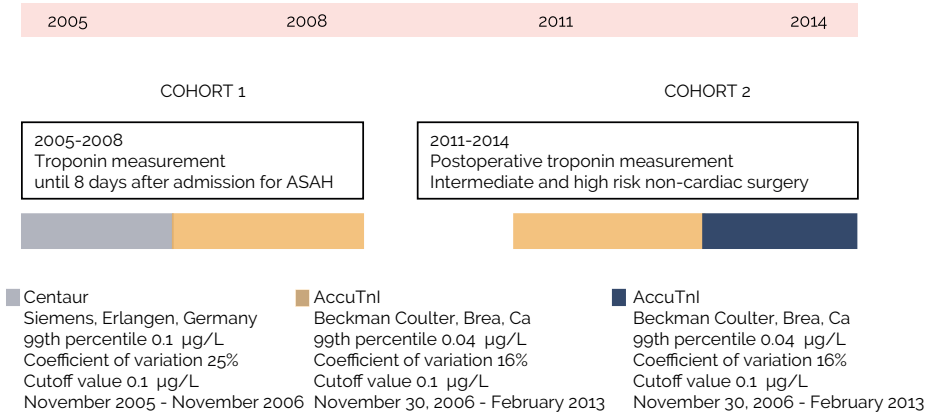
SUPPLEMENTAL MATERIAL



Supplemental Material: Figure 1S. Schematic representation of the used cohorts and troponin assays

ASAH: aneurysmal subarachnoid hemorrhage

Supplemental Material: Table 1S. Classifications

Classification	Description
GOS 1	Death
GOS 2	Persistent vegetative state
GOS 3	Severe disability
GOS 4	Moderate disability
GOS 5	Low disability
RCRI	To assess the risk of perioperative cardiac complications for non-cardiac surgery, each of the following six risk factors is assigned one point. 1. History of ischemic heart disease 2. History of congestive heart failure 3. History of cerebrovascular disease 4. History of insulin dependent diabetes mellitus 5. Pre-intervention serum creatinine >177 µmol/L (or >2mg/dL) 6. High-risk surgery (intrathoracic, intra-abdominal or supra-inguinal vascular surgery) Patients with none, one, or two risk factor(s) are assigned to class I, II or III respectively, with a corresponding risk of 0.4%, 1% and 7%. Patients with more than three point are assigned to class IV with a risk of 11%.
WFNS grade 1	GCS 15, no motor deficit
WFNS grade 2	GCS 13-14, no motor deficit
WFNS grade 3	GCS 13-14, with motor deficit
WFNS grade 4	GCS 7-12, with or without motor deficit
WFNS grade 5	GCS 3-6, with or without motor deficit
ASA I	Healthy, no smoking, minimal drinking
ASA II	Mild systemic disease, no substantive functional limitations
ASA III	Severe systemic disease with functional limitations
ASA IV	Severe systemic disease that is a constant threat to life
ASA V	Moribund patient who is not expected to survive without operation
ASA VI	Brain-dead patient

ASA: American Society of Anesthesiologists physical status. GOS: Glasgow Outcome Scale. RCRI: Revised Cardiac Risk Index. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage.

Supplemental Material: Table 2S. Overview of missing data

Variables	Missing per variable (%)*
Age, sex, intervention type, myocardial infarction, congestive heart failure, (insulin dependent) diabetes mellitus, central/peripheral artery disease, carotid artery disease, antihypertensive medication in general	0 (0.0)
Cerebrovascular disease, hypertension, arrhythmia; anticoagulants	1 (0.6)
Statins	6 (3.8)
β-blocking agents, calcium antagonist, RAAS inhibitor, diuretics	8 (5.0)
Mortality within one year	10 (6.3)
ASA class	12 (7.6)
WFNS on admission	14 (8.8)
Smoking	18 (11.3)
GOS score at three months	23 (14.47)
Post-intervention TnI measurement	30 (18.9)
Pre-intervention creatinine	35 (22.0)
Adverse cardiac event within one year	41 (25.8)
Weight	55 (34.6)
Pre-intervention TnI measurement	106 (66.7)
Total missing data (without pre-intervention TnI)	**280 (6.0)**
Total missing data (with pre-intervention TnI)	**386 (8.1)**

ASA: American Society of Anesthesiologists physical status. GOS: Glasgow outcome scale. RAAS: Renin-Angiotensin-Aldosterone-System. TnI: troponin I. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage. * E.g. one missing value for history of hypertension; also one missing value for use of anticoagulants.

Supplemental Material: Table 3S. Baseline characteristics per cohort

		Cohort 2005-2008	**Cohort 2011-2014**	**p-value**
		N = 92	N = 67	
Age (years, mean (sd))		58.0 (12.9)	67.8 (6.9)	<0.001*
Weight (kg, mean (sd))		73.3 (17.3)	71.3 (14.5)	0.121
Sex (%)	Male	19 (20.7)	14 (20.9)	1.000
WFNS on admission (%)	1	41 (44.6)	28 (41.8)	0.774
	2	25 (27.2)	15 (22.4)	
	3	5 (5.4)	5 (7.5)	
	4	13 (14.1)	14 (20.9)	
	5	8 (8.7)	5 (7.5)	
Intervention	Coiling	64 (69.6)	0 (0.0)	<0.001*
ASA class (%)	I	13 (14.1)	11 (16.4)	0.882
	II	65 (70.7)	45 (67.2)	
	III	14 (15.2)	11 (16.4)	
	IV-V	0 (0.0)	0 (0.0)	
RCRI factors				
Myocardial infarction (%)		6 (6.5)	2 (3.0)	0.469
Congestive heart failure (%)		0 (0.0)	0 (0.0)	NA
Cerebrovascular disease (%)		5 (5.4)	5 (7.5)	0.744
Insulin dependent diabetes mellitus (%)		1 (1.1)	0 (0.0)	1.000
Pre-intervention creatinine (median [IQR])		64.0 [56.0, 73.0]	62.0 [52.0, 76.0]	0.891
Other comorbidities				
Hypertension (%)		24 (26.1)	22 (32.8)	0.454
Diabetes mellitus (%)		4 (4.3)	2 (3.0)	1.000
Arrhythmia (%)		3 (3.3)	2 (3.0)	1.000
Central artery disease (%)		1 (1.1)	2 (3.0)	0.573
Peripheral artery disease (%)		4 (4.3)	4 (6.0)	0.722
Carotid artery disease (%)		1 (1.1)	2 (3.0)	0.573
Smoking (%)	Stopped	7 (7.6)	13 (19.4)	0.006*
	Currently	52 (56.5)	22 (32.8)	

Supplemental Material: Table 3S. Continued

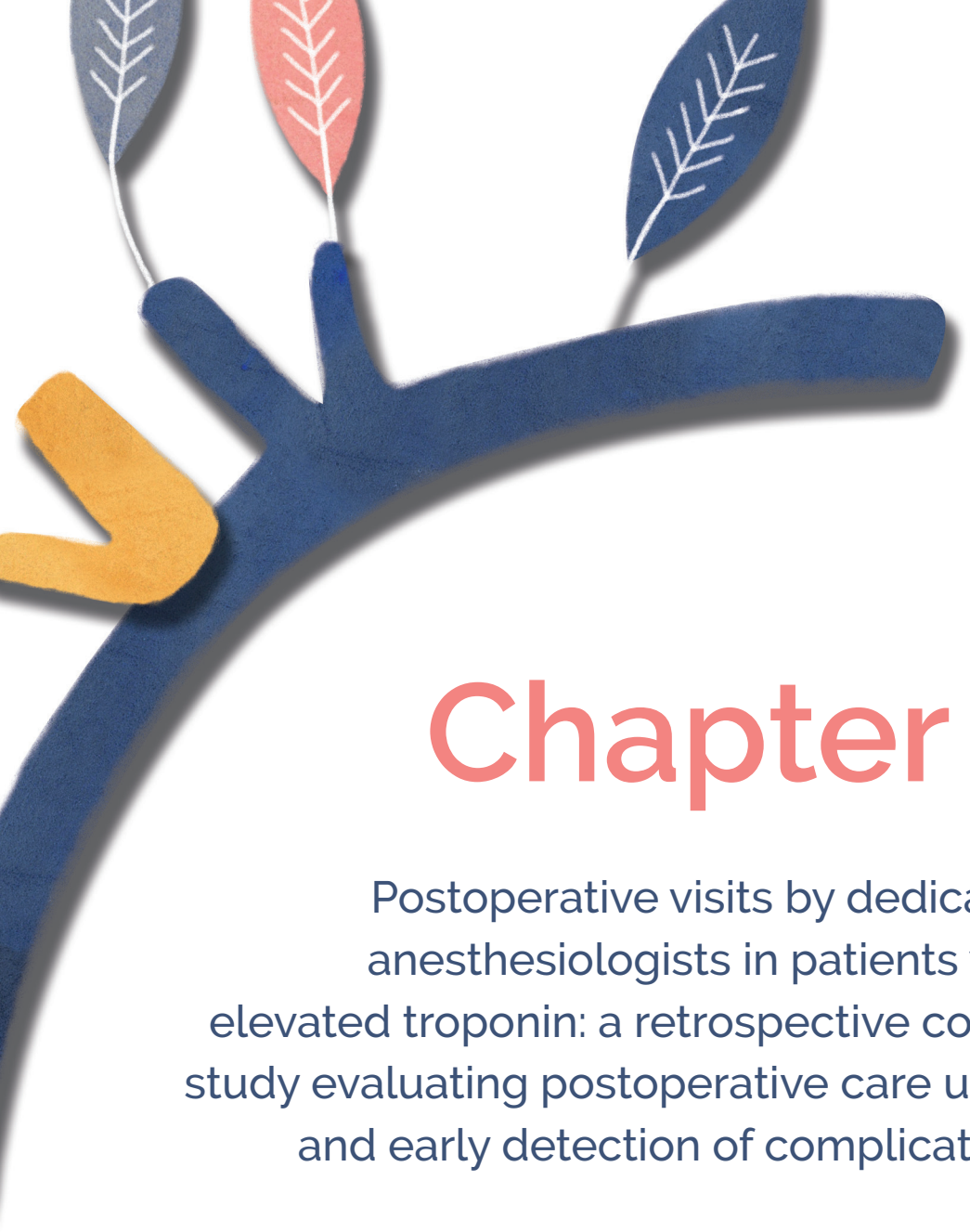
		Cohort 2005-2008	Cohort 2011-2014	p-value
		N = 92	N = 67	
Medication use prior to admission				
Anticoagulants (%)	Coumarin derivate	2 (2.2)	2 (3.0)	0.966
	Acetylsalicylic acid	10 (10.9)	8 (11.9)	
	Multiple anticoagulants	1 (1.1)	1 (1.5)	
Statins (%)		11 (12.0)	9 (13.4)	0.972
Antihypertensive medication (%)		26 (28.3)	24 (35.8)	0.400
	β-blocking agents	9 (9.8)	11 (16.4)	0.316
	Calcium antagonist	9 (9.8)	7 (10.4)	1.000
	RAAS inhibitor	16 (17.4)	14 (20.9)	0.725
	Diuretics	10 (10.9)	6 (9.0)	0.897

ASA: American Society of Anesthesiologists physical status. IQR: interquartile range. NA: not applicable. RAAS: Renin-Angiotensin-Aldosterone-System. RCRI: Revised Cardiac Risk Index. Sd: standard deviation. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage. * Significant difference

Supplemental Material: Table 4S. Survey results at one year after an aneurysmal subarachnoid hemorrhage

Disease symptoms (self-reported, within last year)*	**N = 2,271**
Admission for any heart disease (%)	42 (1.85)
Cardiac complaints for which a general practitioner was visited (%)	44 (1.93)
Ischemic heart disease (Myocardial infarction, revascularization, cardiac arrest) (%)	12 (0.53)
Angina pectoris (%)	3 (0.13)

* Overall response rate: 65.4% (2,271/3,473)



Chapter 7

Postoperative visits by dedicated anesthesiologists in patients with elevated troponin: a retrospective cohort study evaluating postoperative care utility and early detection of complications

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ABSTRACT

Background An elevated cardiac troponin level after non-cardiac surgery is associated with both morbidity and mortality. Guidelines suggest routine troponin monitoring in high-risk patients. We implemented a dedicated anesthesia team to conduct follow-up in patients with postoperative troponin elevation. We hypothesized that these visits would facilitate early detection of complications. Therefore, the aim of this study was to evaluate the effect of postoperative visits by dedicated anesthesiologists on early detection of complications and care utility.

Methods This retrospective observational study included patients aged ≥60 years with an elevated troponin within the first three days after non-cardiac surgery. Troponin elevation was detected by routine biomarker monitoring. The primary outcome was early detected myocardial infarction by the dedicated anesthesiologist. Other outcomes were overall detected complications, additional diagnostic tests and treatment advised by the anesthesiologist, consultation of another medical specialist, and advised postoperative follow-up at the outpatient cardiac clinic, all within one week after surgery.

Results Of the 811 patients, 509 (63%) received a postoperative consultation by the anesthesiologist. Anesthesiologists were involved in the early detection of 59% of all myocardial infarctions and in 12% of all complications within one week after surgery. Besides cardiac ischemia, patients were also often diagnosed with non-cardiac complications, including respiratory failure (8.9%), pneumonia (13.2%) and acute kidney injury (17.5%). In 75% of patients, anesthesiologists ordered additional diagnostics, most frequently existing of electrocardiograms and additional cardiac enzyme testing. Additionally, change in treatment was advised, most often a medication change, in 16% of patients.

Conclusions Standard consultation of a dedicated anesthesiologist resulted in an early detection of 59% of all myocardial infarctions and involved a change in treatment in a considerable number of patients with postoperative troponin elevation. Whether this may improve patient outcomes remains to be elucidated.

INTRODUCTION

An increased serum cardiac troponin level, as a marker for postoperative myocardial injury, has been shown to be an independent predictor of morbidity and mortality within the first year after non-cardiac surgery.[1–4] Depending on the amount of troponin elevation and the surgical population, the incidence of mortality within 30 days varies between 4% and 17%.[2,3,5] As only 15% of patients with postoperative myocardial injury experiences typical ischemic symptoms,[6] routine postoperative troponin surveillance is recommended by several guidelines for postoperative risk stratification to direct secondary prevention.[7,8]

In our center, we implemented a routine postoperative troponin I (TnI) surveillance program in January 2011. In a previous study in which this program was evaluated, it became apparent that only 41% of all patients with postoperative myocardial injury received cardiac consultation.[4] Cardiac etiology was suspected in almost half of the consulted patients. However, troponin elevation has also been related to other disease entities including stroke, sepsis and pulmonary embolism.[4,9–11] We hypothesized that a more general approach to assess postoperative troponin elevation, rather than an approach focusing on cardiac etiology, would be beneficial. As a result, in October 2016 we implemented routine postoperative consultations by a dedicated anesthesia team in patients detected with an elevated troponin in the surveillance program. The goal of these visits was to improve postoperative follow-up and to potentially detect or prevent complications at an early stage. We hypothesized that such routine visits would facilitate early detection of complications with only a limited use of resources. Therefore, this study aimed to evaluate the effect of these visits by dedicated anesthesiologists on early detection of complications and postoperative care utility in patients with troponin elevation after non-cardiac surgery.

METHODS

This study was conducted in adherence to the STROBE statement for observational research.[12] The local Research Ethics Committee assessed the study protocol and waived the need for informed consent (UMC Utrecht Medical Research Ethics Committee 19-029/C).

Patients

This retrospective observational study included patients aged ≥60 years with postoperative elevated troponin levels as detected by routine troponin monitoring within the first three days after non-cardiac surgery between January 1, 2017 and

December 31, 2018 at the University Medical Center Utrecht, a tertiary referral hospital. Patients admitted immediately after the procedure at the Intensive Care Unit (ICU) or the Cardiac Care Unit (CCU) for more than two days were not visited by the dedicated anesthesiologists and were therefore excluded from the analysis, because follow-up in these patients was conducted by intensivists or cardiologists as part of our local protocol. Patients who died within 24 hours or in whom further therapy was withheld directly after surgery were also excluded. Patients, who underwent surgery more than once within the study period, were included as a new case. However, in case the procedure was performed within three days after the previous procedure, only the first procedure was included in the analysis.

Postoperative care

According to our local postoperative care protocol, cardiac troponin I (TnI) is measured in all non-cardiac surgical patients aged ≥60 years once daily on the first three postoperative days during hospital admission. This protocol excludes ophthalmic and plastic surgery patients because of low risk of cardiac complications. Troponin elevation was defined as TnI above the clinical cut-off level, which is the lowest value measurable with a 10% coefficient of variation above the 99th percentile upper reference limit.[7] Two different TnI assays were used over the years. This resulted in a clinical cut-off of TnI ≥60 ng/L (AccuTnI assay, Beckman Coulter, Brea, California, USA) from January 1st, 2017 until May 16th, 2018 and a clinical cut-off of high-sensitive TnI ≥18 ng/L (Unicel DxI 800, Beckman Coulter, Brea, California, USA) from May 17, 2018 until December 31, 2018.

Patients with elevated TnI were consulted within the first three postoperative days, and longer if indicated. Management of these patients was left to the judgement of the attending anesthesiologist, which was based on a local protocol. This protocol advises to optimize myocardial oxygen supply and demand, and to conduct follow-up of troponin and an electrocardiogram (ECG) in patients with TnI >120 ng/L in case of no evident non-ischemic cause (e.g. sepsis, stress induced cardiomyopathy) to rule out myocardial ischemia. This cut-off was based on two times the clinical cut-off of the assay used at that moment. Further, this protocol advises to consider consultation of a cardiologist, follow-up at the outpatient cardiac clinic, and prescription of antiplatelet therapy, a statin or beta-blockade. In patients with troponin >600 ng/L, i.e. more than ten times the clinical cut-off, a cardiology consultation is always recommended. Patients with mild troponin elevation were, per protocol, frequently not visited physically by the anesthesiologist because of a low risk of serious complications, but were only followed up by TnI and ECG. A team of ten dedicated anesthesiologists with a particular interest in perioperative medicine were educated on the protocol.

Data collection

All data were collected from electronic medical files. These data included patient characteristics, comorbidities, Revised Cardiac Risk Index (RCRI),[13] American Society of Anesthesiologists (ASA) physical status,[14] Metabolic Equivalent Task score (METs),[15] and surgical risk as defined by the RCRI,[13] and by the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA).[15] Additionally, data on visits by the dedicated anesthesiologist, diagnostics, in-hospital postoperative complications, severity of complications according to the Clavien-Dindo classification,[16,17] and in-hospital mortality were collected.

Outcome

The primary outcome was early detected (i.e. ≤ 7 days after surgery) myocardial infarction as a result of consultation by the dedicated anesthesiologist. Myocardial infarction was defined as clinically diagnosed by the attending cardiologist. Secondary outcomes were overall detected complications, additional diagnostic tests advised by the dedicated anesthesiologist, treatment advised by the anesthesiologist, consultation of another medical specialist, and advised postoperative follow-up at the outpatient cardiac clinic. Potentially, a cardiologist could already have been consulted by the ward physician in patients with an elevated troponin or other cardiac complications, as the ward physicians were aware of the protocol. Therefore, we also recorded whether a cardiologist was consulted prior to or simultaneously with the visit by the dedicated anesthesiologists.

In addition to myocardial infarction, we assessed the occurrence of the following complications within seven days after the procedure: arrhythmia diagnosed on 12-leads ECG or cardiac monitor, cardiopulmonary resuscitation, cerebrovascular accident (defined as radiologically-confirmed ischemic or hemorrhagic stroke or transient ischemic attack), radiologically-confirmed deep venous thrombosis and pulmonary embolism, sepsis as clinically diagnosed by the treating physician, pneumonia requiring antibiotics, respiratory failure requiring MCU (Medium Care Unit) or ICU admission, acute kidney injury (AKI) defined as an increase in creatinine of 26.4 mmol/L or 25% from the preoperative creatinine value,[17] anemia defined as hemoglobin <6.0 mmol/L (10 g/dL, according to the Dutch guideline on blood transfusion),[18] unexpected MCU or ICU admission, and unplanned re-operations. Additionally, length of hospital stay, mortality within seven days and the cause of death were assessed. Last, the Clavien-Dindo grade of the most severe complication within a week after surgery was recorded. A severe complication was defined as a Clavien-Dindo grade ≥3 as this involves complications requiring a surgical, endoscopic or radiologic intervention, life threatening complications requiring care in a high-dependency unit or ICU, or death. [16,17] Additionally, we assessed the final suspected etiology of the elevated troponin as proposed by the dedicated anesthesiologist.

Statistical analysis

Baseline characteristics were compared dependent on the amount of troponin elevation (i.e. TnI 18-119 ng/L, TnI 120-599 ng/L and TnI ≥ 600 ng/L). These thresholds were chosen based on the thresholds as defined in our local protocol. The contribution of the dedicated anesthesiologist on the early detection of complications was assessed relative to the total number of complications. In addition, complications by their severity, length of stay, unexpected ICU or MCU admission and death were assessed. The consultation rates by the dedicated anesthesiologists were evaluated, as were the number of ordered diagnostics, consulted medical specialties and advised therapies. In order to determine whether care utility and complications were dependent on the height of troponin elevation, these were evaluated in subgroups of patients with different levels of troponin (i.e. TnI 18-119 ng/L, TnI 120-599 ng/L and TnI ≥ 600 ng/L).

Hemoglobin and creatinine measurements were missing in 103 and 204 patients, respectively. Since these variables were only used for descriptive statistics, we did not consider this an important source of bias and we did not impute the data. The statistical analyses were performed with R (Version 3.5.1 – © 2018-07-02, R, Inc., for Windows).[19]

RESULTS

Within the study period, 8,924 patients underwent non-cardiac surgery of whom 1,007 patients (11.2 %) had troponin elevation. Of these patients, 811 were eligible for inclusion (Figure 1). Reason of exclusion was most often ICU admission for >2 days (n=122). Troponin was mildly elevated, i.e. 18-119 ng/L in 543 patients (67%), moderately elevated, i.e. 120-600 ng/L in 192 patients (24%) and highly elevated, i.e. ≥ 600 ng/L in 77 patients (9%).

Baseline characteristics are reported in Table 1. The median age was 74 years [IQR 68-80] and 62% of the patients were males. Most patients underwent general (28%) or vascular (24%) surgery and surgery was emergent in 40% of the patients. There were more patients with a history of ischemic heart disease and peripheral vascular disease in the group with highly elevated troponin compared to the other two categories.

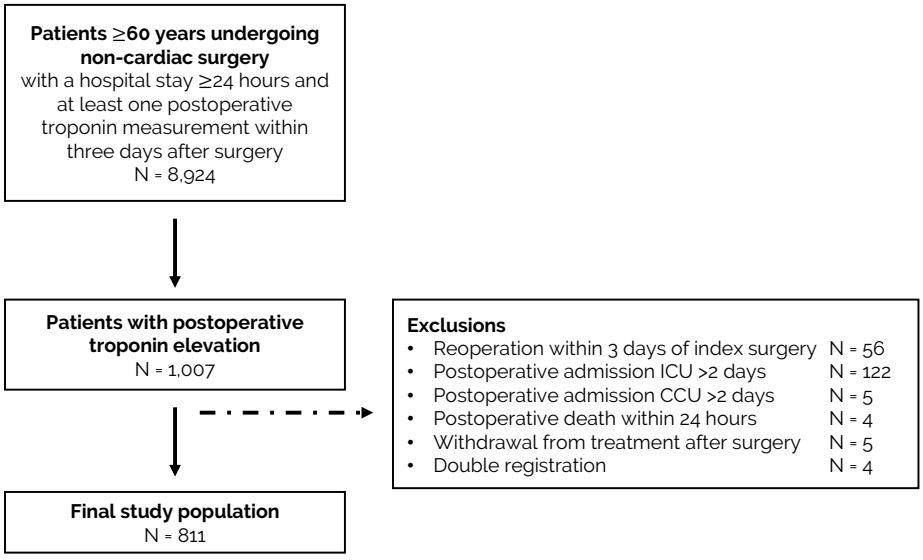

Figure 1. Flow chart of patient inclusion

ICU: Intensive Care Unit. CCU: Cardiac Care Unit.

Postoperative outcomes

A total of 804 complications occurred in 462 patients within seven days after surgery (Table 2). The involvement of the dedicated anesthesiologist led to the diagnosis of 97 (12%) of these complications in 63 patients (14%). Postoperative complications were identified by the anesthesiologist in 18 patients (5%) with a TnI 18-119 ng/L, 21 patients (13%) with a TnI 120-599 ng/L and 24 patients (33%) with a TnI ≥ 600 ng/L. The anesthesiologists were involved in the discovery of 19 (59%) of 32 postoperative myocardial infarctions within one week after surgery. Besides cardiac ischemia, 76 (9.4%) patients developed an arrhythmia, but patients were also often diagnosed with non-cardiac complications, including respiratory failure (8.9%), pneumonia (13.2%) and AKI (17.5%). Patients with higher troponin levels suffered from more complications, had more often an unexpected ICU or MCU admission and had a longer median hospital length of stay. Ten patients (1%) died in the first week after surgery and 251 patients (31%) had a complication graded as Clavien-Dindo ≥ 3 (Table 2).

Table 1. Baseline characteristics dependent on the height of troponin elevation

		Overall	TnI 18-119 ng/L	TnI 120-599 ng/L	TnI ≥ 600 ng/L
		N = 811	N = 543	N = 192	N = 76
Age (years median [IQR])		74 [68-80]	74 [68-80]	74 [68-79]	73 [69-79]
Sex (%)	Male	505 (62.3)	341 (62.8)	115 (59.9)	49 (64.5)
RCRI score (%)	0	196 (24.2)	141 (26.0)	45 (23.4)	10 (13.2)
	1	320 (39.5)	215 (39.6)	77 (40.1)	28 (36.8)
	2	191(23.6)	120 (22.1)	45 (23.4)	26 (34.2)
	≥3	104 (12.8)	67 (12.3)	25 (13.0)	12 (15.8)
High-risk surgery (defined by RCRI) (%)		314 (38.7)	195 (35.9)	82 (42.7)	37 (48.7)
High-risk surgery (defined by ESC/ESA) (%)		124 (15.3)	77 (14.2)	35 (18.2)	12 (15.8)
History of ischemic heart disease (%)		235 (29.0)	145 (26.7)	58 (30.2)	32 (42.1)
History of congestive heart failure (%)		84 (10.4)	60 (11.0)	19 (9.9)	5 (6.6)
History of cerebrovascular disease (%)		201 (24.8)	132 (24.3)	48 (25.0)	21 (27.6)
Insulin dependent diabetes mellitus (%)		109 (13.4)	74 (13.6)	24 (12.5)	11 (14.5)
Preoperative creatinine >177 mmol/L (%)		113 (13.9)	83 (15.3)	18 (9.4)	12 (15.8)
Arrhythmia (%)		185 (22.8)	136 (25.0)	42 (21.9)	7 (9.2)
ICD or pacemaker (%)		65 (8.0)	53 (9.8)	10 (5.2)	2 (2.6)
Valvular disease (%)		113 (13.9)	82 (15.1)	23 (12.0)	8 (10.5)
Peripheral vascular disease (%)		241 (29.7)	140 (25.8)	66 (34.4)	35 (46.1)
Hypertension (%)		516 (63.6)	347 (63.9)	119 (62.0)	50 (65.8)
Pulmonary disease (%)		210 (25.9)	142 (26.2)	54 (28.1)	14 (18.4)
Active malignancy (%)		255 (31.4)	172 (31.7)	60 (31.2)	23 (30.3)
Renal failure (%)		282 (34.8)	194 (35.7)	58 (30.2)	30 (39.5)
Diabetes mellitus (insulin/not) (%)		189 (23.3)	129 (23.8)	41 (21.4)	19 (25.0)
ASA class (%)	I	4 (0.5)	3 (0.6)	0 (0.0)	1 (1.3)
	II	229 (28.2)	161 (29.7)	53 (27.6)	15 (19.7)
	III	481 (59.3)	319 (58.7)	112 (58.3)	50 (65.8)
	IV	88 (10.9)	55 (10.1)	25 (13.0)	8 (10.5)
	V	9 (1.1)	5 (0.9)	2 (1.0)	2 (2.6)
METs (%)	1-3	224 (27.6)	162 (29.8)	42 (21.9)	20 (26.3)
	4-7	373 (46.0)	263 (48.4)	79 (41.1)	31 (40.8)
	8-10	21 (2.6)	10 (1.8)	9 (4.7)	2 (2.6)
	Unknown	193 (23.8)	108 (19.9)	62 (32.3)	23 (30.3)

Table 1. Continued

		Overall	TnI 18-119 ng/L	TnI 120-599 ng/L	TnI ≥ 600 ng/L
		N = 811	N = 543	N = 192	N = 76
Emergency surgery (%)		328 (40.4)	213 (39.2)	83 (43.2)	32 (42.1)
Surgical specialty (%)	General	223 (27.5)	149 (27.4)	58 (30.2)	16 (21.1)
	Gynecological	25 (3.1)	18 (3.3)	5 (2.6)	2 (2.6)
	Head and Neck	78 (9.6)	54 (9.9)	15 (7.8)	9 (11.8)
	Neurological	133 (16.4)	94 (17.3)	28 (14.6)	11 (14.5)
	Orthopedic	104 (12.8)	71 (13.1)	26 (13.5)	7 (9.2)
	Urological	57 (7.0)	42 (7.7)	9 (4.7)	6 (7.9)
	Vascular	191 (23.6)	115 (21.2)	51 (26.6)	25 (32.9)
Locoregional & neuraxial anesthesia (%)		62 (7.6)	45 (8.3)	13 (6.8)	4 (5.3)

ASA: American Society of Anesthesiologists physical status. ESA: European Society of Anaesthesiology. ESC: European Society of Cardiology. ICD: implantable cardioverter defibrillator. IQR: interquartile range. METs: Metabolic Equivalent of Task score. RCRI: Revised Cardiac Risk Index. TnI: troponin I. Troponin thresholds were chosen based on the thresholds as defined in the local protocol of the University Medical Center Utrecht (TnI 18-119 ng/L, TnI 120-599 ng/L and TnI ≥ 600 ng/L). Ischemic heart disease was defined as a history of myocardial infarction or previous revascularization and a history of congestive heart failure was defined as an estimated left ventricular ejection fraction <40%. Cerebrovascular disease was defined as a history of ischemic stroke, hemorrhagic stroke or transient ischemic attack. Renal failure was defined as a glomerular filtration rate (GFR) <60 ml/min in the last three months).

Table 2. Postoperative outcomes dependent on the height of troponin elevation

	TnI 18-119 ng/L		**TnI 120-599 ng/L**		**TnI ≥ 600 ng/L**	
	N = 543		N = 192		N = 76	
Complications ≤ 7 days	*Total*	*By POA ǂ*	*Total*	*By POA ǂ*	*Total*	*By POA ǂ*
Myocardial infarction (%)	1 (0.2)	1 (0.2)	8 (4.2)	2 (1.0)	23 (30.3)	16 (21.1)
Arrhythmia (%)	46 (8.5)	3 (0.6)	22 (11.5)	0 (0.0)	9 (11.8)	3 (3.9)
CPR (%)	0 (0.0)	0 (0.0)	2 (1.0)	0 (0.0)	2 (2.6)	0 (0.0)
Cerebrovascular accident (%)	9 (1.7)	0 (0.0)	2 (1.0)	0 (0.0)	3 (3.9)	0 (0.0)
Deep venous thrombosis (%)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism (%)	10 (1.8)	0 (0.0)	5 (2.6)	0 (0.0)	3 (3.9)	1 (1.3)
Sepsis (%)	20 (3.7)	0 (0.0)	8 (4.2)	1 (0.5)	5 (6.6)	1 (1.3)
Pneumonia (%)	61 (11.2)	6 (1.1)	31 (16.1)	0 (0.0)	15 (19.7)	2 (2.6)
Respiratory failure (%)	33 (6.1)	1 (0.2)	25 (13.0)	6 (3.1)	14 (18.4)	1 (1.3)
Acute kidney injury *(%)	59 (15.1)	1 (0.0)	33 (21.7)	0 (0.0)	14 (22.2)	4 (14.8)
Anemia ǂ (%)	198 (36.5)	6 (6.6)	87 (45.3)	28 (14.6)	42 (55.3)	14 (18.4)
Clavien-Dindo Classification (%)						
Grade 1	73 (13.4)		16 (8.3)		5 (6.6)	
Grade 2	206 (37.9)		67 (34.9)		25 (32.9)	
Grade 3a	11 (2.0)		10 (5.2)		1 (1.3)	
Grade 3b	26 (4.8)		9 (4.7)		2 (2.6)	
Grade 4a	74 (13.6)		47 (24.5)		27 (35.5)	
Grade 4b	19 (3.5)		7 (3.6)		8 (10.5)	
Grade 5	5 (0.9)		4 (2.1)		1 (1.3)	
No complications	129 (23.8)		32 (16.7)		7 (9.2)	
Unexpected ICU admission (%)	21 (3.9)		13 (6.8)		11 (14.5)	
Unexpected MCU admission (%)	91 (16.8)		5 (28.6)		33 (43.4)	
Re-operation (%)	50 (9.2)		19 (9.9)		8 (10.5)	
Length of stay (median [IQR])	7 [4-15]		9 [5-16]		11 [6-16]	
Mortality within one week (%)	5 (0.9)		4 (2.1)		1 (1.3)	

CPR: cardiopulmonary resuscitation. ICU; Intensive Care Unit. IQR; interquartile range. MCU; medium care unit. POA: perioperative anesthesiologist. TnI: troponin I. Troponin thresholds were chosen based on the thresholds as defined in the local protocol of the University Medical Center Utrecht (TnI 18-119 ng/L , TnI 120-599 ng/L and TnI ≥ 600 ng/L). * Acute kidney injury (AKI) was calculated using the KDIGO criteria. AKI was based on 607 patients as no pre- and/or postoperative creatinine was available in 204 patients (25%). ǂ Anemia was defined as a hemoglobin <6.0 mmol/L (10 g/dL), which is based on 708 patients as hemoglobin was not measured in 103 patients (13%). ǂ Early detection of complications (within three days) through contribution of the dedicated team of anesthesiologists (POA).

Postoperative consultation

A total of 509 patients (63%) received consultation by a dedicated anesthesiologist (Table 3). In 35 patients (7%), the anesthesiologists provided advice as recorded in the electronic medical file, without an actual physical visit. In patients who experienced at least one complication (n=462), 161 patients (35%) were not visited by the dedicated anesthesiologist, in 18 patients (4%) only advice was provided without an actual physical visit by the anesthesiologist, 60 patients (13%) were visited once and 99 patients (21%) were visited more than once. In 124 of 509 patients (24%), the cardiologist was already involved in patient care prior to or simultaneously with the dedicated anesthesiologist and the cardiologist was consulted by the dedicated anesthesiologist in 155 patients (30%). In total, 187 of 811 patients (23%) were referred to the cardiac outpatient clinic for further follow-up after discharge.

There were more consultations by the dedicated anesthesiologists in patients with TnI ≥ 600 ng/L compared with the other two categories. In addition, a cardiologist was more frequently consulted (67% vs. 34% and 7% for patients with TnI ≥ 600 ng/L vs. TnI 120-599 ng/L and TnI 18-120 ng/L, respectively) or already involved (28% vs. 24% and 11%, respectively) (Table 3).

Additional diagnostics were ordered by the anesthesiologist in 381 patients (75%). An ECG was most frequently ordered (73%), followed by additional troponin (34%) and other cardiac enzymes (20%). A change in treatment (i.e. a change in medication or red blood cell transfusion) was initiated by the anesthesiologist in 131 patients (16%), with 48 patients receiving blood products (6%). There were more diagnostic tests ordered and treatments initiated by the dedicated anesthesiologist in patients with higher troponin levels (Table 3).

In 449 patients (55%), no clear cause of the troponin elevation was identified (Table 3). In 22% of patients it was considered to be caused by unstable perioperative hemodynamics, including hypotension and tachycardia, followed by ischemic heart disease (9%) and AKI (7%).

Table 3. Consultations, interventions and causes of troponin elevation assigned by the dedicated anesthesiologist, dependent on the height of troponin elevation.

	TnI 18-119 ng/L	**TnI 120-599 ng/L**	**TnI ≥ 600 ng/L**
	N = 543	N = 192	N = 76
Consultation (%)			
No visit, advice only	28 (5.2)	4 (2.1)	3 (3.9)
Only 1-time visit	186 (34.3)	90 (46.9)	39 (51.3)
>1 visit	88 (16.2)	49 (25.5)	22 (28.9)
Any diagnostics ordered (%)	207 (38.1)	126 (65.6)	48 (63.2)
ECG	201 (37.0)	120 (62.5)	47 (61.8)
Echocardiography	3 (0.6)	19 (9.9)	26 (34.2)
CT angiography	2 (0.4)	3 (1.6)	4 (5.3)
Additional troponin	76 (14.0)	61 (31.8)	38 (50.0)
Other enzymes (i.e. CK-MB)	23 (4.2)	43 (22.4)	36 (47.4)
Other specialty consulted (%)			
Cardiology	39 (7.2)	65 (33.9)	51 (67.1)
Pulmonology	5 (0.9)	2 (1.0)	0 (0.0)
Other *	6 (1.1)	2 (1.0)	0 (0.0)
Cardiology already involved (%)	57 (10.5)	46 (24.0)	21 (27.6)
Any change in treatment (%)	55 (10.1)	47 (24.5)	29 (38.2)
Change in medication	24 (4.4)	26 (13.5)	24 (31.6)
Red blood cell transfusion	6 (6.6)	28 (14.6)	14 (18.4)
Follow up at outpatient cardiac clinic (%)	73 (13.4)	64 (33.3)	50 (65.8)

ECG; electrocardiogram. CT; computed tomography. CK-MB; creatine-kinase isoenzyme. MCU: Medium Care Unit. PACU: Post Anesthesia Care Unit. TnI: troponin I. Troponin thresholds were chosen based on the thresholds as defined in the local protocol of the University Medical Center Utrecht (TnI 18-119 ng/L, TnI 120-599 ng/L and TnI ≥ 600 ng/L).* Including nephrologist, hematologist, cardiothoracic surgeon and geriatrician. ǂ Including hypotension and tachycardia. ǂ Including pericarditis, myocardial contusion, neurological conditions (e.g. subarachnoid hemorrhage) and fever.

Table 3. Continued

	TnI 18-119 ng/L	**TnI 120-599 ng/L**	**TnI ≥ 600 ng/L**
	N = 543	N = 192	N = 76
Cause of myocardial injury (%)			
Ischemic heart disease	6 (1.1)	12 (6.2)	28 (36.8)
Arrhythmia	22 (4.1)	8 (4.2)	0 (0.0)
Congestive heart failure	6 (1.1)	2 (1.0)	3 (3.9)
Pulmonary embolism	4 (0.7)	1 (0.5)	2 (2.6)
Pneumonia	7 (1.3)	4 (2.1)	0 (0.0)
Respiratory failure	11 (2.0)	9 (4.7)	1 (1.3)
Sepsis	9 (1.7)	6 (3.1)	2 (2.6)
Acute kidney injury	31 (5.7)	6 (3.1)	0 (0.0)
Anemia	15 (2.8)	8 (4.2)	4 (5.3)
Fluid overload	4 (0.7)	4 (2.1)	0 (0.0)
Hypertension	6 (1.1)	3 (1.6)	0 (0.0)
Perioperative hemodynamics ǂ	66 (12.2)	37 (19.3)	9 (11.8)
Other ǂ	15 (2.8)	8 (4.2)	3 (3.9)
Cause unknown	341 (62.8)	84 (43.8)	24 (31.6)

DISCUSSION

This study evaluated the contribution of follow-up by dedicated anesthesiologists on postoperative care utility and early detection of complications in patients with elevated troponin after non-cardiac surgery. The anesthesiologists were primarily responsible for the early detection of 12% of all postoperative complications within one week after surgery, with an especially large contribution (59%) to detection of myocardial infarctions.

Literature

The current study found that routine postoperative troponin surveillance, supported by routine postoperative consultations by a dedicated anesthesiologist can be used to detect postoperative complications at an early stage. Increasing rates of both cardiovascular, i.e. myocardial infarction and pulmonary embolism, and non-cardiac complications, i.e. sepsis, respiratory failure, renal failure and anemia, were found in patients with elevated troponin in a dose-dependent manner. Substantially more patients with postoperative troponin elevation were consulted after implementation of a dedicated anesthesia team to conduct these visits (41% were consulted by cardiologists in the study by Van Waes et al.[4] versus 63% in the current study). Around 15% of patients with elevated troponin received a change in medication, which is in accordance with a previous study.[4] Six percent received red blood cell transfusion after involvement of the dedicated anesthesiologist, aiming at a hemoglobin level >6 mmol/L (10g/dL). Interestingly, a previous study found that the cardiologist only advised red blood cell transfusion in 2% of patients with postoperative troponin elevation.[4]

Clinical implications

Prediction of the risk of postoperative complications has been shown to be difficult using only preoperative parameters.[20] Although preoperative patient optimization and planning of perioperative care might have a larger effect on clinical outcome and costs than postoperative visits by trained anesthesiologist solely,[21] we do believe there may be an additive beneficial effect provided by these visits. Ideally, one might argue that anesthesiologists should consult all patients receiving intermediate or high-risk surgery, but resources are scarce. By identifying patients at risk not only before surgery, but again in the postoperative phase using additional data, resources can be directed towards where needed most. Troponin surveillance may be an efficient manner to conduct this postoperative selection.[3,4,22] Therefore, we focused on patients with elevated troponins to select those at risk of postoperative complications and to first determine the effect of this intervention, before unrolling it to a broader patient population.

The present study found that follow-up by dedicated anesthesiologists enabled early detection of 12% of all complications and 59% of all postoperative myocardial infarctions within one week after surgery. The experience of anesthesiologists with procedure-related complications in addition to their knowledge of the cardiopulmonary and central nervous system can provide a valuable contribution to postoperative care by surgeons and care by cardiologists in case of postoperative troponin elevation. In our institution, the resources needed for a dedicated team of anesthesiologists conducting postoperative visits in this group of patients are low. One dedicated anesthesiologist on call spends on average one hour per day on screening and follow-up of patients with postoperative troponin elevation. In case of any emergent complications caught by this anesthesiologist, additional time is needed for extra diagnostics, consultation of other medical specialties and follow-up. The remaining time is spent on clinical tasks at the outpatient clinic not evaluated in this study, such as preoperative assessment of patients and multidisciplinary meetings. In our center, no extra personnel needed to be employed to implement this program. In addition, a cardiologist was consulted in only 30% of patients instead of 41% as reported previously.[4] Although additional diagnostic procedures were performed, these were mostly low-cost such as an ECG, while the number of patients in whom a complication was diagnosed and medical treatment was changed, was substantial. Importantly, in a majority of the patients (55%) a clear cause of troponin elevation could not be identified. Therefore, treatment options are often limited. Prospective studies are necessary to further determine the potential effect of postoperative visits by dedicated anesthesiologists on patient outcome.

Strengths and limitations

To the best of our knowledge, this is the first study reporting on the effect of postoperative anesthesia visits on resource utility and detection of postoperative complications in patients with postoperative troponin elevation. It was conducted in the non-cardiac surgery population, making these results generalizable to a large group of patients.

This study has some important limitations. First, because of the retrospective design of the study and the limited number of patients, we were unable to estimate whether the implementation of routine postoperative anesthesia visits resulted in better patient outcomes. Second, two different troponin assays, i.e. normal TnI and the highly sensitive TnI, were used during the inclusion period. As the second assay is more sensitive, this might have resulted in a higher incidence of troponin elevation. However, there were no differences in preoperative characteristics, but we did find more myocardial infarctions in the period the normal TnI assay was used together with more cardiology consultations, extra ordered diagnostics and change in medication. Third, many patients were referred to the cardiac outpatient clinic for further follow-up, but often this was conducted in

other institutions, since the UMC Utrecht is a tertiary referral hospital. This hampered our ability to track down diagnostics and interventions instituted during these follow-up visits. Fourth, there were some missing values for creatinine and hemoglobin. Incidence rates of postoperative anemia and AKI are probably overestimated as their markers were mostly missing in healthier patients. Fifth, because myocardial infarction was defined as a clinical diagnosis made by a cardiologist, the incidence of myocardial infarction may have been higher when it retrospectively would have been based on the 4th universal definition,[7] as previously shown.[4,6,9] Finally, only documented consultations by the anesthesiologist were recorded as consultation, which potentially explains why 37% of the patients did not receive a consultation. As part of the local protocol, anesthesiologists determined whether consultation was necessary based on clinical course reported in the electronic medical files and consultation of treating physicians by phone. We presume that in patients with elevated but low troponin levels (especially with TnI 19-120 ng/L), an ECG was remotely assessed by the anesthesiologist and discussed with the treating physician. In case of no abnormalities nothing was documented in the electronical medical files, although in fact remote consultation did occur.

Conclusion

Implementation of routine postoperative consultations by dedicated anesthesiologists resulted in early detection and treatment of complications in patients with postoperative elevated troponin levels.

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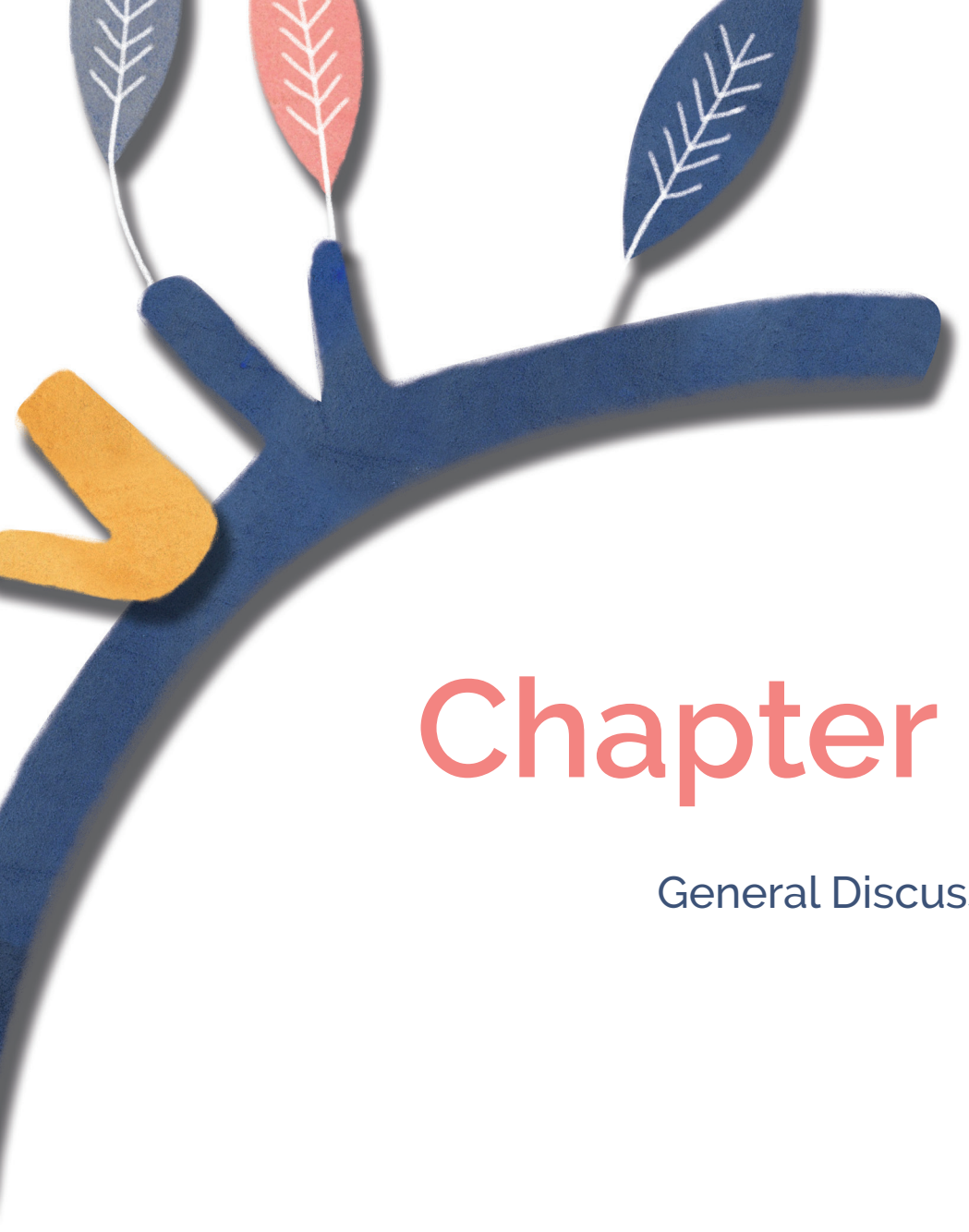
Part IV

Discussion and summary



Chapter 8

General Discussion

GENERAL DISCUSSION

Patients with cerebrovascular diseases such as an aneurysmal subarachnoid hemorrhage (ASAH) or moyamoya disease often require anesthetic care to facilitate procedures such as neurosurgical clipping, endovascular coiling or cerebral bypass surgery. Unfortunately, these patients are susceptible to perioperative neurological complications such as cerebral ischemia[1–3] and cardiopulmonary complications such as pneumonia and myocardial ischemia.[4,5] Anesthesiologists can potentially help to reduce the risk of these complications by providing their expertise throughout the entire perioperative phase. In 2016, at the start of this thesis, guidelines did not suggest boundaries or targets for respiratory (i.e. end-tidal carbon dioxide ($ETCO_2$) concentrations) and hemodynamic parameters (i.e. blood pressure and cardiac output) during interventions in ASAH patients and patients with moyamoya disease.[1,6] This created a large inter-provider variability among anesthesiologists and neurocritical care physicians.[7] Therefore, in this thesis we first aimed to explore the effects of different intraoperative $ETCO_2$ concentrations and blood pressure levels on outcome in ASAH patients. Additionally, we aimed to study whether not only blood pressure, but also cardiac output would be an important vital parameter to target in patients presenting for cerebrovascular interventions. Finally, we explored the potential benefit of postoperative consultations by anesthesiologists, in addition to a routine postoperative troponin surveillance program, as an additional tool to influence outcome in patients presenting for cerebrovascular interventions.

Perioperative respiratory management

Most studies on the effect of ventilation and respiration on clinical outcome, focus on the critical care population, leaving surgical patients underrepresented.[8–14] Therefore, we first set out to explore the practice patterns in $ETCO_2$ in the general surgery population and several subgroups **(Chapter 2)**. It turned out that $ETCO_2$ concentrations have increased over time from a median of 33 mmHg [IQR 31-35] in 2008 to a median of 35 mmHg [IQR 33-38] in 2016 (p-value <0.001). We considered this 2 mmHg change over time not to be clinically relevant. Interestingly, some studies suggested that $ETCO_2$ concentrations of 40 mmHg or higher might be associated with better outcomes in mechanically-ventilated patients.[11,13–16] We did not find a preferred $ETCO_2$ concentration of ≥40 mmHg when studying the effect of different intraoperative $ETCO_2$ concentrations on postoperative pulmonary complications, in-hospital mortality and postoperative length of stay **(Chapter 3)**. The optimal median $ETCO_2$ concentration to limit the risk of pulmonary complications appeared to be around 38 mmHg. Especially the occurrence of severe hypocapnia ($ETCO_2$ <28 mmHg) was associated with pulmonary complications, mortality and increased postoperative length of stay. Also, hypercapnia (>45 mmHg) was associated with postoperative pulmonary

complications. In current clinical anesthesia practice, as studied in **Chapter 2**, the median $ETCO_2$ is lower than the optimum as found in **Chapter 3**, especially in neurosurgical patients where we found an overall median $ETCO_2$ of 32 mmHg [29-34].

We observed a large variation in intraoperative $ETCO_2$ concentrations **(Chapter 2)**. Only a minority of this variation could be attributed to institution and anesthesia provider, while controlling for patient characteristics. This large practice variation might indicate that anesthesia providers do not focus on $ETCO_2$ concentrations or there might still be insufficient knowledge about the effects of $ETCO_2$ to guide them in setting targets. The same large practice variation was found for patients presenting for intracranial & carotid artery surgery, despite an historical emphasis on strict $ETCO_2$ management during these types of procedures.[8] This may indicate that neuro-anesthesiologists are also uncertain which $ETCO_2$ concentrations are targeted best.

In an effort to provide further guidance for treatment of cerebrovascular patients, we studied whether several $ETCO_2$ thresholds (<30 mmHg, <35 mmHg, <40 mmHg and <45 mmHg) were associated with neurologic outcome in ASAH patients presenting for endovascular coiling or neurosurgical clipping **(Chapter 4)**. None of the studied $ETCO_2$ ranges were associated with neurologic outcome at discharge, irrespective of the duration below or above the threshold and irrespective of preoperative clinical condition, timing of treatment or treatment modality. Even extreme hypocapnia was not associated with poor neurologic outcome. It is important to stress that this retrospective study was conducted within the ranges of current clinical practice. Interestingly, we found a much higher median $ETCO_2$ of 43 mmHg [41-45] during neurosurgical clipping and 44 mmHg [42-46] during endovascular coiling, as compared to the median $ETCO_2$ of the neurosurgical population studied in **Chapter 2**. This strengthened the hypothesis that local (institutional, national or even continental) customs rather than solid evidence currently guides anesthesia providers in setting $ETCO_2$ targets, both in general surgery patients as well as in neurosurgical patients.

Perioperative blood pressure management

After ASAH, the cerebral autoregulation can be disrupted and cerebral blood flow may become blood pressure dependent. A comparable disruption of the cerebral autoregulation can be found in cardiac surgery patients on cardiopulmonary bypass, patients after an ischemic stroke, traumatic brain injury or patients with moyamoya disease.[17–20] In all these patients, maintenance of adequate blood pressure levels is considered important to avoid hypotension-related cerebral ischemia (and hypertension-related re-bleeding in the case of ASAH).[21–23] However, solid recommendations on peri-procedural blood pressure targets are lacking.[1,6,23,24]

For ASAH patients specifically, expert opinion is to aim at a systolic blood pressure (SBP) below 160-180 mmHg in patients with unsecured ruptured cerebral aneurysms.[1,24] Current guidelines were unable to formulate an advice regarding the lower limit of blood pressure. Therefore, we studied the association between several mean arterial pressure (MAP) thresholds during neurosurgical clipping or endovascular coiling of a ruptured cerebral aneurysm and neurologic outcome at discharge **(Chapter 4)**. Although we studied several thresholds, no association was found, irrespective of duration below or above the threshold. Preoperative clinical condition, timing of treatment and treatment modality did not influence these results. Extreme hypotension (MAP < 60 mmHg) was also not associated with poor neurologic outcome at discharge. These findings could suggest that adherence to strict intraoperative blood pressure levels is not required during treatment of ruptured cerebral aneurysms, although this may not be concluded from this study because of its retrospective design.

Should we abandon $ETCO_2$ and blood pressure regulation all together?

This thesis aimed to explore the effects of different intraoperative $ETCO_2$ concentrations and blood pressure levels on outcome in ASAH patients and found no association between any of the studied thresholds and neurologic outcome at discharge or at three months **(Chapter 4)**. However, we cannot conclude that we can abandon strict intraoperative $ETCO_2$ and MAP regulation. As the study presented in **Chapter 4** was a retrospective study, results should be interpreted in light of the local protocol used at the UMC Utrecht, urging anesthesiologists to maintain $ETCO_2$ concentrations between 35-45 mmHg and SBP <180 mmHg before treatment and <220 mmHg after securing the aneurysm, while maintaining a MAP >80 mmHg. The local protocol might have limited the occurrence of extremes (i.e. far below or above the baseline, for a long duration of time), resulting in too little practice variation. Possibly, outliers only occurred due to patient- and procedure-related factors, despite efforts of anesthesiologists to prevent them from occurring. Therefore, it cannot be precluded that abandoning of strict $ETCO_2$ and blood pressure regulation might harm ASAH patients. We would suggest to still maintain $ETCO_2$ concentrations and MAP values within strict ranges. Unfortunately, we were unable to confirm whether the ranges used in the local protocol of the UMC Utrecht are indeed the best ranges to use.

When first exploring the effect of $ETCO_2$ further, some smaller studies have found harmful effects for hypocapnia in Intensive Care Unit (ICU) patients with traumatic brain injury, ischemic stroke and after a cardiac arrest[14,25,26] and beneficial effects for hypercapnia in ASAH patients and after a cardiac arrest.[27–29] However, the association between $ETCO_2$ (or arterial carbon dioxide pressure ($PaCO_2$) for that matter) and patient outcome might not be a simple linear one, as shown in **Chapter 3 and 4**, where models using splines resulted in the best fit. Findings from a large retrospective study support the

hypothesis of a non-linear association.[30] Uncompensated hypercapnia (i.e. hypercapnic acidosis; mean $PaCO_2$ 56.7 mmHg, mean pH 7.19) was associated with an increased in-hospital mortality in patients with acute cerebral injury. In contrast, compensated hypercapnia (mean $PaCO_2$ 52.2 mmHg, mean pH 7.39) was not associated with a change in survival. Another recent retrospective study in 150 ASAH patients, looking at all $PaCO_2$ concentrations obtained during mechanical ventilation in the ICU, found that patients with a favorable outcome had a lower proportion of $PaCO_2$ concentrations >40 mmHg.[31] In conclusion, although (mild) hypercapnia was suggested to improve neurologic outcome in patients with cerebral injury, the last two studies suggest that too much hypercapnia might be harmful. Whether a median $ETCO_2$ of 32 mmHg [29-34] as found in the neurosurgical population of **Chapter 2** is harmful, needs to be studied further as $ETCO_2$ levels of 32 mmHg or below were insufficiently prevalent in the cohort of **Chapter 4**. Also, different thresholds might be of importance for different postoperative outcomes as shown in **Chapter 3**, where an intraoperative median $ETCO_2$ concentration of 38 mmHg appeared to be optimal to prevent postoperative pulmonary complications.

When secondly considering the effect of MAP, we did not find an association between MAP thresholds and neurologic outcome in ASAH patients. However, others have found that deliberately induced hypotension and severe hypertension have harmful effects.[32–34] We do believe that this stresses that cerebral blood flow regulation might not be a simple linear process with clear cut-of points as once described by Lassen in 1959.[35] There even appears to be a large inter- and intra-individual variability in the lower limit of cerebral autoregulation.[36,37] Some suggest that optimal individual blood pressure levels can be determined using the pressure reactivity index based on the intracranial pressure and the tissue oxygenation index based on near-infrared spectroscopy (NIRS).[37] Both intracranial pressure (invasively with an external ventricular drain) and NIRS (non-invasively) can be measured continuously, enabling adaptation of optimal blood pressure levels over time. Although the accuracy of regional cerebral oxygen saturation obtained with NIRS is known to suffer from extracranial contamination and is influenced by vasopressors causing vasoconstriction of the skin, the tissue oxygenation index seems to perform quite well.[38,39] With further optimization of the algorithm, NIRS can potentially provide us with a relatively cheap, non-invasive and easy tool to study the effect of personalized blood pressure management in ASAH patients and neurosurgical patients alike.

The illusion of "one size fits all"

To the best of our knowledge, the study described in **Chapter 4** is the largest study conducted thus far exploring the association between intraoperative $ETCO_2$ and MAP thresholds and neurologic outcome in ASAH patients and neurovascular patients alike. We did not find an association between any of the thresholds and neurologic

outcome, while others did. We believe that there may be several reasons to explain this inconsistency. First, the use of the aforementioned local protocol might have limited the amount of practice variation, making it difficult to study the effect of extreme $ETCO_2$ and MAP values. These extreme values might be the ones we are actually interested in considering the presumably non-linear relationship between $ETCO_2$, MAP and cerebral perfusion. However, this is difficult to study in a non-observational setting due to ethical concerns. Second, the large sample size potentially cancelled out significant effects found by other, much smaller studies. Third, throughout this thesis we chose to use a time-weighted average area-under-the-curve (TWA-AUC) to model $ETCO_2$ and MAP **(Chapter 2, 3, 4)**. Previous studies into the effects of $ETCO_2$ used a mean or median $ETCO_2$ per case[9,13,14] or used hypocapnia ($ETCO_2$ <35 mmHg) as a binary variable.[40] MAP was often also summarized in a mean or binary variable[33,41] and there is a variety of definitions for intraoperative hypotension. This makes the interpretation of incidences and associations with postoperative outcome complex.[42,43] Thus far no single method to express intraoperative hypotension seems to be outperforming.[43] A systematic review studying the effect of intraoperative hypotension in non-cardiac surgery revealed that the risk of organ injury increases with severity of hypotension and duration of hypotension, stressing the importance to look at vital parameters as continuous and longitudinal data rather than just a mean or median, as regression to the mean can occur.[44] Therefore, we believe that AUC is a more appropriate measure to summarize vital parameters. As the duration of the intervention can potentially have a large influence on postoperative outcome (i.e. a difficult and complicated procedure often takes longer) and deviations from thresholds are more likely to occur during longer interventions, we chose to correct AUC for duration, resulting in a TWA-AUC. Although we acknowledge that a TWA-AUC might be difficult to interpret in a clinical setting, we believe that this is the preferred measure when studying the effect of $ETCO_2$ and MAP in the complex situation of compromised cerebral perfusion, where short derangements can potentially provide a second hit. We would therefore suggest to use a TWA-AUC in further observational studies regarding this topic. Fourth, others have suggested that we did not find an association between any of the studied $ETCO_2$ and MAP ranges and neurologic outcome in **Chapter 4**, because we used the Glasgow Outcome Scale (GOS) to classify our outcome.[45] Potentially, GOS would not be sensitive enough to detect subtle effects. However, if GOS is not sensitive enough, one can argue that the effects are so subtle, that they might not be clinically relevant. This brings us to our fifth and final explanation. The impact of different intraoperative $ETCO_2$ and MAP values, occurring within current clinical practice, might be of far less importance when compared to other factors such as comorbidities and disease severity. It might be that we are thriving to determine more strict targets and thresholds, that are relatively not that important after all.

Based on the findings from **Chapter 4** we believe that although we cannot abandon strict $ETCO_2$ and MAP management altogether, we should focus on cerebral perfusion as a dynamic process. In this, the idea of "one size fits all" is misleading for several reasons. First, inter- and even intra-individual differences should be considered. Even in healthy patients different lower limits for cerebral autoregulation have been described, ranging from a MAP of 40 mmHg to even 110 mmHg,[46,47] and a small study in 31 ASAH patients determined that personalized optimal MAP values varied between 70 and 140 mmHg.[37] Also, intraoperative complications such as thrombo-embolic events or bleedings can occur and change optimal ranges, while different brain regions can act differently.[37] Second, the brain never stands on its own. It is all about prioritizing and finding the right balance between the needs of different organ systems (e.g. postoperative pulmonary complications can also affect neurologic outcome, an increased myocardial oxygen demand caused by use of vasopressors to increase MAP can harm patient outcome). Third, time is an important variable to be considered, which is why we studied a TWA-AUC. For example, hypotension can be tolerated briefly, but will cause harm when sustained, causing depleting of the blood flow reserve.[36] Fourth, cerebral perfusion appears to be a joint effort of much more than only blood pressure and $ETCO_2$. Another potential important contributor, although hardly measured (and perhaps even neglected) during neurosurgical procedures is cardiac output. In patients undergoing cerebral bypass surgery dobutamine - by increasing cardiac output, while decreasing MAP - was found to increase graft flow, similar to phenylephrine - by increasing MAP and maintaining cardiac output **(Chapter 5)**. In this, graft flow can be seen as a proxy for cerebral perfusion. In current clinical practice inotropes are hardly used to improve cerebral perfusion, whereas vasopressor use is the standard.[6,7] Although there was no preference for one method over the other, the results from **Chapter 5** show that dobutamine has a good potential to increase cerebral perfusion. Therefore, dobutamine should be considered when targeted graft flow (or cerebral blood flow) is not reached or only at the cost of (severe) systemic hypertension, when using vasopressors. Although patients included in this study suffered from recurrent cerebral ischemia due to moyamoya disease or atherosclerotic carotid artery occlusion, the results might also be applicable to a broader population at risk for perioperative cerebral ischemia, as cardiac surgery patients and patients with ASAH or traumatic brain injury all suffer from a disrupted cerebral autoregulation.[17–20]

Early detection of postoperative complications

The risk of postoperative complications is difficult to predict based on preoperative parameters.[48] By identifying patients at risk not only in the preoperative, but throughout the entire perioperative phase, care can be directed more appropriately. The anesthesiologist as a "perioperativist" can contribute to many aspects of perioperative

care, including, but not limited to, intraoperative respiratory and hemodynamic management. Routine postoperative troponin surveillance by anesthesiologists can be a potential tool to identify those at risk of complications.[49–51] Besides myocardial injury, troponin elevation has been related to diseases such as stroke, sepsis and pulmonary embolism.[50,52] Elevated troponin levels are reported in half of all ASAH patients[53] and are probably due to a tremendous sympathetic surge after the initial bleeding.[54] Troponin elevation on admission is associated with a worse neurologic outcome.[55] However, a second troponin elevation after occlusion of a ruptured cerebral aneurysm is also frequent and might reflect perioperative myocardial injury **(Chapter 6)**. Although not associated with neurologic outcome and mortality, postoperative troponin elevation is associated with major adverse cardiac events (MACE). Patients with ASAH, like patients with other kinds of stroke, are at risk of future cardiovascular events and suffer from long-term excess mortality, with cardiovascular death being overrepresented.[56] Postoperative elevated troponin levels can predict MACE within one year **(Chapter 6)**, thus helping us to identify those ASAH patients that are primarily at risk and direct secondary cardiovascular risk management accordingly.

The predictive value of postoperative troponin levels has been more extensively studied in the general non-cardiac surgery population where routine postoperative troponin surveillance programs are utilized to identify patients with an increased risk of future MACE and mortality.[50,51] Postoperative troponin levels are in a dose-dependent manner associated with increasing rates of cardiovascular, i.e. myocardial infarction and pulmonary embolism, but also non-cardiac complications, i.e. sepsis, respiratory failure, renal failure and anemia in the non-cardiac surgery population **(Chapter 7)**. Secondary prevention strategies towards these complications have to be explored. Anesthesiologists could, by using their knowledge on both procedure-related complications and the cardiopulmonary system, provide a valuable contribution to postoperative care. We found that anesthetic consultation of patients with postoperative troponin elevation, enabled early detection of 12% of all complications within one week after surgery **(Chapter 7)**. Anesthesiologists were involved in the early detection of 59% of all myocardial infarctions within the first postoperative week, which is primarily of interest as most patients with perioperative myocardial injury do not experience ischemic symptoms.[57] Whether the early detection of complications results in improved clinical outcomes remains to be elucidated. However, it does lead to a change in medication and red blood cell transfusion in a substantial proportion of patients **(Chapter 7)**. Additionally, the resources needed for a dedicated team of anesthesiologists conducting postoperative visits are low, making these visits easy to implement. Obviously, a multidisciplinary approach remains essential.

The utopia of large database studies

In this thesis several large databases were explored. Although randomized clinical trials are considered the gold standard, large clinical databases, to the extent of "big data" are vastly gaining terrain.[58] Machine learning and artificial intelligence are supposedly the future of healthcare research. In the field of anesthesiology and critical care, automated information management systems offer us almost unlimited amounts of data, especially of vital signs.[59] Although we definitely acknowledge the value of databases for healthcare quality assessment and to study questions that cannot be easily studied in trials, we encountered several difficulties that we would like to discuss. First, when the data in your database is incorrect, this will influence your output. In other words: "garbage in" also means "garbage out." Some of the data is stored in a structured way, using consistently defined and mostly accurate data (e.g. laboratory results). However, artifacts can still occur and are especially important to consider when handling vital parameters.[60] Take for example invasive blood pressure measurements. When the sensor falls on the ground, the blood pressure is falsely high and should be classified as artifact. We tried to eliminate as many artifacts as possible using filters as described in **Chapter 2, 3 and 4**. Although we used an automated process, it is still time-consuming and presumable also still imperfect.[61] Second, anesthesia record-keeping systems still collect large amounts of free-text data, that is unstructured and often filled with spelling mistakes. Although filtering can also be partly automated, cleaning free-text data is very time-consuming. Finally, the use of large databases also makes the analyses more complex. We found an important effect for both year of procedure and institution in the multicenter studies described in **Chapter 2 and 3**. We adjusted for these variables in a mixed-effect model, which required large computational power. It is pivotal to take year and institution into account in future multicenter database studies. Not only can there be a difference in quality of care between institutions and years, but the quality of documentation can also change.

Directions for future research regarding intraoperative cerebral perfusion management

A recent study in patients undergoing brain tumor surgery found that ephedrine significantly increased cerebral blood flow in the healthy part of the brain, when compared to phenylephrine.[62] The investigators used positron emission tomography to reliably assess and quantify cerebral perfusion. As cerebral perfusion is not easily and reliable measured in other types of procedures than the one used in **Chapter 5**,[38,63] we believe that the future lies within new imaging techniques such as positron emission tomography to measure cerebral perfusion in a research setting, while challenging long-standing beliefs in neuro-anesthesia. Unfortunately, most imaging techniques are costly and cannot easily be used in a clinical setting. Alternatively, the tissue oxygenation index obtained with NIRS can be used as a non-invasive, cheap and easy

tool to explore the potential of individualized blood pressure, $ETCO_2$ and cardiac output management during cerebrovascular interventions.[37] Although algorithm updates have improved the reliability, NIRS can still only provide regional estimates of cerebral oxygenation, complicating assessment of general cerebral perfusion in patients with local vasospasm.[39] NIRS and imaging techniques such as positron emission tomography should be combined to assess cerebral perfusion and oxygenation for research purposes and to further validate NIRS for personalized intraoperative respiratory and hemodynamic management. After further validation, NIRS can presumably be used for a more tailor-made approach in a clinical setting.

An important overlooked parameter in neuro-anesthesia research is cardiac output. For ASAH patients in particular, cardiac output enhancement is suggested to provide benefit for those with vasospasm by increasing cerebral blood flow, even despite a minor decrease in MAP.[64,65] There is a need for randomized trials to explore the potential role of inotropes in treating ASAH-induced cerebral vasospasm.[45] Unfortunately, such trials have been shown to be difficult to conduct.[34] We would therefore suggest to first explore the direct effect of cardiac output on cerebral perfusion and oxygenation further, using techniques such as NIRS and positron emission tomography.

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Chapter 9

Summary | Samenvatting in het Nederlands

SUMMARY

Cerebrovascular interventions aim to improve long-term neurologic outcome by preventing complications from cerebrovascular disease such as a cerebral hemorrhage and ischemic stroke. Unfortunately, these procedures and the required general anesthesia are accompanied by a risk of perioperative cerebral hypoperfusion and ischemia, with potentially disastrous effects on the neurologic outcome. While maintenance of adequate cerebral perfusion is crucial, inadequacy of this perfusion is difficult to determine under general anesthesia and often only becomes apparent after awakening of the patient. Many factors, such as end-tidal carbon dioxide ($ETCO_2$) concentrations, blood pressure and cardiac output, can potentially influence cerebral perfusion. The exact influence of these parameters on postoperative outcome was unknown at the beginning of this thesis for patients presenting for procedures such as neurosurgical clipping or endovascular coiling after an aneurysmal subarachnoid hemorrhage (ASAH) or cerebral bypass surgery in case of moyamoya disease.

In **Part I** of this thesis, perioperative respiratory management was studied by assessing the trends in $ETCO_2$ as seen in clinical practice in the non-cardiothoracic surgery population. In **Chapter 2,** we found a very large inter-hospital and inter-provider variability in $ETCO_2$ concentrations after adjustment for patient characteristics, ventilation parameters and intraoperative blood pressure levels. In addition, we found a median $ETCO_2$ of 35 mmHg [IQR 33-38], which is much lower than the preferred target of 40 mmHg, suggested by some in recent literature. These results suggest that there might still be a lack of evidence to support a specific targeted range and/or there might be a broad range of tolerance for $ETCO_2$ during general anesthesia.

Postoperative pulmonary complications are relatively frequent in patients presenting for neurosurgery and can have adverse effects on postoperative (neurologic) outcome. In **Chapter 3**, the association between $ETCO_2$ (studying several absolute thresholds (<28, <35, <45 and >45 mmHg) and a median) and postoperative pulmonary complications was assessed in an effort to collect more evidence supporting a specific $ETCO_2$ target. Both hypercapnia ($ETCO_2$ >45 mmHg) and severe hypocapnia ($ETCO_2$ <28 mmHg) were associated with an increased risk of pulmonary complications. The latter was also associated with mortality and an increased postoperative length of stay. A median $ETCO_2$ around 38 mmHg showed the smallest association with pulmonary complications, but further prospective studies are required to confirm or refute this target.

Results from **Chapter 2** were also used as a starting point to further explore the effect of $ETCO_2$ on neurologic outcome in **Part II.** Additionally, **Part II** focused on the effect of blood pressure and cardiac output on cerebral perfusion and neurologic outcome in patients with severe cerebrovascular disease presenting for cerebrovascular interventions. In **Chapter 4** we studied the association between several $ETCO_2$ and mean arterial pressure (MAP) thresholds and neurologic outcome in patients presenting for clipping or coiling of a ruptured cerebral aneurysm. In a retrospective study design, we studied the following absolute thresholds: $ETCO_2$ <30, <35, <40, <45mmHg and MAP <60, <70, <80, >90, >100mmHg and the following relative thresholds: MAP <70%, <60%, <50% (compared to pre-induction MAP). We hypothesized that intraoperative hypocapnia (arterial carbon dioxide <35 mmHg), hypotension (MAP <80 mmHg) and hypertension (MAP >100 mmHg) would be associated with a worse neurologic outcome at discharge and after three months. We included a total of 1,099 ASAH patients and found that none of the studied thresholds were associated with a poor neurologic outcome. These results were not influenced by preoperative neurologic condition, treatment modality and timing of the intervention. As this was a retrospective study, it is important to stress that this study was conducted within the context of current clinical practice. This study does not show that we can abandon strict $ETCO_2$ and blood pressure regulation; it merely shows that no further subgroups of preferred $ETCO_2$ and MAP values could be identified during clipping or coiling of a ruptured cerebral aneurysm.

In **Chapter 5** we conducted a randomized crossover study in ten patients presenting for cerebral bypass surgery to explore the effect of cardiac output on graft flow, as a proxy for cerebral perfusion. Patients randomly and sequentially received dobutamine – to increase cardiac index – and phenylephrine – to increase MAP, in order to determine which drug (and thus an increase in cardiac output or an increase in blood pressure) would result in higher graft flow. Both drugs increased graft flow without a preference for one drug over the other. Currently, it is common practice to increase blood pressure in an effort to increase graft flow. Our study showed that dobutamine can also increase graft flow and should be considered when targeted flows are not reached or only at the cost of (severe) systemic hypertension, when using phenylephrine.

Anesthesiologists have a rather wide medical scope as they are trained to deal with the cardiopulmonary and central nervous system and have experience with procedure-related complications. This can be of benefit not only during cerebrovascular interventions, but also in the postoperative setting. The role of the anesthesiologist as "perioperativist" was further explored in **Part III.**

Survivors of ASAH have an increased long-term incidence of cardiovascular events compared to the general population. Timely identification of patients at risk for the development of adverse cardiovascular events might enable the implementation of preventive measures and improve long-term outcome after ASAH. Surgical procedures are both mentally and physically stressful, exposing the myocardium to a stress test. Studies among non-cardiac surgery patients have suggested that perioperative myocardial injury is a predictor of future major adverse cardiac events (MACE). Whether this is also the case for ASAH patients remained to be elucidated. Therefore, we explored whether perioperative myocardial injury, reflected in an increased troponin I (TnI) level after occlusion of a ruptured aneurysm, was also associated with MACE and mortality in ASAH patients **(Chapter 6)**. Indeed, patients with an increased postoperative TnI had a higher cumulative incidence for MACE at one year, i.e. 1.63% (95% CI -0.71-3.97) for no elevation versus 12.95% (95% CI 2.34-22.71) for any elevation of TnI. The accompanying relative risk was 7.67 (95% CI 1.52-38.7). Also, postoperative TnI was an independent predictor for MACE within one year after ASAH.

It is not only important to identify patients at risk of complications, but to also implement interventions where possible. One potentially beneficial intervention is routine follow-up visits by specialized anesthesiologists in patients with an elevated postoperative troponin. The implementation of this intervention was evaluated in **Chapter 7**. We included 811 non-cardiac surgery patients with elevated troponins of whom 509 (63%) received a postoperative consultation by dedicated anesthesiologists. These anesthesiologists were involved in the early detection of 59% of all myocardial infarctions and in 12% of all complications within one week after surgery. Changes in treatment were initiated by the anesthesiologist in 16% of patients. Unfortunately, we were unable to further study the effect of this intervention on patient outcome and we did not study the effect of this intervention for cerebrovascular patients specifically.

In summary, this thesis describes that there is a large variation in intraoperative $ETCO_2$ concentrations in clinical practice. Hypercapnia ($ETCO_2$ >45 mmHg) and severe hypocapnia ($ETCO_2$ <28 mmHg) were associated with postoperative pulmonary complications and the optimal median $ETCO_2$ appeared to be around 38 mmHg. Severe hypocapnia was also associated with mortality and an increased length of stay. However, we were unable to determine any further subgroups of preferred $ETCO_2$ concentrations during clipping or coiling of a ruptured cerebral aneurysm with regard to neurologic outcome. This thesis was also unable to determine strict MAP targets during treatment of ruptured cerebral aneurysms to further optimize

neurologic outcome; all studied within the context of current clinical practice. Dobutamine – to increase cardiac output – can increase cerebral perfusion and can be used when vasopressors such as phenylephrine – to increase blood pressure – cannot provide sufficient cerebral perfusion or only at the cost of severe systemic hypertension.

Anesthesiologists can have a valuable contribution to postoperative care in patients presenting for cerebrovascular interventions. First, they can help identify patients at risk of myocardial infarction and cardiac death by implementation of routine postoperative troponin surveillance programs. Second, consultation by dedicated anesthesiologists in patient with postoperative troponin elevation can help to diagnose and treat postoperative complications at an early stage.

SAMENVATTING IN HET NEDERLANDS

Er bestaan verschillende aandoeningen aan de hersenvaten, waaronder een subarachnoïdaal aneurysma en de ziekte van moyamoya. Een subarachnoïdaal aneurysma is een verwijding of uitstulping van een bloedvat dat gelegen is in de ruimte tussen de hersenen en de schedel. Het vormt een zwakke plek, waardoor het vat kan openscheuren met een hersenbloeding tot gevolg. Een subarachnoïdale bloeding komt bij relatief jonge patiënten voor en kan desastreuze gevolgen hebben. Ongeveer 30% van de patiënten overlijdt binnen enkele dagen tot weken na de bloeding en ongeveer 20% van de overlevenden houdt blijvende beperkingen over. Alhoewel er vooruitgang is geboekt in de behandeling van deze patiënten, is er nog veel ruimte voor verbetering. Patiënten met een subarachnoïdale bloeding krijgen een radiologische behandeling of een hersenoperatie om te voorkomen dat het aneurysma opnieuw openbarst. Bij de radiologische behandeling wordt met behulp van een katheter een coil (een soort spiraaltje) geplaatst in het aneurysma zodat daar geen bloed meer kan stromen. Deze behandeling is minimaal invasief: de katheter wordt opgevoerd via een bloedvat in de lies. Het alternatief is een hersenoperatie, waarbij er een clip (een soort klemmetje) op het aneurysma wordt geplaatst. Voor beide ingrepen is algehele anesthesie (narcose) noodzakelijk.

Bij de ziekte van moyamoya zijn er vaatvernauwingen in bepaalde bloedvaten, waardoor er te weinig bloed naar de hersenen gaat. Bij deze patiënten kan een neurochirurgische ingreep onder algehele anesthesie nodig zijn om herseninfarcten te voorkomen. Daarbij wordt er een omleiding aangelegd van een vat buiten de hersenen naar een vat binnen de hersenen, een zogenaamde extracraniële-intracraniële bypass.

Zowel het behandelen van een aneurysma als het plaatsen van een bypass brengt risico's met zich mee. Helaas lopen sommige patiënten hersenschade op tijdens de ingreep. De anesthesioloog is actief betrokken bij deze ingrepen en past het beleid waar mogelijk aan om hersenschade te beperken, bijvoorbeeld door de doorbloeding van de hersenen te stimuleren. De doorbloeding van de hersenen wordt door veel verschillende factoren beïnvloed, zoals het koolstofdioxide gehalte (CO_2, een uitademingsgas) en de bloeddruk. Zowel het CO_2 gehalte als de bloeddruk kunnen door de anesthesioloog beïnvloed worden. De exacte invloed van beide parameters op het herstel van bovengenoemde patiënten is echter niet geheel duidelijk. Daarnaast speelt het hartminuutvolume (de hoeveelheid bloed die per minuut door het hart wordt rondgepompt) mogelijk ook een belangrijke rol, maar ook dat is niet geheel duidelijk.

Dit proefschrift heeft onderzocht hoe de zorg voor patiënten met vataandoeningen in de hersenen verbeterd kan worden vanuit het perspectief van de anesthesioloog. Allereerst is geprobeerd te bepalen welke waardes voor CO_2 en bloeddruk voor het beste herstel van patiënten zorgden. In **Deel I, Hoofdstuk 2** hebben we eerst gekeken welke intra-operatieve CO_2 concentraties gangbaar zijn in de huidige praktijk door data van acht academische ziekenhuizen te bestuderen. We vonden dat de meeste patiënten tijdens chirurgische ingrepen een CO_2 waarde van 33-38 mmHg hadden, hetgeen veel lager is dan de 40 mmHg die in sommige literatuur geadviseerd wordt. Daarnaast varieerden CO_2 concentraties tussen de verschillende centra en zelfs tussen de verschillende anesthesiologen en anesthesieteams (anesthesioloog met anesthesiemedewerker) binnen een centrum. Mogelijk komt dit doordat er onvoldoende bewijs is om een ideale streefwaarde te definiëren, dan wel doordat anesthesiologen een brede spreiding van CO_2 accepteren.

Complicaties aan de longen komen relatief vaak voor bij patiënten die een (neuro-) chirurgische ingreep ondergaan en kunnen het herstel nadelig beïnvloeden. Daarom hebben we in **Hoofdstuk 3** gekeken of we streefwaardes voor CO_2 konden definiëren. Bij patiënten die kwamen voor algemene chirurgische ingrepen hebben we bestudeerd welke CO_2 concentraties geassocieerd waren met postoperatieve complicaties aan de longen, sterfte en een langere ziekenhuisopname. We vonden dat een CO_2 concentratie rond 38 mmHg vermoedelijk het laagste risico op complicaties aan de longen geeft. Een lage CO_2 concentratie (<28 mmHg) en een hoge concentratie (CO_2 >45 mmHg) waren geassocieerd met postoperatieve complicaties aan de longen. Een lage CO_2 concentratie was eveneens geassocieerd met sterfte en een langere opnameduur.

In **Deel II, Hoofdstuk 4** hebben we specifiek gekeken naar het effect van verschillende CO_2- en bloeddrukwaardes op het herstel van patiënten met een subarachnoïdale bloeding die geclipt of gecoild werden. We vonden dat geen enkele streefwaarde geassocieerd was met een slechter (of beter) herstel. Het is daarbij belangrijk op te merken dat dit is bestudeerd binnen de huidige klinische praktijk. Hele hoge of hele lage waardes kwamen daardoor relatief weinig voor. Dit betekent niet dat strikte CO_2- en bloeddrukregulatie volledig kan worden losgelaten, maar dat we simpelweg geen strikt optimum hebben kunnen vaststellen. Bovendien is het waarschijnlijk dat CO_2 en bloeddruk maar een klein onderdeel vormen van een veel grotere, complexe puzzel die bijdraagt aan het herstel van deze patiënten.

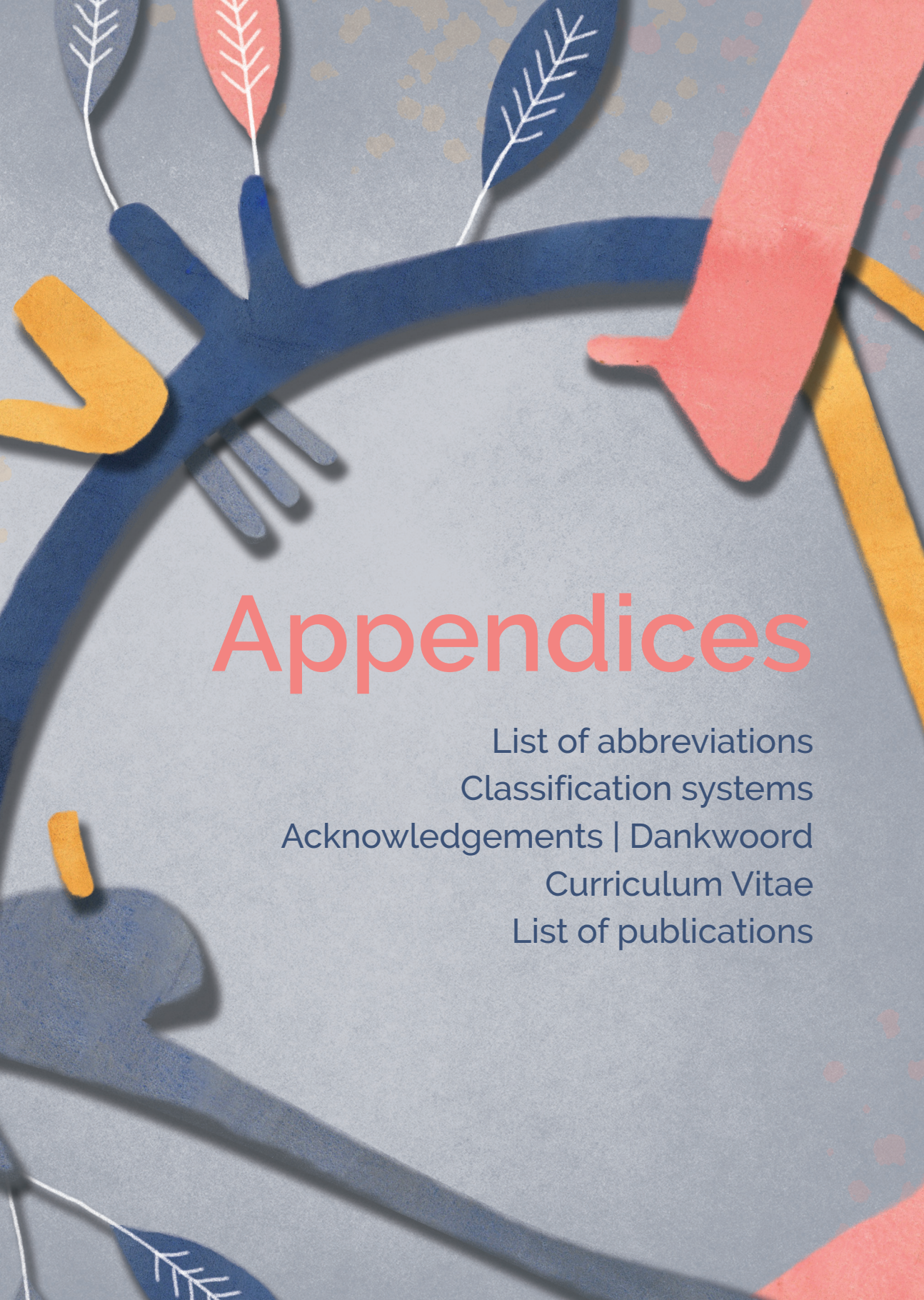
Een andere mogelijk belangrijke parameter is het hartminuutvolume, zeker aangezien veel patiënten met een subarachnoïdale bloeding (tijdelijke) hartschade hebben ten gevolge van de stress die het lichaam ervaart door de hersenbloeding. Ook het hartminuutvolume kan door de anesthesioloog worden beïnvloed. In **Hoofdstuk 5**

hebben we onderzocht of het verhogen van het hartminuutvolume beter is voor de doorbloeding van een extracraniële-intracraniële bypass dan het verhogen van de bloeddruk. Als de doorbloeding van de bypass toeneemt, is het aannemelijk dat de doorbloeding van de hersenen ook toeneemt. De studie in **Hoofdstuk 5** laat zien dat zowel dobutamine – een middel dat het hartminuutvolume verhoogt – als fenylefrine – een middel dat de bloeddruk verhoogt – goed in staat zijn om de doorbloeding van de bypass te vergroten. Fenylefrine wordt in de huidige praktijk veel gebruikt om de doorbloeding van de bypass en de hersenen te vergroten, waarbij als nadelig gevolg ook andere organen worden blootgesteld aan een hogere bloeddruk. Daarom valt het te overwegen dobutamine te gebruiken als de doorbloeding van de hersenen onvoldoende blijkt of alleen bereikt wordt ten koste van een fors verhoogde bloeddruk.

De anesthesioloog is niet alleen betrokken bij de patiëntenzorg tijdens hersenoperaties, maar kan ook in de postoperatieve fase een bijdrage leveren door zijn kennis op het gebied van operaties en de werking van het hart, de longen en de hersenen. Die postoperatieve bijdrage hebben we onderzocht in **Deel III.** Iedere operatieve ingreep is een stressvol moment, zowel psychisch als fysiek, en kan daardoor een zuurstoftekort bij de hartspier veroorzaken. Uit studies onder patiënten die komen voor een grote operatie (bijv. een buik- of heupoperatie) weten we dat het optreden van hartschade tijdens deze ingrepen een voorspeller is voor het ontstaan van een hartinfarct en vroegtijdig overlijden. Om deze hartschade vast te stellen, kan een eiwit in het bloed bepaald worden dat vrijkomt uit beschadigde hartcellen, het zogenaamde troponine. Inmiddels bepalen verschillende centra wereldwijd standaard een troponine na operatieve ingrepen. Van patiënten die een subarachnoïdale bloeding overleefd hebben, weten we dat ze in de daaropvolgende jaren een verhoogd risico op hart- en vaataandoeningen en vroegtijdige sterfte hebben. Het was echter onduidelijk of het ook bij deze groep van meerwaarde zou zijn om standaard een troponine te bepalen na de operatie om het risico op toekomstige hart- en vaataandoeningen te kunnen inschatten. In de studie beschreven in **Hoofdstuk 6** bleek een verhoogd troponine na een ingreep aan een gebarsten aneurysma inderdaad een onafhankelijke voorspeller te zijn voor een hartinfarct of sterfte binnen een jaar na de ingreep. Nog belangrijker dan het voorspellen van een hartinfarct of sterfte, is het voorkomen daarvan. Daarom hebben we in **Hoofdstuk 7** bestudeerd wat het effect zou zijn van postoperatieve bezoeken door een anesthesioloog aan patiënten met een verhoogde postoperatieve troponine waarde. We hebben patiënten geïncludeerd die voor verschillende grote ingrepen kwamen. Anesthesiologen bleken postoperatief betrokken bij de vroegtijdige opsporing van 59% van alle hartinfarcten en 12% van alle complicaties die zich binnen een week na de ingreep voordeden. Daarnaast stelden de anesthesiologen een beleidsverandering

voor bij 16% van de patiënten. Helaas was het niet mogelijk om te onderzoeken of deze vroegtijdige opsporing van complicaties, gecombineerd met beleidsveranderingen, ook daadwerkelijk het herstel van patiënten verbeterd heeft.

Samengevat beschrijft dit proefschrift dat er in de huidige praktijk veel variatie bestaat in CO_2 concentraties waarbij het moeilijk blijkt strikte streefwaardes te definiëren voor patiënten die geopereerd worden aan de hersenvaten. Bovendien kon dit proefschrift de huidige gehanteerde streefwaardes voor bloeddruk tijdens dergelijke operaties niet strikter definiëren. Er is wel duidelijk een rol weggelegd voor het verhogen van het hartminuutvolume naast het verhogen van de bloeddruk om de doorbloeding van de hersenen te doen toenemen. Daarnaast kunnen anesthesiologen ook na operaties aan de hersenvaten een belangrijke bijdrage leveren aan het herstel van patiënten. Allereerst kunnen patiënten met een verhoogd risico op een hartinfarct of overlijden geïdentificeerd worden door gestandaardiseerde postoperatieve troponine monitoring. Daarnaast lijkt een geprotocolleerd postoperatief consult door anesthesiologen bij te dragen aan het vroegtijdig herkennen en behandelen van postoperatieve complicaties.



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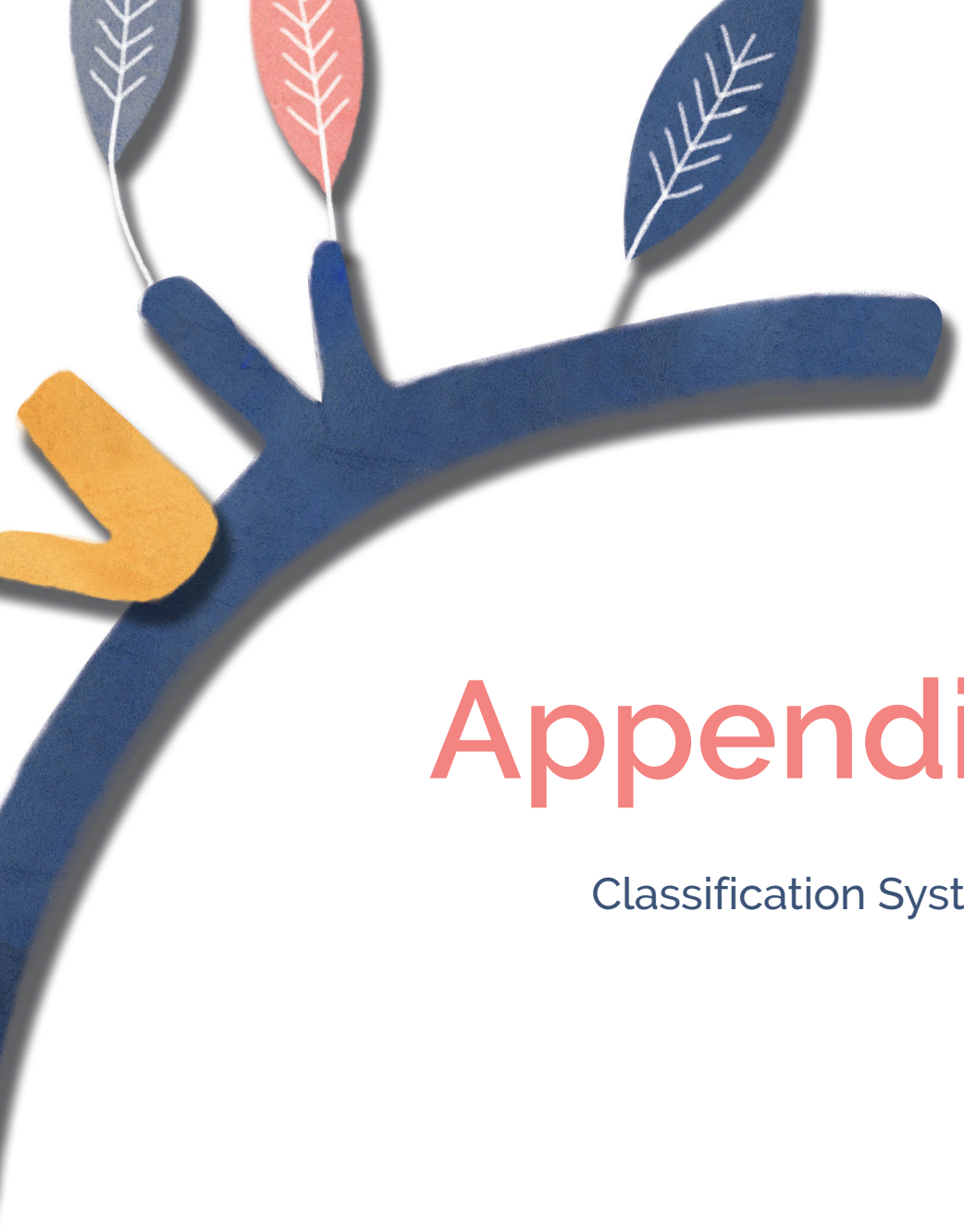
Appendix

List of Abbreviations

LIST OF ABBREVIATIONS

ABG	arterial blood gas
AKI	acute kidney injury
ARKS	anesthesia record-keeping system
ASA	American Society of Anesthesiologists
ASAH	aneurysmal subarachnoid hemorrhage
BMI	body mass index
CCU	Cardiac Care Unit
CI	confidence interval / cardiac index
CK-MB	creatine-kinase isoenzyme
COPD	chronic obstructive pulmonary disease
CPR	cardiopulmonary resuscitation
CPT	Current Procedural Terminology
CSF	cerebral spinal fluid
CT	computed tomography
DBP	diastolic blood pressure
DNC	did not converge
ECG	electrocardiogram
ESA	European Society of Anaesthesiology
ESC	European Society of Cardiology
$ETCO_2$	end-tidal carbon dioxide
GA	general anesthesia
GCS	Glasgow Coma Scale
GFR	glomerular filtration rate
GOS	Glasgow Outcome Scale
Hb	hemoglobin
HR	hazard ratio / heart rate
Ht	hematocrit
ICD	implantable cardioverter defibrillator / International Statistical Classification of Diseases and Related Health Problems
ICU	Intensive Care Unit
IDI	Integrated Discrimination Improvement index
IQR	interquartile range
IRB	Institutional Review Board
IRR	incidence rate ratio
LMA	laryngeal mask airway
MACE	major adverse cardiac events
MAP	mean arterial pressure

MCU	Medium Care Unit
METs	Metabolic Equivalent of Task score
MPOG	Multicenter Perioperative Outcomes Group
NA	not applicable
OR	odds ratio
$PaCO_2$	arterial carbon dioxide pressure
PACU	Post Anesthesia Care Unit
PBW	predicted body weight
PEEP	Positive end-expiratory pressure
POA	perioperative anesthesiologist
PP	pulse pressure
PPC(s)	postoperative pulmonary complication(s)
PCRC	Perioperative Clinical Research Committee
Q	quantile
RAAS	Renin-Angiotensin-Aldosterone-System
RCRI	Revised Cardiac Risk Index
Ref	reference
RMV	respiratory minute volume
RR	risk ratio
SBP	systolic blood pressure
Sd	standard deviation
Sign.	significant
SHR	subdistribution hazard ratio
TnI	troponin I
TWA-AUC	time-weighted average area-under-the-curve
UMC	University Medical Center
WFNS	World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage



Appendix

Classification Systems

CLASSIFICATION SYSTEMS

Classification	Description
ASA I	Healthy, no smoking, minimal drinking
ASA II	Mild systemic disease, no substantive functional limitations
ASA III	Severe systemic disease with functional limitations
ASA IV	Severe systemic disease that is a constant threat to life
ASA V	Moribund patient who is not expected to survive without operation
ASA VI	Brain-dead patient
GOS 1	Death
GOS 2	Persistent vegetative state
GOS 3	Severe disability
GOS 4	Moderate disability
GOS 5	Low disability
RCRI	To assess the risk of perioperative cardiac complications for non-cardiac surgery, each of the following six risk factors is assigned one point. 1. History of ischemic heart disease 2. History of congestive heart failure 3. History of cerebrovascular disease 4. History of insulin dependent diabetes mellitus 5. Pre-intervention serum creatinine >177 µmol/L (or >2mg/dL) 6. High-risk surgery (intrathoracic, intra-abdominal or supra-inguinal vascular surgery) Patients with none, one, or two risk factor(s) are assigned to class I, II or III respectively, with a corresponding risk of 0.4%, 1% and 7%. Patients with more than three point are assigned to class IV with a risk of 11%.
WFNS grade 1	GCS 15, no motor deficit
WFNS grade 2	GCS 13-14, no motor deficit
WFNS grade 3	GCS 13-14, with motor deficit
WFNS grade 4	GCS 7-12, with or without motor deficit
WFNS grade 5	GCS 3-6, with or without motor deficit

ASA: American Society of Anesthesiologists physical status. GOS: Glasgow Outcome Scale. RCRI: Revised Cardiac Risk Index. WFNS: World Federation of Neurological Surgeons Grading System for aneurysmal subarachnoid hemorrhage.

Appendix

Acknowledgements | Dankwoord

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– Sheryl Sandberg –

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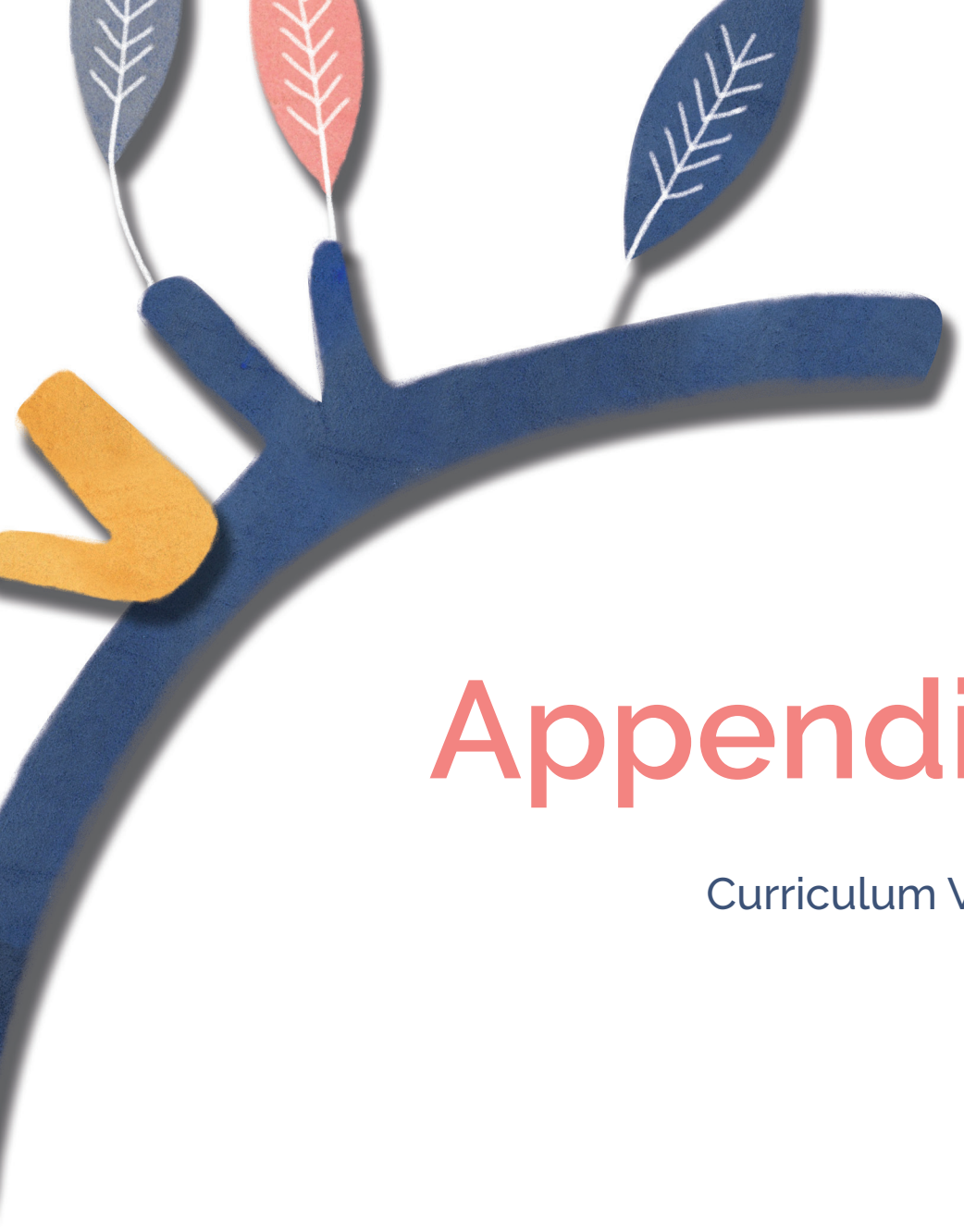
A



Appendix

Curriculum Vitae

CURRICULUM VITAE

Annemarie Akkermans was born on March 21st, 1988 in Oosterhout. She graduated from high school at the Stedelijk Gymnasium of Breda in 2006 (cum laude) and entered medical school at Maastricht University afterwards. She combined medical school with being an active sorority member, playing field hockey and long-distance running. She went on several clinical rotations abroad, e.g. to Kubang Kerian (Malaysia) and Stellenbosch (South-Africa).

Her interest in clinical research started during medical school. She participated in an elective research project on carboxymethyllysine in hepatic steatosis at the Laboratory for Metabolism and Vascular Medicine of Maastricht University, in 2009-2010. Afterwards, she did a research elective at the department of Ear-Nose-Throat surgery of the Maastricht University Medical Center, where she looked at laryngeal complications after general anesthesia. During this research elective, she developed her first interest in the field of anesthesiology. After graduation from medical school in 2012, she started working as an intensive care resident (not in training) at the Elisabeth-TweeSteden Hospital in Tilburg. In 2014, she started her anesthesiology training at the University Medical Center Utrecht (UMC Utrecht) under the supervision of Prof. dr. R.G. Hoff. During her first year as a resident, she participated in a joined neurosurgery-anesthesiology research project on postoperative ischemia after glioma resection. In 2016, she was given the opportunity to combine her residency with a PhD trajectory within the Clinical and Experimental Neuroscience program of the Graduate School of Life Sciences and the department of anesthesiology of the UMC Utrecht. She worked under the supervision of Prof. dr. W.A. van Klei, Prof. dr. G.J.E. Rinkel, dr. L.M. Peelen (until February 2019) and dr. J.A.R. van Waes. She conducted part of her research in collaboration with the Multicenter Perioperative Outcomes Group (MPOG) of the University of Michigan, Ann Arbor (U.S.), where she worked as a research fellow in 2016-2017. Throughout her PhD training, she obtained a degree in epidemiology and she audited several healthcare courses at Northwestern's Kellogg School of Management in Evanston, Illinois (U.S.).

Currently, she is finishing her anesthesiology residency and fellowship in intensive care medicine at the UMC Utrecht. She is married to Bram Philippen and they live in Utrecht with their son Noud.

Appendix

List of Publications

LIST OF PUBLICATIONS

Peer-reviewed articles

1. **Akkermans A,** van Waes JAR, van Doormaal TPC, de Waal EEC, Rinkel GJE, van der Zwan A, Kalkman CJ, van Klei WA; The effect of dobutamine and phenylephrine on cerebral perfusion in patients undergoing cerebral bypass surgery: a randomized crossover trial. BJA. 2020;125(4):539-547
2. **Akkermans A,** Vernooij LM, van Klei WA, van Waes JAR; Postoperative visits by dedicated anesthesiologists in patients with elevated troponin: a retrospective cohort study evaluating postoperative care utility and early detection of complications; Perioper Med (Lond). 2020:9:22:1-10
3. **Akkermans A,** Peelen LM, van Waes JAR, Rinkel GJ, van Klei WA; Cardiac events in patients with aneurysmal subarachnoid hemorrhage: predictive value of troponin elevation after aneurysm occlusion. Eur J Prev Cardiol. 2019;26(4):420-428.
4. **Akkermans A,** van Waes JAR, Thompson A, Shanks A, Peelen LM, Aziz MF, Biggs DA, Paganelli WC, Wanderer JP, Helsten DL, Kheterpal S, van Klei WA, Saager L; An observational study of end-tidal carbon dioxide trends in general anesthesia; Can J Anaesth. 2019;66(2):149-160
5. **Akkermans A,** van Waes JAR, Peelen LM, Rinkel GJE, van Klei WA; Blood pressure and end-tidal carbon dioxide ranges during aneurysm occlusion and neurologic outcome after an aneurysmal subarachnoid hemorrhage; Anesthesiology. 2019;130(1):92-105.
6. Brunings JW, Vanbelle S, **Akkermans A**, Heemskerk NMM, Kremer B, Stokroos RJ, Baijens LWJ; Observer Agreement for Measurements in Videolaryngostroboscopy; J Voice. 2018;32(6):756-762.

Non-peer reviewed articles

1. **Akkermans A,** Bijker JB; Perioperatief CVA; A&I; 2015; 4; 56-61

Abstracts

1. **Akkermans A,** Thompson A, Shanks AM, Saager L, Kheterpal S, van Waes JAR, Peelen LM, van Klei WA; An observational study of end-tidal CO2 trends in general anesthesia. A report from the Multicenter Perioperative Outcomes Group; Anesthesiology. 2017; 126: A2113 (www.asa-abstracts.com)
2. van der Boog ATJ, Rados M, **Akkermans A,** Dankbaar JW, Kizilates U, Hendrikse J, Hoff RG, Robe PAJ; P16.33 Postoperative ischemia and neurological deficits after glioma resection: incidence and risk factors; Neuro Oncol. 2017; 19(Suppl 3): iii116-iii116

Submitted articles:

1. **Akkermans A,** van Waes JAR, Kheterpal S, Pasma W, Saager L, Thompson A, van Klei WA; End-tidal carbon dioxide in general anesthesia and its association with postoperative pulmonary complications. A report from the Multicenter Perioperative Outcomes Group; Submitted

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