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Mechanisms contributing to hypotension after anesthetic induction with sufentanil, propofol, and rocuronium: a prospective observational study

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ORIGINAL RESEARCH

Mechanisms contributing to hypotension after anesthetic induction with sufentanil, propofol, and rocuronium: a prospective observational study

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Abstract

It remains unclear whether reduced myocardial contractility, venous dilation with decreased venous return, or arterial dilation with reduced systemic vascular resistance contribute most to hypotension after induction of general anesthesia. We sought to assess the relative contribution of various hemodynamic mechanisms to hypotension after induction of general anesthesia with sufentanil, propofol, and rocuronium. In this prospective observational study, we continuously recorded hemodynamic variables during anesthetic induction using a finger-cuff method in 92 non-cardiac surgery patients. After sufentanil administration, there was no clinically important change in arterial pressure, but heart rate increased from baseline by 11 (99.89% confidence interval: 7 to 16) bpm ($P < 0.001$). After administration of propofol, mean arterial pressure decreased by 23 (17 to 28) mmHg and systemic vascular resistance index decreased by 565 (419 to 712) dyn*s*cm^{-5}*m^2 (P values < 0.001). Mean arterial pressure was < 65 mmHg in 27 patients (29%). After propofol administration, heart rate returned to baseline, and stroke volume index and cardiac index remained stable. After tracheal intubation, there were no clinically important differences compared to baseline in heart rate, stroke volume index, and cardiac index, but arterial pressure and systemic vascular resistance index remained markedly decreased. Anesthetic induction with sufentanil, propofol, and rocuronium reduced arterial pressure and systemic vascular resistance index. Heart rate, stroke volume index, and cardiac index remained stable. Post-induction hypotension therefore appears to result from arterial dilation with reduced systemic vascular resistance rather than venous dilation or reduced myocardial contractility.

Keywords Intraoperative hypotension · Blood pressure · Cardiac output · Hemodynamic monitoring · Cardiovascular dynamics

1 Introduction

Intraoperative hypotension is associated with myocardial injury, acute kidney injury, and death [1–7]. The harm threshold appears to be a mean arterial pressure of about 65 mmHg, with risk progressively increasing at lower pressures and longer durations [8]. About a third of all intraoperative hypotension occurs between anesthetic induction and surgical incision [9, 10]. Since surgery has yet to start when

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this post-induction hypotension occurs, it is largely determined by patients' baseline risk and anesthetic management [10, 11]—with the latter being modifiable.

Anesthesia is often induced with a combination of sufentanil, propofol, and rocuronium. The neuromuscular blocking agent rocuronium probably has little effect on arterial pressure besides hemodynamic effects related to paralysis itself [12]. However, opioids promote post-induction hypotension [11, 13], as does propofol [14–17]. It remains unclear, though, whether post-induction hypotension is primarily due to reduced myocardial contractility, venous dilation with decreased venous return, or arterial dilation with reduced systemic vascular resistance [18–20]. The relative contribution of different potential pathophysiologic mechanisms to hypotension after anesthetic induction thus remain unclear.

A better understanding of pathophysiologic mechanisms contributing to post-induction hypotension may guide management and reduce hypotension. We therefore sought to assess the relative contribution of various hemodynamic mechanisms to hypotension after induction of general anesthesia with sufentanil, propofol, and rocuronium in adults having non-cardiac surgery.

2 Methods

2.1 Study design

This was a prospective observational study performed in the Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany between April and August 2018. The study was approved by the Ethics Committee of the Medical Association of Hamburg on January 9, 2018. All patients provided written informed consent. This observational study adheres to the STROBE guidelines.

2.2 Inclusion and exclusion criteria

We included adults with American Society of Anesthesiologists (ASA) physical status class I-III scheduled for elective gynecologic, urologic, otolaryngologic, or oral and maxillofacial surgery with general anesthesia and tracheal intubation. Patients were excluded if they had heart failure (New York Heart Association Functional Classification class II or higher), atrial fibrillation or other high-grade cardiac arrhythmias, peripheral artery occlusive disease (Fontaine stage II or higher), took beta blockers, had edema of the hands or fingers, had a history or suspicion of difficult airway, or an indication for rapid sequence induction. Patients were also excluded when regional anesthesia was performed before induction of anesthesia.

2.3 Study protocol and measurements

Patients were not premedicated. Preoxygenation was performed with a sealed face mask at a positive end-expiratory pressure of 5 mbar. Anesthesia was induced with sufentanil (0.2–0.5 $\mu g*kg^{-1}$), propofol (1.5–2.5 $mg*kg^{-1}$), and rocuronium (0.5–0.9 $mg*kg^{-1}$). Patients' tracheas were intubated and mechanical ventilation was initiated with a tidal volume of 6–8 $mL*kg^{-1}$ at a positive end-expiratory pressure of 5 mbar. After induction, general anesthesia was maintained with either propofol or inhaled sevoflurane.

In addition to routine anesthetic monitoring, we continuously measured hemodynamic variables using a non-invasive finger-cuff method (CNAP; CNSystems Medizintechnik GmbH, Graz, Austria). The CNAP system was calibrated to brachial arterial pressure obtained from the system's upper-arm cuff. The CNAP system provides continuous arterial pressure values and waveforms. Using pulse wave analysis, the CNAP system also estimates advanced hemodynamic variables including cardiac output and systemic vascular resistance. The CNAP system was validated in several clinical studies showing that it reliably estimates arterial pressure and cardiac output [21–25].

We recorded arterial pressure, heart rate, cardiac index, stroke volume index, and systemic vascular resistance index at the following time points (Fig. 1): before induction of general anesthesia, during preoxygenation, 45 s after administration of sufentanil, 45 s after administration of propofol, 90 s after administration of rocuronium, 60 s after tracheal intubation, and 180 s after tracheal intubation.

2.4 Statistical analysis

Data are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables. Linear mixed effects models were used to estimate change from baseline (i.e., before induction of anesthesia) in various hemodynamic variables to 6 time points during induction using an autoregressive (AR (1)) covariance structure. The overall significance level was 0.05; Bonferroni correction was used to control the type I error for 7 outcomes and 6 comparisons within each outcome, and the significant level for each comparison was 0.0011 (i.e., alpha = 0.05/7/6 = 0.0011).

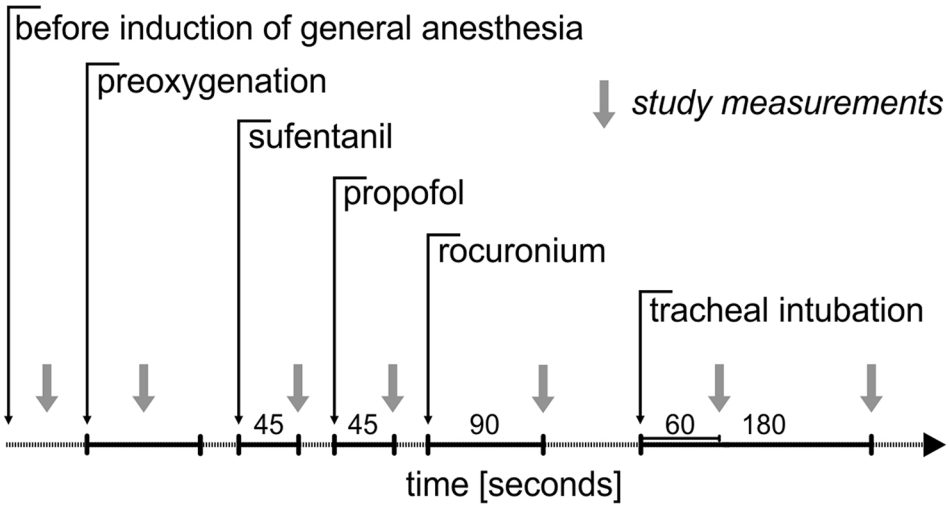

Fig. 1 Measurement time points. We recorded hemodynamic variables before induction of general anesthesia, during preoxygenation, 45 s after administration of sufentanil, 45 s after administration of propofol, 90 s after administration of rocuronium, 60 s after tracheal intubation, and 180 s after tracheal intubation

Table 1 Baseline characteristics

Factor	$n_{missing}$	Total (n = 92)
Demographic		
Age, years	0	36 ± 13
Female, n (%)	0	55 (60)
Height, cm	0	172 ± 9
Weight, kg	0	74 ± 17
Body mass index, $kg*m^{-2}$	0	25 ± 5
ASA physical status class, n (%)	0	
1		35 (38)
2		49 (53)
3		8 (9)
Induction medication		
Sufentanil (μg)	0	35 ± 6
Propofol (mg)	0	187 ± 39
Rocuronium (mg)	0	37 ± 8

Statistics presented as mean ± standard deviation

ASA, American Society of Anesthesiologists

3 Results

We enrolled 125 patients but excluded 28 who were given norepinephrine (14 patients) or additional doses of propofol (14 patients) during the study period. We also excluded 5 patients because of technical problems during data recording. We thus included 92 patients in the final analysis.

Participating patients were young, with a mean ± SD age of 36 ± 13 years and relatively healthy with 91% having ASA physical status class I or II (Table 1). General anesthesia was induced with 35 ± 6 μg of sufentanil, 187 ± 39 mg of propofol, and 37 ± 8 mg of rocuronium.

Hemodynamic variables at specified time points are shown in Fig. 2 and Supplemental Table S1. Patients were normotensive at baseline with mean arterial pressure being 96 ± 13 mmHg. At baseline, heart rate was 72 ± 13 bpm, cardiac index was 3.2 ± 0.6 $L*min^{-1}*m^{-2}$, stroke volume index was 45 ± 6 $mL*m^{-2}$, and systemic vascular resistance index was 2309 ± 544 $dyn*s*cm^{-5}*m^2$.

After sufentanil administration, heart rate increased from baseline by 11 (99.89% confidence interval: 7 to 16) bpm (P < 0.001). As there was no clinically important change in stroke volume index after sufentanil administration the increase in heart rate resulted in a slight increase in cardiac index of 0.5 (0.3 to 0.7) $L*min^{-1}m^{-2}$. There was no clinically important change in arterial pressure after sufentanil administration.

After administration of propofol, mean arterial pressure decreased by 23 (17 to 28) mmHg and systemic vascular resistance index decreased by 565 (419 to 712) $dyn*s*cm^{-5}*m^2$ (P values < 0.001). After propofol administration, mean arterial pressure was < 65 mmHg in 27 patients (29%). Heart rate returned to baseline after administration of propofol, and stroke volume index and cardiac index remained stable compared to baseline.

After administration of rocuronium, mean arterial pressure, systemic vascular resistance index, and heart rate all were below baseline values (P values < 0.001), but transiently increased to baseline levels after tracheal intubation.

180 s after tracheal intubation, there were no clinically important differences compared to baseline in heart rate, stroke volume index, or cardiac index. However, arterial pressure and systemic vascular resistance index remained well below baseline. 180 s after tracheal intubation, mean arterial pressure was 15 (10 to 20) mmHg lower than at baseline and it was < 65 mmHg in 21 patients (23%).

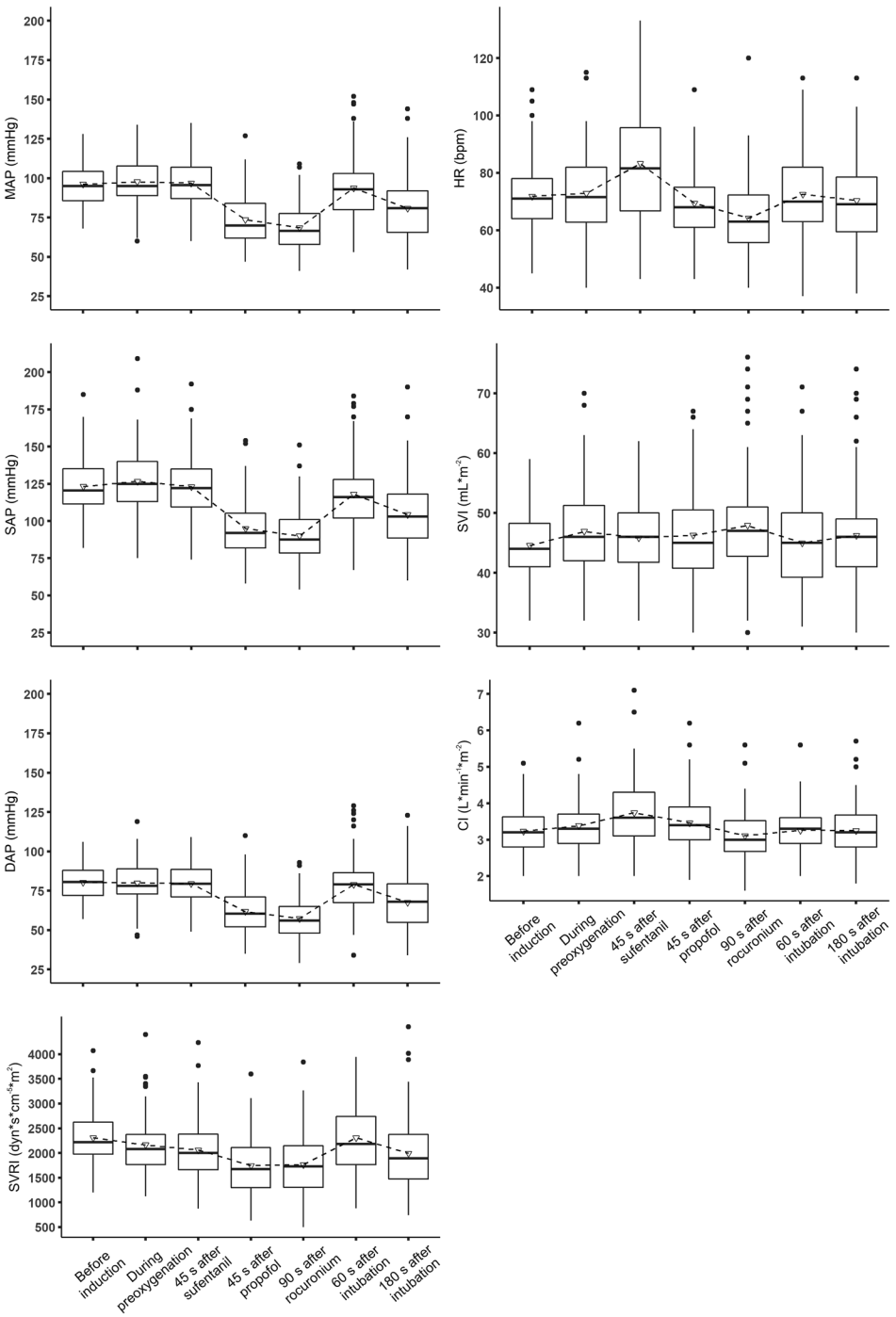

Fig. 2 Hemodynamic variables during the induction of general anesthesia. Boxplots showing mean (triangle) and median (horizontal bar) with 25th–75th percentile (box) of hemodynamic variables during the induction of general anesthesia. Whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively. Circles represent outliers. *MAP* mean arterial pressure, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *SVRI* systemic vascular resistance index, *HR* heart rate, *SVI* stroke volume index, *CI* cardiac index

Supplemental Figure S1 shows Spaghetti plots for individual patients and Supplemental Figure S2 shows boxplots of changes in hemodynamic variables over time.

4 Discussion

In this prospective observational study, we sought to assess the relative contribution of various hemodynamic mechanisms to hypotension after induction of general anesthesia with sufentanil, propofol, and rocuronium in adults having non-cardiac surgery.

Heart rate and cardiac index increased after sufentanil administration, but presumably not due to a pharmacological

effect of sufentanil. Instead, the increases likely reflect stress-induced sympathetic activation in anticipation of anesthetic induction. Propofol caused a clinically important reduction in arterial pressure. In addition, systemic vascular resistance index decreased significantly, by about 25%, after propofol administration. Heart rate returned to baseline after administration of propofol, and stroke volume index and cardiac index remained stable compared to baseline. Hypotension after propofol administration thus was linked to a decrease in systemic vascular resistance. Rocuronium administration had no additional clinically relevant effect on cardiovascular dynamics.

A controversy remains about propofol-induced post-induction hypotension. The main mechanisms proposed are a decrease in myocardial contractility, venous dilation with a decrease in venous return, and arterial dilation with a decrease in systemic vascular resistance [18–20]. Experimental and animal studies suggest that propofol reduces myocardial contractility. For example, propofol directly depresses myocardial contractility in isolated guinea pig myocardial trabeculae [26] and isolated perfused guinea pig hearts [27]. Propofol similarly reduces myocardial contractility in anesthetized rabbits [28]. Propofol decreases inotropy in anesthetized dogs, but also reduces arterial and venous vascular tone [29]. In 23 major abdominal surgery patients, propofol markedly decreased mean arterial pressure, heart rate, and cardiac output [17]. We found that neither stroke volume index nor cardiac index were reduced after propofol administration, suggesting that myocardial contractility was hardly influenced. Venous dilation has been proposed as a cause of propofol-induced hypotension [19, 30]. Venous dilation alone would reduce venous return to the heart, causing stroke volume to decrease. Since we did not observe a significant decrease in stroke volume index, propofol-induced venous dilation in our study seems unlikely. Our results thus suggest that propofol-induced post-induction hypotension results from arterial dilation with reduced systemic vascular resistance rather than venous dilation or reduced myocardial contractility. Our results are consistent with a previous small study which also reported decreased afterload without a compensatory increase in heart rate or cardiac output resulting in hypotension [31].

About a third of our patients had mean arterial pressures < 65 mmHg after propofol administration. While there is strong evidence that intraoperative hypotension is associated with postoperative organ failure and death [1–7] research only recently focused on characterizing different phases of intraoperative hypotension [9, 10]. For anesthesiologists it is crucial to acknowledge that about a third of all intraoperative hypotension occurs between anesthetic induction and surgical incision and that hypotension during this period appears equally harmful as hypotension that occurs during surgery [9]. Because post-induction hypotension is consequent to anesthetic drugs, much of it is presumably preventable—and probably should be prevented.

This reinforces the need to mitigate the potential cardiovascular effects of induction of general anesthesia. Our results indicate that post-induction hypotension results largely from arterial dilation, and therefore that vasopressors will generally be the most appropriate treatment. Which vasopressor(s) might be best remains unclear as there are sparse data related to the treatment or prophylaxis of post-induction hypotension by using vasopressors. In a preliminary study, phenylephrine and norepinephrine boluses effectively counteracted intraoperative hypotension caused by propofol anesthesia [32]. Although logic suggests that fluid loading may help prevent hypotension, pre-induction crystalloid loading does not prevent post-induction hypotension [33, 34]. Colloid loading may somewhat be more effective, but still fails to prevent much hypotension [35]. Vasopressors thus appear to be a preferable clinical strategy.

In our study, induction agents were standardized, but exact doses were not and remained at the discretion of the attending anesthesiologist. Additionally, we used a non-invasive finger-cuff method to assess advanced hemodynamic variables. The non-invasive monitoring system we used is well validated for the measurement of continuous blood pressure [21–23] and cardiac output [24, 25]. It is therefore unlikely that our overall conclusions would differ with invasive measurements. Further, we did not use echocardiography that could have provided important information on myocardial function. Our study was restricted to relatively young healthy adults and may thus not be generalizable to older and sicker patients, especially patients with cardiovascular co-morbidities.

5 Conclusions

In patients having non-cardiac surgery, anesthetic induction with sufentanil, propofol, and rocuronium was associated with a clinically important (and statistically significant) reduction in arterial pressure and systemic vascular resistance index. Heart rate and stroke volume index, and therefore cardiac index, basically remained stable during anesthetic induction. Post-induction hypotension therefore appears to result from arterial dilation with reduced systemic vascular resistance rather than venous dilation or reduced myocardial contractility. Future research should evaluate strategies for early detection and avoidance of post-induction hypotension, especially the (preemptive) use of vasopressors.

Supplementary Information The online version of this article (https://doi.org/10.1007/s10877-021-00653-9) contains supplementary material, which is available to authorized users.

Author contributions BS conceived and designed the study, was responsible for data analysis and interpretation, drafted the manuscript, performed the statistical analyses, supervised the study. E-JB was responsible for acquisition of data, was responsible for data analysis and interpretation, critically revised the manuscript for important intellectual content. LB was responsible for data analysis and interpretation, critically revised the manuscript for important intellectual content. PH was responsible for data analysis and interpretation, critically revised the manuscript for important intellectual content. GG was responsible for data analysis and interpretation, critically revised the manuscript for important intellectual content. DY was responsible for data analysis and interpretation, performed the statistical analyses, drafted the manuscript. CM was responsible for data analysis and interpretation, performed the statistical analyses, critically revised the manuscript for important intellectual content. EJM was responsible for data analysis and interpretation, performed the statistical analyses, critically revised the manuscript for important intellectual content. DIS was responsible for data interpretation, drafted the manuscript. DER conceived and designed the study, was responsible for acquisition of data, was responsible for data analysis and interpretation, drafted the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data availability Department of Anesthesiology, Center of Anesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.

Compliance with ethical standards

Conflict of interest Bernd Saugel has received institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from CNSystems Medizintechnik GmbH (Graz, Austria). Bernd Saugel has received honoraria for consulting, honoraria for giving lectures, and refunds of travel expenses from Edwards Lifesciences Inc. (Irvine, CA, USA). Bernd Saugel has received honoraria for consulting, institutional restricted research grants, honoraria for giving lectures, and refunds of travel expenses from Pulsion Medical Systems SE (Feldkirchen, Germany). Bernd Saugel has received institutional restricted research grants from Retia Medical LLC. (Valhalla, NY, USA). Bernd Saugel has received honoraria for giving lectures from Philips Medizin Systeme Böblingen GmbH (Böblingen, Germany). Bernd Saugel has received honoraria for consulting, institutional restricted research grants, and refunds of travel expenses from Tensys Medical Inc. (San Diego, CA, USA). Daniel I. Sessler is a consultant for Edwards Lifesciences Inc and Sensifree (Cupertino, CA, USA). The Department of Outcomes Research conducts research funded by Edwards Lifesciences Inc.. All other authors have no conflicts of interest.

Consent to participate All patients provided written informed consent.

Consent to publish All patients signed informed consent regarding publishing their data.

Ethical approval The study was approved by the Ethics Committee of the Medical Association of Hamburg, Hamburg, Germany (Chairperson Prof. R. Stahl) on January 9, 2018.

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2 Introduction

Intraoperative hypotension (IOH) is common. A 2007 review lists 140 different definitions of IOH in the literature searched, thus incidences range from 5% to 99% (Bijker et al., 2007). Studies show an association between IOH and myocardial injury (Sessler and Khanna, 2018, van Waes et al., 2016, Walsh et al., 2013), acute kidney injury (Maheshwari et al., 2018b, Sun et al., 2015, Walsh et al., 2013), and death (Monk et al., 2015). In its 2019 consensus paper, The PeriOperative Quality Initiative indicated that even brief episodes of low arterial blood pressure (BP) are harmful (Sessler et al., 2019).

2.1 Approach of the study

It has been shown that approximately one third of all IOH happens before incision, and is thus understood to be related to the anesthesiologic procedure (Maheshwari et al., 2018b). Whether a decrease in myocardial contractility, venous dilation with decreased return flow, or arterial dilation with reduced systemic vascular resistance (SVR) represents the primary mechanism leading to hypotension after anesthetic induction has not been fully clarified (Goodchild and Serrao, 2015, Green, 2015, Kakazu and Lippmann, 2015). A detailed understanding of the pathophysiology is desirable, as it could further tailor anesthesiologic management and potentially reduce the incidence of IOH. By using advanced hemodynamic monitoring during induction of general anesthesia, our study was designed to help estimate the relative contribution of predefined hemodynamic variables to the development of hypotension after induction of anesthesia. Heart rate (HR), systolic, diastolic, and mean arterial blood pressure (SAP, DAP, MAP), cardiac index, stroke volume index (SVI), and systemic vascular resistance index (SVRI) were continuously recorded. For the continuous, noninvasive collection of these variables, we used the CNAP® (continuous noninvasive blood pressure) system, provided by CNSystems Medizintechnik GmbH (Graz, Austria). The following section is intended to provide an overview of the CNAP system and some of the generated hemodynamic variables that exceed basic hemodynamic monitoring.

2.2 Basic hemodynamic monitoring

Basic hemodynamic monitoring includes the electrocardiogram, noninvasive measurement of BP, and peripheral oxygen saturation measured by pulse oximetry. Variables are collected either continuously or intermittently. Basic hemodynamic monitoring serves the purpose of detecting instabilities of the cardiovascular system (Rex, 2010).

However, it does not allow for accurate assessment of abnormalities of other variables, such as altered volume status or changes in cardiac output (CO) (Janssens et al., 2016). These variables can potentially provide information on the underlying mechanisms resulting in hemodynamic instability, and are assessed using advanced hemodynamic monitoring (Rex, 2010).

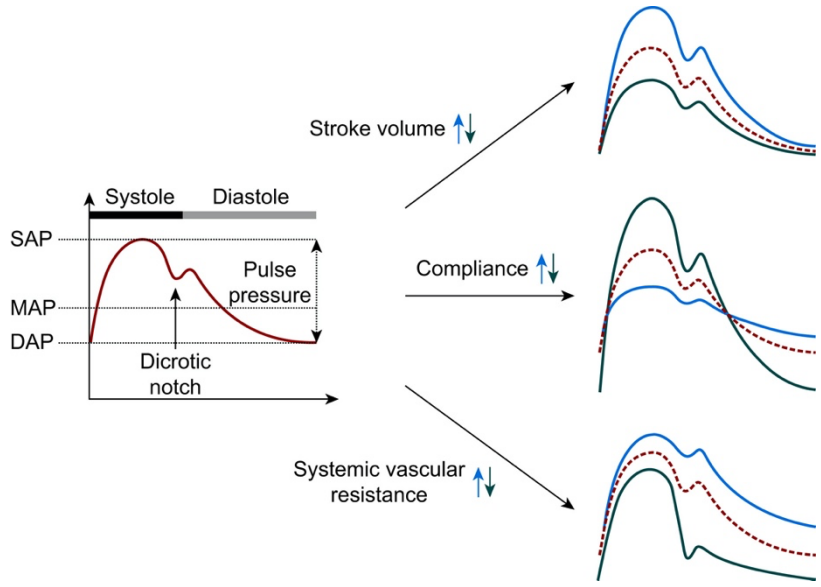
2.3 Advanced hemodynamic monitoring

Advanced hemodynamic monitoring allows for more accurate monitoring of the cardiorespiratory system, and is a common tool to assess critically ill patients (Janssens et al., 2016). Variables can be collected invasively, minimally-invasively, and noninvasively (Kaufmann et al., 2020), the latter including the finger-cuff method (Saugel et al., 2021) used in our study. Hemodynamically unstable, i.e., hypotensive, tachycardic, or clinically hypoperfused patients, require goal-directed diagnostics and, ideally, causal therapy, targeting optimized tissue, and organ perfusion (Janssens et al., 2016). Knowledge of the hemodynamic disorder's origin helps to select therapeutic paths and monitor their effects (Teboul et al., 2016). Advanced hemodynamic monitoring allows for the assessment of preload, afterload, and contractility, all determinants of CO (Janssens, 2000). CO, in turn, can be interpreted as the primary determinant of oxygen delivery (Saugel et al., 2017), and is thus of vital importance in therapeutic decision making. Changes in CO can reflect macrocirculatory disorders, such as hypovolemia, myocardial dysfunction, or altered vascular tone (Teboul et al., 2016). Specifically, CO represents the blood volume pumped by the left ventricle within one minute (Janssens et al., 2016). Other advanced hemodynamic variables are cardiac index, SVI, and SVRI, all monitored in our study. The cardiac index represents CO in relation to the body surface area in m^2. The SVI represents stroke volume (SV), i.e., the volume pumped out of the left ventricle per heartbeat, in relation to the body surface area in m^2. The SVRI represents SVR in relation to the body surface area in m^2 (Janssens, 2000). SVR is calculated by subtracting central venous pressure from MAP and then dividing the value by CO, following Ohm's law (Grissmer, 2021). In the clinical setting, SVRI is understood as a surrogate for cardiac afterload (Anetsberger and Jungwirth, 2015), i.e., the cardiac wall tension required to overcome end-diastolic aortic and pulmonary pressure (Köster and Hamm, 2018).

2.4 CNAP system

The CNAP system provides BP measurement based on the volume clamp method (Saugel et al., 2014) and uses pulse wave analysis (PWA) to estimate CO (Saugel et al., 2021). The arterial blood pressure waveform (see Fig. 1) is therefore mathematically analyzed by PWA to estimate CO (Kouz et al., 2021).

Figure 1: Arterial blood pressure waveform

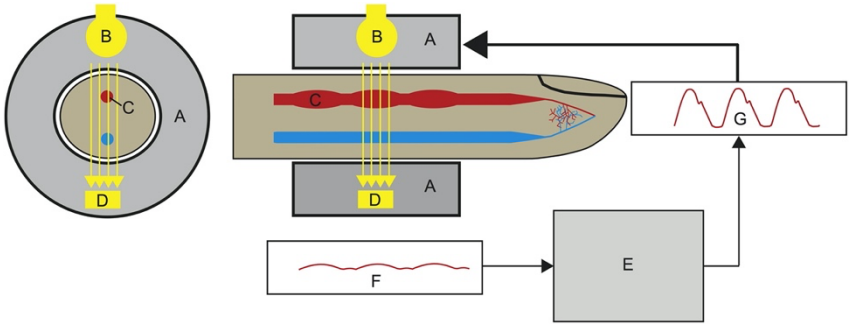


The arterial blood pressure waveform represents changing arterial pressure within a cardiac cycle. It shows SAP, DAP and MAP, as well as pulse pressure, i.e., the difference between SAP and DAP. The dicrotic notch represents the aortic valve closure at the end of systole. The waveform is determined by left ventricular SV, aortic compliance, and SVR, and changes in the determinants each lead to changes in the waveform (Saugel et al., 2021).

The CNAP system consists of an upper arm cuff performing a noninvasive oscillometric BP measurement over the brachial artery (Saugel et al., 2014). The oscillometric measurement is performed by inflating the cuff to above the patient's SAP. When pressure is released, arterial vascular wall oscillations at the cuff become measurable. MAP is represented by the cuff pressure at which the highest pulsation amplitude is measured (Kuck and Baker, 2018, Schröder, 2016). The system further consists of a two-finger sensor placed on the index and ring finger. The finger sensor is connected to a CNAP controller attached to the patient's forearm. Values measured by the finger sensor are calibrated to brachial BP (Saugel et al., 2014). The underlying method was initially described by Penáz and colleagues (Penáz et al., 1976) and will only be briefly discussed here. The finger sensor holds an inflatable cuff as well as an infrared plethysmograph measuring the blood volume of the finger arteries (see Fig. 2). The blood volume in the finger arteries changes according to the changing BP within a cardiac cycle. By applying constant counterpressure, the inflatable cuff inside the finger

sensor keeps the blood volume in the finger arteries and therefore their diameter constant during the pressure pulse; in other words, a constant volume is “clamped”. This is achieved by an integrated, automated feedback system that rapidly inflates or deflates the cuff. Based on the required back pressure needed to keep a constant volume in the finger arteries, the arterial BP waveform can be reconstructed indirectly. Thus, by means of PWA, CO can be estimated (Kuck and Baker, 2018, Saugel et al., 2021). As a noninvasive instrument, the CNAP system is easy to handle, has few side effects, and allows for the collection of advanced hemodynamic variables in real time.

Figure 2: The volume clamp method



Exemplary presentation of the volume clamp method: **A**: Inflatable cuff around the patient’s finger. **B**: Infrared plethysmograph within the cuff. **C**: Artery of the finger. **D**: Light detector within the sensor to measure absorbed light, i.e., monitor change in blood volume. **E**: Automated feedback system for adjustment of back pressure on the artery for constant diameter. **F**: Pressure required to keep a constant diameter. **G**: Indirect reconstruction of the arterial waveform. (Saugel et al., 2014).

3 Methods

3.1 Study design

After receiving approval by the Ethics Committee of the Hamburg Medical Association in January 2018, we conducted this prospective observational study in the Department of Anesthesiology and Intensive Care Medicine at the University Medical Center Hamburg-Eppendorf between April and August 2018, adhering to the STROBE guidelines (Saugel et al., 2022).

3.2 Inclusion and exclusion criteria

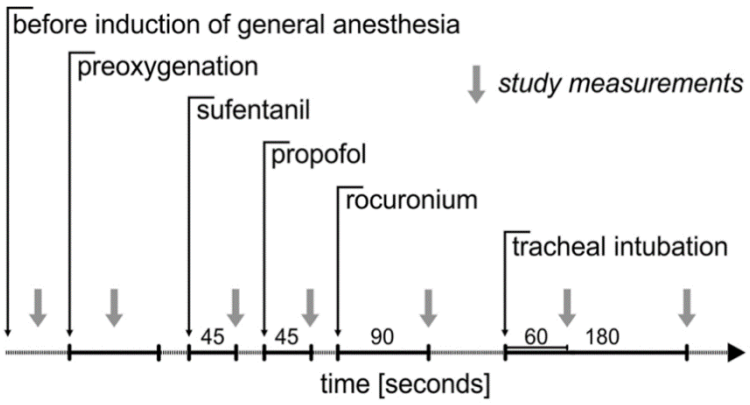
Inclusion criteria were met by adults with American Society of Anesthesiologists (ASA) physical status I-III. We included patients who were scheduled for elective gynecologic, oral and maxillofacial, otolaryngologic or urologic surgery under general anesthesia with tracheal intubation. Patients showing signs of heart failure (New York Heart Association Functional Classification class II or higher), atrial fibrillation, or other high-grade cardiac arrythmias were excluded from the study. Peripheral artery occlusive disease (Fontaine stage II or

higher), edema of hands or fingers, and the use of beta blockers also led to exclusion. With a history or suspicion of difficult airway, an indication for rapid sequence induction, or regional anesthesia performed before induction of general anesthesia, patients had to be excluded from the study as well (Saugel et al., 2022).

3.3 Study protocol and measurements

There was no premedication given. Preoxygenation was performed with a sealed face mask at a positive end-expiratory pressure of 5 mbar. For induction of general anesthesia, 0.2-0.5 $\mu g*kg^{-1}$ sufentanil, 1.5-2.5 $mg*kg^{-1}$ propofol, and 0.5-0.9 $mg*kg^{-1}$ rocuronium were administered. Patients were intubated and mechanically ventilated with a tidal volume of 6-8 $mL*kg^{-1}$ at a positive end-expiratory pressure of 5 mbar. General anesthesia was either maintained by propofol or inhaled sevoflurane. Routine anesthetic monitoring was present. Additionally, hemodynamic variables were continuously collected using a noninvasive finger-cuff method (CNAP, CNSystems Medizintechnik GmbH, Graz, Austria). The CNAP system was calibrated to brachial BP measured by the system's upper arm cuff. Continuous BP values and waveforms as well as advanced hemodynamic variables such as CO and SVR are provided by the CNAP system, the latter two estimated using PWA. Several clinical studies show reliable estimates of BP and CO by the CNAP system, validating the technique (Jeleazcov et al., 2010, Smolle et al., 2015, Wagner et al., 2016). BP, HR, cardiac index, SVI, and SVRI were measured at predefined time points (see Fig.3): before induction of general anesthesia, during preoxygenation, 45 s after application of sufentanil, 45 s after application of propofol, 90 s after application of rocuronium, 60 s, and 180 s after tracheal intubation (Saugel et al., 2022).

Figure 3: Collection of hemodynamic variables: timepoints



Predefined hemodynamic variables were collected at 6 different time points using the CNAP system (Saugel et al., 2022).

3.4 Statistical analysis

Categorial variables are listed as n (%) and continuous variables as mean ± standard deviation (SD). To assess change from baseline (i.e., patients' hemodynamic state before general anesthesia was induced) in several hemodynamic variables to 6 predefined time points during anesthetic induction, we applied linear mixed effect models using an autoregressive covariance structure. The level of overall significance was 0.05. We used Bonferroni correction to control the type I error for 7 outcomes and 6 comparisons within each outcome. The significance level for each comparison was 0.0011 (i.e., alpha 0.05/7/6) = 0.0011) (Saugel et al., 2022).

4 Results

Between April and August 2018, we collected data from 125 patients. 33 had to be excluded due to technical problems during measurement, or additional doses of epinephrine or propofol during induction of general anesthesia. In the end, we included 92 patients, most of whom were young, with a mean ± SD age of 36 ± 13 years, and with 91% having ASA physical status I or II. To induce general anesthesia, 35 ± 6 µg sufentanil, 187 ± 39 mg propofol, and 37 ± 8 mg rocuronium were administered. Patients presented with a normotensive baseline, MAP being 96 ± 13 mmHg. At baseline, HR was 72 ± 13 bpm, cardiac index was 3.2 ± 0.6 $L*min^{-1}*m^{-2}$, SVI was 45 ± 6 $mL*m^{-2}$, and SVRI was 2309 ± 544 $dyn*s*cm^{-5}*m^2$. After application of sufentanil, HR increased from baseline by 11 (99.89% confidence interval (CI): 7 to 16) bpm (P <0.001). There was no clinically important change in SVI after sufentanil administration, thus the increase in HR resulted in a slight increase in cardiac index of 0.5 (CI 0.3 to 0.7) $L*min^{-1}m^{-2}$. No clinically relevant change in BP was seen after sufentanil was given. After application of propofol, MAP decreased by 23 (CI 17 to 28) mmHg and was <65 mmHg in 27 patients (29%). SVRI decreased by 565 (CI 419 to 712) $dyn*s*cm^{-5}*m^2$ (P values <0.001). HR returned to baseline after application of propofol, while SVI and cardiac index remained stable compared to baseline. After application of rocuronium, MAP, SVRI, and HR all remained below baseline values (all P values <0.001). During intubation, the values temporarily increased to baseline levels. 180 seconds after tracheal intubation, no clinically relevant differences compared to baseline in HR, SVI, or cardiac index were noted. However, BP and SVRI stayed below baseline. At this time point, MAP was 15 (CI 10 to 20) mmHg below baseline, and it was <65 mmHg in 21 patients (23%) (Saugel et al., 2022).

5 Discussion

This prospective observational study was designed to help estimate the relative contribution of predefined hemodynamic variables to the development of hypotension after induction of general anesthesia with sufentanil, propofol, and rocuronium. To collect variables, we used the CNAP system, which allows for noninvasive continuous BP measurement based on the volume clamp method and estimation of CO by PWA. We observed a clinically significant decrease in BP and SVRI after administration of propofol with concomitant stable HR, SVI, and cardiac index, i.e., stable CO in relation to the body surface area in m^2. Our results suggest that hypotension after propofol administration during induction of general anesthesia occurs due to arterial dilation with decreased SVRI.

5.1 Discussion of results

Hypotension and decreased SVR following propofol administration are well known (Fairfield et al., 1991, Pensado et al., 1993, Larsen et al., 1988) and shown in our study. Discussed pathomechanisms leading to hypotension after propofol administration include a decrease in SVR as well as reduced myocardial contractility (Green, 2015). A reduction in contractility after propofol administration has been demonstrated in isolated guinea pig myocardial trabeculae (Klarenbosch et al., 2001). In our study, we understood stable SVI and cardiac index after propofol administration as a sign of unimpaired myocardial contractility. With regard to significantly reduced SVRI, we interpreted arterial dilation with reduced SVR as the probable cause of hypotension after propofol administration (Saugel et al., 2022). Our findings match the results of an observational study in which variables were invasively collected during elective hip surgery. 10 patients were administered propofol for induction and maintenance of anesthesia. A decrease in SVR and BP was observed while HR, SV, and CO remained stable. The authors concluded that hypotension after propofol administration occurred mainly due to reduced cardiac afterload without a responding increase in HR or CO (Claeys et al., 1988). A contribution of arterial and venous vasculature to hypotension and change in SVR after propofol administration is also discussed (Green, 2015, de Wit et al., 2016). In our study, patients did not show significant change in SVI after propofol administration. We concluded that hypotension with decreased SVRI was not likely caused by venous dilation, which would have resulted in reduced venous return and consequently reduced SV (Saugel et al., 2022). In contrast to our observations, results from many years ago demonstrate venous dilation with increased venous capacity as a cause for hypotension after propofol administration. Studies investigated the effect of propofol on isolated venous and

arterial rat vessels (Bentley et al., 1989) and observed cardiovascular effects in dogs, in which influences of the autonomic nervous system had been eliminated before propofol administration (Goodchild and Serrao, 1989). The results showed no effect on the arterial vascular system (Goodchild and Serrao, 2015). Venous dilation was also demonstrated in 36 patients' forearms during general anesthesia induced with propofol, reinforcing the hypothesis that the venous vasculature takes a role in the development of hypotension after propofol administration (Muzi et al., 1992). Recent work shows ongoing research concerning the venous system. Variables were invasively collected in 15 patients during induction of general anesthesia with propofol. The authors demonstrated a decrease in mean systemic filling pressure (MSFP) as a possible cause of decreased return flow to the right heart (Zucker et al., 2022). MSFP is the prevailing adapted pressure in all blood vessels in the absence of blood flow during asystole (Ehmke, 2019). Its measurability has been described in ventilated patients (Maas et al., 2009) and MSFP is understood to be a good indicator of pressure in the venous system (Zucker et al., 2022). A previous study had focused on the effect of propofol on intravascular volume and capacity for the first time. In addition to other invasively collected variables, MSFP was observed in 17 patients who had undergone major thoracoabdominal surgery. After surgery, general anesthesia was maintained by propofol, and patients were administered 3 different dosages of propofol. Results showed a decrease in MAP with increasing propofol dosages with little change in CO, consistent with the results observed in our study. In addition, a decrease in MSFP, as well as decreased venous and SVR, were shown with increasing propofol dosages (de Wit et al., 2016). The influence of propofol on CO seems not to have been conclusively determined (de Wit et al., 2016). Observations show both reduced (Fairfield et al., 1991, Kakazu and Lippmann, 2015, Larsen et al., 1988, Möller Petrun and Kamenik, 2013) and stable (Claeys et al., 1988, Pensado et al., 1993, de Wit et al., 2016) CO, as also observed by us.

5.2 Limitations of our study

The question to be explored in this study aimed at general hemodynamic considerations. Inclusion and exclusion criteria did not explicitly aim for a young and relatively healthy cohort. It can be argued that studying a patient population like ours and thus initially considering the presumed physiological state of the cardiovascular system seems reasonable. However, it may not be possible to apply our observations to older and more impaired patients. It should be noted that with 92 patients, we observed a small cohort in a single-center study. For comparability of results, general anesthesia was induced using sufentanil, propofol, and

rocuronium followed by tracheal intubation. Our protocol provided a dosage frame according to the Standard Operating Procedure of the Department of Anesthesiology. Within this frame, individual dosages were at the physicians' discretion. Individual patient needs justify this approach. We did not use methods to objectively monitor the depth of anesthesia, such as bispectral index monitoring. The method provides thresholds below which unconsciousness is highly probable (Johansen, 2006). The non-strictly standardized administration of anesthetic medication and the shortage of objectification of depth of anesthesia must be considered when assessing the generalizability of our observations. We used the CNAP system to noninvasively collect variables. The system is easy to handle, has few side effects, and provides advanced hemodynamic variables in real time. To our knowledge, there are no CNAP validation studies on the collection of SVI and SVRI. Induction of general anesthesia is often accompanied by rapid changes in BP (Gayat et al., 2013). An observational study comparing intraarterial BP measurement with data obtained by the CNAP system demonstrated delayed detection of maximum and minimum BP values during induction of anesthesia and intubation by the CNAP system (Gayat et al., 2013). This is contradicted by results of an earlier study, which showed that the CNAP system detected rapid changes in BP as reliably as intraarterial BP measurement (Jeleazcov et al., 2010). We did not use methods to assess myocardial contractility, in contrast to other authors who chose transthoracic echocardiography to assess cardiac performance after induction of general anesthesia (Yang et al., 2014). We also did not use methods to assess the venous vasculature. This could have contributed to a more detailed consideration of the discussed pathomechanisms of hypotension after induction of anesthesia. Other authors who also collected hemodynamic variables after propofol administration used intraarterial BP measurement as well as a central venous line combined with a pressure transducer (de Wit et al., 2016).

5.3 Outlook

IOH is common. It is associated with severe organ damage (Sessler and Khanna, 2018, Walsh et al., 2013), and is an important focus of research. Attempts have been made to categorize IOH and identify risk factors as well as future scientific assignments (Südfeld et al., 2017, Maheshwari et al., 2018b). Even brief episodes seem harmful (Sessler et al., 2019), thus strategies for patient care seem obvious: prevention and early detection of IOH, as well as adequate and rapid therapy to shorten the time spent in IOH. Knowledge of predisposing factors of IOH may influence the choice of anesthetic procedure. Thus, identification of risk factors, as done by retrospective data analysis (Reich et al., 2005), seems useful. It has been

demonstrated that the use of noninvasive continuous monitoring reduces the time spent in hypotension, as well as its extent in patients. A study compared oscillometric intermittent BP measurement with noninvasive continuous BP measurement using the volume clamp method in 316 patients. The authors attributed their results to a more rapid detection of a decrease in BP with continuous measurement (Maheshwari et al., 2018a). This clearly shows how the use of noninvasive monitoring systems could complement perioperative basic monitoring and contribute to the reduction of IOH. Patients with no indication for invasive monitoring may nevertheless be at risk for IOH. The use of noninvasive continuous monitoring systems would allow for a better assessment of underlying causes of IOH and a more targeted selection of the appropriate therapy, in addition to reducing the time spent in hypotension.

6 Conclusion

Induction of general anesthesia with sufentanil, propofol and rocuronium resulted in a clinically relevant (and statistically significant) decrease in BP and SVRI in patients undergoing non-cardiac surgery, while HR, SVI, and consequently cardiac index, remained stable. Hypotension after induction of anesthesia thus appears to occur because of arterial dilation with reduced SVR rather than venous dilation or a decrease in myocardial contractility. Future research should investigate strategies of early detection and prevention of hypotension secondary to anesthetic induction (Saugel et al., 2022).

7 List of abbreviations

ASA	American Society of Anesthesiologists
BP	Arterial blood pressure
CI	Confidence interval
CNAP	Continuous noninvasive blood pressure
CO	Cardiac output
DAP	Diastolic arterial pressure
HR	Heart rate
IOH	Intraoperative hypotension Intraoperative Hypotonie
MAP	Mean arterial pressure
MSFP	Mean systemic filling pressure
PWA	Pulse wave analysis
SAP	Systolic arterial pressure
SD	Standard deviation
STROBE	Strengthening The Reporting of Observational Studies
SV	Stroke volume
SVI	Stroke volume index
SVR	Systemic vascular resistance
SVRI	Systemic vascular resistance index Systemischer vaskulärer Widerstandsindex

8 List of figures

9 References

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10 Summary/Zusammenfassung

IOH is common and about one third of it happens between anesthetic induction and the beginning of surgery. Our study was designed to help estimate the relative contribution of predefined hemodynamic variables to the development of hypotension after induction of general anesthesia with sufentanil, propofol, and rocuronium. We continuously collected advanced hemodynamic variables during anesthetic induction using the CNAP system, which allows for noninvasive continuous BP measurement based on the volume clamp method and estimation of CO by PWA. We observed a clinically significant decrease in BP as well as SVRI after administration of propofol with concomitant stable HR, SVI, and cardiac index. Our results suggest that hypotension after propofol administration during induction of general anesthesia occurs due to arterial dilation with decreased SVRI rather than venous dilation or a decrease in myocardial contractility. Future research should investigate strategies of early detection and prevention of hypotension secondary to anesthetic induction.

Die intraoperative Hypotonie (IOH) ist häufig und tritt in etwa einem Drittel der Fälle zwischen der Narkoseeinleitung und dem Beginn der Operation auf. Unsere Studie sollte dazu beitragen, den relativen Beitrag vordefinierter hämodynamischer Parameter zur Entwicklung einer Hypotonie nach Einleitung einer Allgemeinanästhesie mit Sufentanil, Propofol und Rocuronium abzuschätzen. Wir erhoben während der Narkoseeinleitung kontinuierlich erweiterte hämodynamische Parameter mit dem CNAP-System, das eine nichtinvasive, kontinuierliche Blutdruckmessung auf der Grundlage der Volume Clamp Methode und eine Schätzung des Herzzeitvolumens durch Pulskonturanalyse ermöglicht. Wir beobachteten einen klinisch signifikanten Abfall des Blutdrucks sowie des systemischen vaskulären Widerstandsindex (SVRI) nach Verabreichung von Propofol bei gleichzeitig stabiler Herzfrequenz, stabilem Schlagvolumen- und Herzindex. Unsere Ergebnisse deuten darauf hin, dass eine Hypotonie nach Verabreichung von Propofol während der Einleitung einer Allgemeinanästhesie eher auf eine arterielle Vasodilatation mit vermindertem SVRI als auf eine venöse Vasodilatation oder eine Abnahme der myokardialen Kontraktilität zurückzuführen ist. Zukünftige Forschungsarbeiten sollten Strategien zur frühzeitigen Erkennung und Vorbeugung einer IOH als Folge der Narkoseeinleitung untersuchen.

11 Eigenanteil

Prof. Dr. med. Bernd Saugel und Dr. med. Dorothea E. Rogge konzipierten die Studie, die ich im Rahmen meiner Doktorandinnentätigkeit im Folgenden betreute. Wir erhielten ein positives Ethikvotum der Ärztekammer Hamburg und wurden von der Firma CNSystems Medizintechnik GmbH in Graz, Österreich, mit dem notwendigen Messinstrument ausgestattet. Es oblag meiner Verantwortung für unser Studiendesign geeignete Patient:innen zu identifizieren und die Einwilligung zur Studienteilnahme vorzubereiten. Die Patient:innen wurden durch Ärzt:innen über die Studie informiert und willigten dann in die Studienteilnahme ein. Als primäre Ansprechpartnerin war ich für die tägliche Kommunikation mit allen involvierten Disziplinen verantwortlich, insbesondere mit den Kolleg:innen der Anästhesiepflege, sowie den ärztlichen Kolleg:innen der anästhesiologischen Abteilung. Es galt vor Messbeginn die zu untersuchende Fragestellung und das Studienprotokoll zu verdeutlichen und die Einleitung der Intubationsnarkose während des Messzeitraums zu überwachen. Die Vorbereitung und Durchführung der Messungen, die Datenerhebung und schließlich die Datensicherung sowie -übertragung fielen ebenfalls in meinen Aufgabenbereich. An 70 Messtagen führte ich 125 Messungen durch. Von diesen 125 Patient:innen konnten 33 nicht in die finale Auswertung eingeschlossen werden. Gründe hierfür waren der Bedarf an weiterer Medikation, die im Studienprotokoll nicht vorgesehen war, oder technische Probleme. Weitere 24 für unsere Studie geeignete und aufgeklärte Patient:innen konnten aufgrund verschobener OP-Zeiten, parallel stattfindender Narkoseeinleitungen, technischer Probleme, oder Einleitungsmethoden wie einer Rapid Sequence Induction keiner Messung zugeführt werden. Im Anschluss an den praktischen Teil der Studie war ich an der Datenanalyse und -interpretation sowie an der inhaltlichen Überprüfung des Manuskripts beteiligt.
Neben oben genannter Tätigkeit war Prof. Saugel für die Analyse und Interpretation der gewonnen Daten verantwortlich. Er war Mitverfasser des Manuskripts, führte die statistische Datenanalyse durch und betreute die Studie. Dr. med. L. Briesenick war an Datenanalyse und -interpretation sowie an inhaltlicher Überprüfung des Manuskripts beteiligt. Dies war ebenso der Fall bei Dr. med. P. Hoppe und Dr. med. G. Greiwe. Auch Dongsheng Yang, Chao Ma und Edward J. Mascha waren in dieser Form beteiligt. Darüber hinaus führten letztere ebenfalls die statistische Datenanalyse durch und waren Mitverfasser:innen des Manuskripts. Daniel I. Sessler war für die Interpretation der Daten verantwortlich und Mitverfasser des Manuskripts. Dr. med. D. Rogge war neben oben genannter Tätigkeit mitverantwortlich für die Analyse und Interpretation der Daten und verfasste das Manuskript.

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13 Lebenslauf

– entfällt aus datenschutzrechtlichen Gründen –

14 Eidesstattliche Erklärung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Publikationspromotion bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Publikationspromotion vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Hamburg, 22.09.23 Elisa Bebert

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Ort, Datum Unterschrift