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Energy expenditure and oxygen consumption under general anaesthesia: a single-center observational study using indirect calorimetry in patients having elective non-cardiac surgery.

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1. Research question and working hypotheses

Perioperative hemodynamic goal-directed therapy aims at optimising oxygen delivery and cardiac output to reduce perioperative morbidity, especially in high-risk patients (Pearse et al., 2014, Futier et al., 2017, Saugel et al., 2020). It is assumed that this ensures that oxygen delivery meets cellular metabolic needs (Parker et al., 2019, Molnar et al., 2020, Briesenick et al., 2023). Cellular metabolic needs are reflected by energy expenditure (Weissman, 1990, Leiner et al., 2020, Briesenick et al., 2023). Therefore, energy expenditure could be used as a therapy target to tailor hemodynamic goal-directed therapy protocols to the patients' individual cellular metabolic needs. As presented in our publication from 2023, we measured in this single-center observational study perioperative energy expenditure and oxygen consumption in 60 patients undergoing elective non-cardiac surgery (Briesenick et al., 2023). We measured energy expenditure and oxygen consumption using the gold standard, indirect calorimetry. Our primary research question was to investigate how energy expenditure and oxygen consumption change under general anaesthesia. In a subgroup of 20 patients undergoing abdominal surgery, we additionally measured intraoperative energy expenditure and oxygen consumption on an exploratory basis. Our primary hypothesis was that energy expenditure and oxygen consumption would decrease under general anaesthesia, due to decreased body functions under deep sedation (Terao et al., 2003, Jakobsson et al., 2019, Jakobsson et al., 2021). Additionally, we hypothesised that intraoperative energy expenditure and oxygen consumption might increase, caused by the physiologic stress and systemic inflammation associated with surgery (Gillis and Carli, 2015, Leiner et al., 2020).

2. Introduction

Perioperative morbidity in patients undergoing surgery was reduced in the past years due to advanced perioperative management and better surgical techniques (Habicher et al., 2016). Still, an optimal hemodynamic management in patients undergoing surgery remains a challenge for anaesthesiologists around the world. It is known that major surgery and general anaesthesia significantly change the cardiovascular dynamics of the patient (Molnar et al., 2020). Perioperative episodes of hemodynamic instability compromise the perfusion of vital organs, leading to cellular oxygen dept and unfulfilled cellular metabolic needs (Parker et al., 2019, Molnar et al., 2020). This can lead to perioperative morbidity and postoperative complications like acute kidney injury, myocardial injury, or even death (Janßen et al., 2019, Kaufmann et al., 2019, Molnar et al., 2020, Wijnberge et al., 2021). To prevent these hemodynamic instabilities, various protocols of hemodynamic goal-directed therapy have been introduced. Goal-directed therapy relies on perioperative hemodynamic monitoring giving information about the patients' cardiovascular status. The aim of perioperative hemodynamic goal-directed therapy is to optimise cardiac output and blood pressure - assuming that this ensures adequate oxygen delivery to the cells (Pearse et al., 2014, Futier et al., 2017, Saugel et al., 2020, Briesenick et al., 2023). Actual perioperative hemodynamic goal-directed therapy protocols already show a positive impact on perioperative patient morbidity (Habicher et al., 2016, Chong et al., 2018, Giglio et al., 2019, Leiner et al., 2020, Nicklas et al., 2020, Messina et al., 2021). However, to improve goal-directed therapy, there is a need to customise therapy protocols to the individual needs of the patient (Saugel et al., 2018, Molnar et al., 2020, Nicklas et al., 2020).

2.1. Advanced perioperative hemodynamic monitoring

Optimal perioperative hemodynamic management relies on optimal perioperative hemodynamic monitoring. During perioperative hemodynamic monitoring, variables giving information about the patients' cardiovascular system and end organ oxygen delivery are monitored. To assure adequate end organ oxygen delivery, the patients' volume, and the blood's oxygenation status need to be optimal (Kirov et al., 2010, Parker et al., 2019). Basic hemodynamic monitoring focusses on rather traditional static variables like heart rate, arterial blood pressure, central venous pressure, and urine output to monitor the patients' volume status (Joosten et al., 2015).

However, these variables are less specific and have for instance limited value in diagnosing perioperative complications like compensated shock (Mikhail, 1999). Additionally, they seem to be poor predictors of fluid responsiveness, which is an important therapy target in hemodynamic goal-directed therapy (Goodrich, 2006, Marik and Cavallazzi, 2013, Saugel et al., 2019). The blood's oxygenation status is traditionally monitored by performing blood gas analyses (see 2.1.1). In advanced perioperative hemodynamic monitoring, in addition to basic cardiovascular variables, important cardiovascular dynamic flow related variables like cardiac output, stroke volume variation, and pulse pressure variation can be monitored. These variables are needed to better titrate fluids and vasoactive agents, a crucial element in perioperative hemodynamic goal-directed therapy (Saugel et al., 2018). To obtain these variables, a mathematical analysis of the arterial blood pressure wave form – a pulse wave analysis – has to be performed (Kouz et al., 2021). The arterial blood pressure wave form is created by measuring pressure changes in the arterial vascular system. This is enabled via an intraarterial catheter, or non-invasively, via the volume clamp technology (Kouz et al., 2021). With the pulse wave analysis, aforementioned cardiovascular dynamic flow related variables are calculated. Since this is a continuous process, these variables can be assessed in real time (Kouz et al., 2021). This allows real time monitoring of the reaction of the cardiovascular system to surgery and perioperative therapeutic interventions (Figure 1).

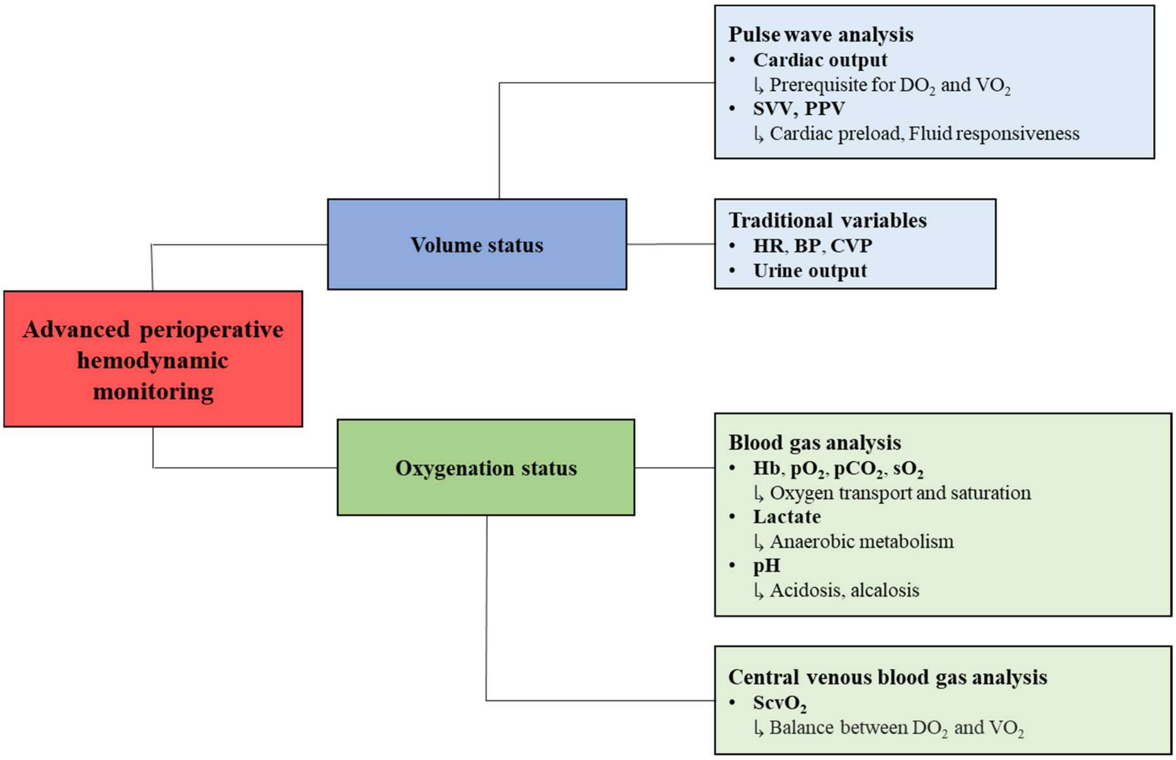

Figure 1: Advanced perioperative hemodynamic monitoring
Shown is a flow chart presenting the objectives of advanced perioperative hemodynamic monitoring. BP = blood pressure; CVP = central venous pressure; DO_2 = oxygen delivery; Hb = haemoglobin; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; PPV = pulse pressure variation; $ScvO_2$ = central venous oxygen saturation; sO_2 = oxygen saturation; SVV = stroke volume variation; VO_2 = oxygen consumption. Adapted from Kirov et al., 2010.

2.1.1. Variables in advanced perioperative hemodynamic monitoring

During the continuous pulse wave analysis, dynamic variables reflecting the patients' volume status are monitored. Important variables are cardiac output, stroke volume variation and pulse pressure variation. Cardiac output most importantly determines oxygen delivery, since oxygen delivery is the product of cardiac output and arterial oxygen content (Leiner et al., 2020). An increase in cardiac output can compensate decreased arterial oxygen content over a wide range (Vincent and De Backer, 2004). Moreover, cardiac output determines cellular oxygen consumption. Cellular oxygen consumption is the product of cardiac output, and the difference between arterial oxygen content and venous oxygen content (Leiner et al., 2020). Consequently, measuring cardiac output is important, to gain information about oxygen delivery, oxygen consumption, and eventually tissue oxygenation (Leiner et al., 2020). Furthermore, so-called dynamic variables like stroke volume variation and pulse pressure variation can be derived from the pulse wave analysis (Kouz et al., 2021).

These variables can be used to estimate cardiac preload and to predict the fluid responsiveness of the patient. This gives guidance about adequate fluid therapy and titration of vasoactive agents (Piccioni et al., 2017, Saugel et al., 2018).

In addition to cardiovascular variables reflecting the patients' volume status, advanced perioperative hemodynamic monitoring includes the determination of parameters reflecting the oxygenation status of the patients' blood. By performing a blood gas analysis, the bloods' pH, oxygen saturation, haemoglobin concentration, lactate concentration, and partial pressure of oxygen and carbon dioxide can be specified. These allow further insights on whether oxygen delivery is adequate. Firstly, haemoglobin concentration and oxygen saturation give information about the blood's ability to transport oxygen, and oxygenation. Secondly, high lactate concentrations and low pH are markers for anaerobic metabolism and acidosis, being a result of inadequate end organ perfusion (Vincent and De Backer, 2004, Molnar et al., 2020). Furthermore, the central venous oxygen saturation can be determined from blood samples drawn from central venous catheters (Molnar et al., 2020). Central venous oxygen saturation is used to evaluate the balance between oxygen consumption and oxygen delivery and is one of the most commonly used methods to estimate global oxygen extraction (Molnar et al., 2020). It reflects the degree of oxygen extraction from the upper body parts. Low levels of central venous oxygen saturation indicate a mismatch between oxygen delivery and tissue oxygenation demands and are associated with an increase of postoperative complications (Futier et al., 2010). Central venous oxygen saturation is affected by the patients' haemoglobin concentration and its arterial oxygen saturation, cardiac output, and oxygen consumption. If three out of these four variables are kept constant, changes in central venous oxygen saturation reflect alternations of the fourth one (Molnar et al., 2020).

All of the discussed variables contribute to a better understanding of the patients' hemodynamic situation and the end organ oxygen delivery. However, deciding whether they are adequate to determine actual demands of the individual patient requires a thorough evaluation of the full clinical picture (Leiner et al., 2020). The combination and interpretation of all variables is complex and requires trained personnel. Thus, the challenge of the future is to facilitate perioperative hemodynamic monitoring, allowing its better integration in the clinical everyday life (Leiner et al., 2020).

2.2. Perioperative hemodynamic goal-directed therapy

Optimal perioperative hemodynamic monitoring only has a positive impact on the patients' outcome if it is followed by adequate therapy. Thus, numerous protocols of perioperative hemodynamic goal-directed therapy have already been established. Most goal-directed therapy protocols intent to optimise oxygen delivery by targeting mean arterial pressure, cardiac output, and pulse pressure variation (Kaufmann et al., 2019).

2.2.1. The concept of perioperative hemodynamic goal-directed therapy

When deciding whether perioperative hemodynamic goal-directed therapy is indicated, it has been suggested to follow the rule of the 'five T's'. The 'five T's' include: target population, timing of intervention, type of intervention, target variable, and target value (Saugel et al., 2019) (Figure 2).

Target population

High risk patients at substantial risk for postoperative complications

- Surgery factors: emergency-, major abdominal-, and cardiovascular surgery
- Patient factors: higher age, cardiovascular or pulmonary comorbidities

Timing of intervention

- **Beginning of the perioperative period**

Type of intervention

- **Optimisation of cardiac output**
    - Contractility: positive inotropes
    - Preload: fluids
    - Afterload: vasoactive agents
- **Optimisation of arterial oxygen content**
- **Optimisation of end organ microcirculation**

Target variable

- **Dynamic flow related variables: SV, CO, DO_2**
- Dynamic cardiac preload variables: PPV, SVV

Target value

- **Personalised target values**

Figure 2: The concept of perioperative hemodynamic goal-directed therapy
Shown are the 'five T's' of hemodynamic goal-directed therapy. CO = cardiac output; DO_2 = oxygen delivery; PPV = stroke volume variation; SV = stroke volume. Adapted from Kirov et al., 2010 and with permission from Saugel et al., 2019.

The target population has to be chosen wisely, since not all patients benefit from perioperative hemodynamic goal-directed therapy. Only around ten percent of all surgical patients account for over eighty percent of postoperative deaths (Pearse et al., 2006). Therefore, it is of crucial importance to identify these high-risk patients in substantial risk for postoperative complications who would benefit from an implementation of hemodynamic goal-directed therapy (Saugel et al., 2019). The risk for perioperative complications of a surgical intervention depends on its urgency, the type of surgery, and patient risk factors (Talmor and Kelly, 2017). Especially urgent, major abdominal surgery, as well as cardiac or vascular surgery are associated with higher risk for postoperative complications (Talmor and Kelly, 2017). Patient risk factors include higher age, cardiovascular or pulmonary comorbidities, or impaired preoperative functional capacity (Talmor and Kelly, 2017).

Also, the timing of the intervention is of crucial importance. Knowing that surgery and general anaesthesia lead to a significant alteration of cardiovascular parameters, perioperative hemodynamic goal-directed therapy should anticipate to treat these alternations early, or even prevent them (van Genderen et al., 2013, Saugel et al., 2018, Saugel et al., 2019, Molnar et al., 2020). The earlier goal directed therapy is started, the bigger is its positive impact on the patients' outcome (Kern and Shoemaker, 2002). Not only intraoperative, but also preoperative hemodynamic instabilities seem to cause postoperative organ dysfunction (Maheshwari et al., 2018, Wesselink et al., 2018, Sessler et al., 2019). Thus, when goal-directed therapy is implemented early, postoperative organ dysfunction could be prevented (Südfeld et al., 2017, Saugel et al., 2018). Therefore, goal-directed therapy should be started at the beginning of the perioperative period, or even before the induction of general anaesthesia (Futier et al., 2017, Joosten et al., 2018a, Joosten et al., 2018b, Saugel et al., 2019).

The types of interventions used to improve oxygen delivery during goal-directed therapy are numerous. The arterial oxygen content can be improved by an adequate respiratory support and an optimal haemoglobin concentration, which is ensured through red blood cell transfusion and blood saving technologies (Kirov et al., 2010). Furthermore, the cardiac performance, represented by cardiac output, can be optimised by targeting cardiovascular dynamic flow related variables, derived from the pulse wave analysis (Kirov et al., 2010).

The administration of fluids optimises the intravascular fluid status and consequently cardiac preload. The arterial blood pressure can be raised by vasoactive agents, leading to a constriction of small arteries and the optimisation of cardiac afterload. Myocardial contractility is amplified by positive inotropes (Kirov et al., 2010, Chong et al., 2018, Kaufmann et al., 2019, Saugel et al., 2019). Moreover, goal-directed therapy aims at optimising oxygen delivery by improving the end organ microcirculation and oxygen uptake of the cells (Kirov et al., 2010). In any case, studies have shown that perioperative hemodynamic goal-directed therapy needs to include the use of fluids and vasoactive agents to have a positive impact on the patients' outcome (Bundgaard-Nielsen et al., 2010, Cecconi et al., 2013, Chong et al., 2018, Foss and Kehlet, 2019, Saugel et al., 2019).

The targeted variables in goal-directed therapy are, as already mentioned in 2.1, basic traditional static variables and cardiovascular dynamic flow related variables. Basic traditional static variables are: heart rate, blood pressure, and central venous pressure. Cardiovascular dynamic flow related variables are cardiac output, pulse pressure variation, and stroke volume variation. To improve the patients' outcome, perioperative hemodynamic goal-directed therapy should primarily address cardiovascular dynamic flow related variables (Saugel et al., 2019). When considering the target values, there should be a focus on personalisation of the targets, especially when adjusting blood pressure or cardiac output to the patients' individual cardiovascular physiology (Saugel et al., 2019).

2.2.2. The effect of perioperative hemodynamic goal-directed therapy

Adequate implementation of perioperative hemodynamic goal-directed therapy seems to be associated with a reduction of postoperative complications (Habicher et al., 2016, Chong et al., 2018, Giglio et al., 2019, Leiner et al., 2020, Nicklas et al., 2020, Messina et al., 2021). Postoperative complications include pneumonia, acute kidney injury, bleeding, and wound infection. In addition, a reduction in length of intensive care unit and post anaesthesia care unit stay, as well as hospitalization has been observed (Habicher et al., 2016). Patients with major abdominal surgery seem to benefit the most from this approach, showing less postoperative complications and shorter time of hospitalization (Habicher et al., 2016, Deng et al., 2020, Leiner et al., 2020). However, there does not seem to be an association between goal-directed therapy and a reduction of overall perioperative patient mortality (Pearse et al., 2014, Ripolles-Melchor et al., 2016, Ripolles et al., 2016, Messina et al., 2021).

Even though the positive effects of goal-directed therapy are commonly known, it is still scarcely used, even in high resource settings (Ahmad et al., 2015, Saugel et al., 2019). Moreover, an approach of goal-directed therapy can only be as good as the algorithm used to guide administration of vasoactive agents and inotropes, as well as titration of fluids (Saugel et al., 2018, Saugel et al., 2019). However, perioperative therapeutic interventions in actual clinical settings are rather performed based on subjective criteria of the treating anaesthesiologist than on structured treatment algorithms, that rely on advanced hemodynamic monitoring (Saugel et al., 2019). Additionally, there is a lack of consensus on which protocols to use, since they are not standardized (Joosten et al., 2015). This complicates daily goal-directed therapy use and hinders the positive effect that goal-directed therapy could have on postoperative outcome of high-risk patients.

2.2.3. The need of individualized perioperative hemodynamic goal-directed therapy

The positive effects of hemodynamic goal-directed therapy on postoperative complications are already a progress in perioperative hemodynamic management. However, a meta-analysis from 2018 showed that therapy targets in goal-directed therapy are inhomogeneous and may not target the patients' individual needs (Saugel et al., 2018). It seems, that different circumstances (e.g., major abdominal surgery, distributive shock, early septic shock etc.) require different therapy targets in goal-directed therapy. Therefore, there is a need to customise hemodynamic goal-directed therapy to the individual needs of the patient (Saugel et al., 2018, Molnar et al., 2020, Nicklas et al., 2020). As mentioned in 2.2, goal-directed therapy most commonly monitors and targets cardiovascular variables, for them to correspond to the norm. However, other signs reflecting the patient's individual reactions to general anaesthesia and surgery might not be monitored and therefore remain unknown. There are already different approaches to individualise goal-directed therapy to be found in the scientific literature. For instance, it was shown that the central venous oxygen saturation could be a therapeutic target in high-risk surgery. It could be used as a complimentary tool in goal-directed therapy to identify whether perioperative end organ perfusion and oxygen delivery is adequate (Futier et al., 2010, Pearse et al., 2014). Patients with postoperative complications showed lower perioperative central venous oxygen saturation (Futier et al., 2010). Still, fluctuations in this value do not always associate with changes in oxygen delivery, suggesting that the central venous oxygen saturation is also influenced by other factors like oxygen consumption (Futier et al., 2010, Pearse et al., 2014).

Furthermore, a randomised single-centre clinical trial targeted hemodynamic management to individual needs of high-risk patients by maintaining personal baseline cardiac index (which is mathematically coupled with cardiac output) during major abdominal surgery. The study showed a reduction of major postoperative complications in the intervention group (Nicklas et al., 2020). To improve hemodynamic goal-directed therapy, more studies on new approaches to better adjust today's protocols to the patients' individual needs are needed.

2.2.4. Energy expenditure in perioperative hemodynamic goal-directed therapy

Perioperative hemodynamic goal-directed therapy aims at optimising blood pressure and cardiac output – assuming that this ensures adequate oxygen delivery (Pearse et al., 2014, Futier et al., 2017, Briesenick et al., 2023). Adequate oxygen delivery is assumed to meet cellular metabolic needs (Parker et al., 2019, Molnar et al., 2020). Cellular metabolic needs are reflected by energy expenditure (Weissman, 1990, Leiner et al., 2020, Briesenick et al, 2023). Energy expenditure is expressed in calories per day and is independently influenced by patients' body weight, height, minute ventilation, and body temperature (Faisy et al., 2003). The gold standard to assess energy expenditure is via indirect calorimetry (Delsoglio et al., 2019). Indirect calorimetry is non-invasive and performed by measuring oxygen consumption and carbon dioxide production in the inspired and expired gas volume of the patient (Oshima et al., 2019). It is already used to measure real time energy expenditure in critically ill patients and thus facilitates personalised nutrition therapy, resulting in a better clinical outcome (Singer et al., 2011, Oshima et al., 2017a, Delsoglio et al., 2019, Tatucu-Babet et al., 2020, Duan et al., 2021). Since energy expenditure reflects cellular metabolic needs, it could be an interesting therapy target to tailor perioperative hemodynamic goal-directed therapy protocols to the individual needs of the patient (Briesenick et al., 2023). However, perioperative energy expenditure is not routinely measured during surgery and currently an under-researched field (Jakobsson et al., 2019, Briesenick et al., 2023). A recent meta-analysis investigated the effect of general anaesthesia on oxygen consumption (Jakobsson et al., 2019). Oxygen consumption is physiologically and mathematically coupled to energy expenditure and therefore closely related (Delsoglio et al., 2019). The authors summarise that general anaesthesia seems to reduce oxygen consumption, but the estimate remains uncertain (Jakobsson et al., 2019, Briesenick et al., 2023). However, considerable study heterogeneity and low quality of available evidence was reported (Jakobsson et al., 2019).

Most studies included in the meta-analysis give little guidance on perioperative oxygen consumption in the modern high-risk patient population, since they were published more than 20 years ago (Briesenick et al., 2023).
A recent study examined oxygen consumption under general anaesthesia and during abdominal surgery (Jakobsson et al., 2021). The authors showed that general anaesthesia reduces oxygen consumption by approximately one third in elderly patients who are over 65 years old. Intraoperative oxygen consumption was reduced compared to preoperative values (Jakobsson et al., 2021).

Another study examined the effect of liver transplantation surgery on perioperative oxygen consumption. It showed that patients with higher oxygen consumption during surgery tended to have shorter length of hospital stay (Shibata et al., 2015). In addition, it seems that an increase in depth of sedation is associated with a decrease of oxygen consumption (Terao et al., 2003). Perioperative energy expenditure itself has also already been investigated. Two studies compared preoperative and postoperative energy expenditure of patients undergoing elective abdominal surgery, showing no significant difference between the two time points (Tannus et al., 2001, Silva et al., 2021). Considering the sparse data available on this matter, more studies are needed to examine how energy expenditure changes during general anaesthesia and surgery. This may help to better understand perioperative hemodynamic changes in our modern patient population.

2.3. Objective

Perioperative monitoring of energy expenditure and oxygen consumption is not included, neither recommended in modern perioperative hemodynamic goal-directed therapy protocols (Jakobsson et al., 2019). Perioperative hemodynamic management aims at optimising oxygen delivery – by targeting cardiac output and blood pressure – assuming to meet cellular metabolic needs (Pearse et al., 2014, Futier et al., 2017, Parker et al., 2019, Molnar et al., 2020, Briesenick et al., 2023). Cellular metabolic needs are reflected by energy expenditure (Weissman, 1990, Leiner et al., 2020). Therefore, it is important to further understand how energy expenditure changes during general anaesthesia and surgery. This understanding could help adjusting perioperative hemodynamic goal-directed therapy protocols to the individual cellular metabolic needs of the patient (Briesenick et al., 2023).

On the one hand general anaesthesia may reduce energy expenditure and oxygen consumption due to a reduction of body functions under deep sedation (Terao et al., 2003, Jakobsson et al., 2019, Jakobsson et al., 2021). On the other hand, surgery itself and the associated physiologic stress and systemic inflammation may consequently increase the patients' perioperative energy expenditure (Gillis and Carli, 2015, Leiner et al., 2020).
To further explore perioperative energy expenditure, we performed a single-center observational study, measuring energy expenditure and oxygen consumption under general anaesthesia in patients undergoing elective non-cardiac surgery. On an exploratory basis, we additionally measured intraoperative energy expenditure and oxygen consumption in patients undergoing abdominal surgery. As presented in our publication from 2023, we used indirect calorimetry, as it is the gold standard to measure energy expenditure and oxygen consumption (Delsoglio et al., 2019, Briesenick et al., 2023). We hypothesised that energy expenditure and oxygen consumption would be reduced under general anaesthesia.

3. Material and Methods

3.1. Study design and setting

The study was approved by the ethics committee (Ethikkommission der Ärztekammer Hamburg, Hamburg, Germany; ethics committee number PV 6067; Chair: Prof. Dr. R. Stahl; on 29th July 2019). As presented in our publication from 2023, the ethics committee approval covered to continue the process of inclusion until inclusion of 20 patients per surgical group – 20 having abdominal surgery, 20 having orthopaedic/trauma surgery, and 20 having head/neck surgery (Briesenick et al., 2023). In total, the sample size included 60 patients. All patients included provided written informed consent. This observational study was conducted according to good scientific practice and the Declaration of Helsinki on Ethical Principles for Medical research Involving Human Subjects (World Medical Association, 2013). It was conducted in the time period between September 2019 and March 2020 in the Department of Anaesthesiology, Center of Anaesthesiology and Intensive Care Medicine, University Medical Center Hamburg-Eppendorf (Hamburg, Germany). The University Medical Center Hamburg-Eppendorf is a maximum-care university hospital with more than 45.000 surgical procedures performed annually (Briesenick et al., 2023).

3.2. Patient recruitment

Suitable patients were selected in the premedication area according to their scheduled surgery type. Patients receiving non-cardiac surgery, specifically abdominal surgery, orthopaedic/trauma surgery, and head/neck surgery were included. The patients were informed about the study and asked to participate voluntarily. We included patients who were between 18 and 80 years old, scheduled for elective surgery with general anaesthesia and tracheal intubation. Patients were not included if they weighed less than 50kg (potential cancer-related cachexia), were pregnant (ethical concerns), had cardiac arrhythmia (impact on cardiac index measurements), were in need of a professional interpreter for informed consent (ethical concerns), were managed with a supraglottic airway device (inability to sample respiratory gases and accurately assess energy expenditure), or were in a palliative situation (ethical concerns). Furthermore, patients were excluded if the anaesthetic management changed, e.g., if a supraglottic airway device was unexpectedly used instead of an endotracheal tube. Also, patients were excluded if the surgical management changed, e.g., if laparoscopic surgery was performed unexpectedly instead of open surgery, which could distort indirect calorimetry due to intraabdominal/intrathoracic carbon dioxide.

3.3. Perioperative anaesthesia management

Perioperative anaesthesia management was conducted following the guidelines of our hospital. All patients were not premedicated and had no food intake at least six hours before surgery. If clinically indicated, abdominal surgery patients received an epidural catheter before induction of general anaesthesia. Patients were pre-oxygenated by giving 100% fraction of inspired oxygen over a face mask. General anaesthesia was induced through the intravenous administration of an opioid (sufentanil or remifentanil), propofol, and a neuromuscular blocking agent (rocuronium bromide, mivacurium or cisatracurium). After tracheal intubation the fraction of inspiratory oxygen was reduced to under 60%. Ventilator settings were under the discretion of the treating anaesthesiologist. The ventilator used was the Perseus A500 (Dräger, Lübeck, Germany). General anaesthesia was maintained during surgery via continuous intravenous propofol infusion or inhaled sevoflurane. Analgesia was maintained with repeated sufentanil boluses or continuous intravenous remifentanil infusion. In patients with epidural catheters, a mix of bupivacaine [2.5 mg mL^{-1}] and sufentanil [0.75 µg mL^{-1}] was administered repetitively during surgery in addition to general anaesthesia. During surgery mean arterial pressure was under the discretion of the treating anaesthesiologist. Usually, a mean arterial pressure of 65 mmHg is considered the lower intervention threshold at our institution.

3.4. Energy expenditure and oxygen consumption

We measured the patients' energy expenditure and oxygen consumption performing indirect calorimetry with the Q-NRG+ system (Cosmed, Rome, Italy). We measured the patients' energy expenditure [kcal d^{-1} m^{-2}] and oxygen consumption [ml min^{-1}] using indirect calorimetry. Indirect calorimetry is considered the gold standard for real time estimation of energy expenditure (Delsoglio et al., 2019). Alternatives to indirect calorimetry to determine energy expenditure are explained in 3.5. The heat production and therefore energy usage of the body depends on the type of energy substrate used. Energy expenditure is mathematically correlated to the patients' oxygen consumption and carbon dioxide production (Delsoglio et al., 2019). Thus, indirect calorimetry, performed by measuring inspired oxygen and expired carbon dioxide concentrations, enables the calculation of the patients' energy expenditure (Delsoglio et al., 2019).

To perform this calculation, the indirect calorimeter uses the modified Weir equation (Weir, 1949, Oshima et al., 2017b). Energy expenditure is presented as calories per day.

$$\mathbf{EE = [(3.94 \cdot VO_2) + (1.11 \cdot VCO_2)] \cdot 1440}$$

Modified Weir Equation
EE = energy expenditure; VCO_2 = carbon dioxide production; VO_2 = oxygen consumption (Weir, 1949, Delsoglio et al., 2019).

To conduct indirect calorimetry in spontaneously breathing patients, the inspired and expired gas was collected with a fitted face mask. In mechanically ventilated patients, gas samples were drawn from the circuit linking the endotracheal tube to the mechanical ventilator (Oshima et al., 2019, Delsoglio et al., 2020, Oshima et al., 2020). The indirect calorimeter contains a mixing chamber in which air samples are collected and analysed. The mixing chamber contains a chemical fuel oxygen sensor and a non-dispersive infrared adsorption digital carbon dioxide sensor, allowing the accurate estimation of inspired oxygen and expired carbon dioxide (Delsoglio et al., 2020). Inhaled and exhaled gas samples are analysed separately to observe the global change between the two samples (Oshima et al., 2017a). Biometrical data of the patient such as age, weight, hight, and sex were inserted into the system. The indirect calorimeter was used in mask mode in awake breathing patients. If the patient was intubated, the system was used in in flowmeter mode (Figure 3). During the recording, every 30 seconds a value was generated by the system. According to the manufacturers' recommendations, room air calibrations were performed before each measurement in mask mode, and once a day in flowmeter mode. The internal turbine flowmeter and gas analysers were calibrated monthly to optimize the measurement's accuracy. We performed the measurements over a 10-minute time period. Values of each time point were averaged over the duration of the measurement for each patient.

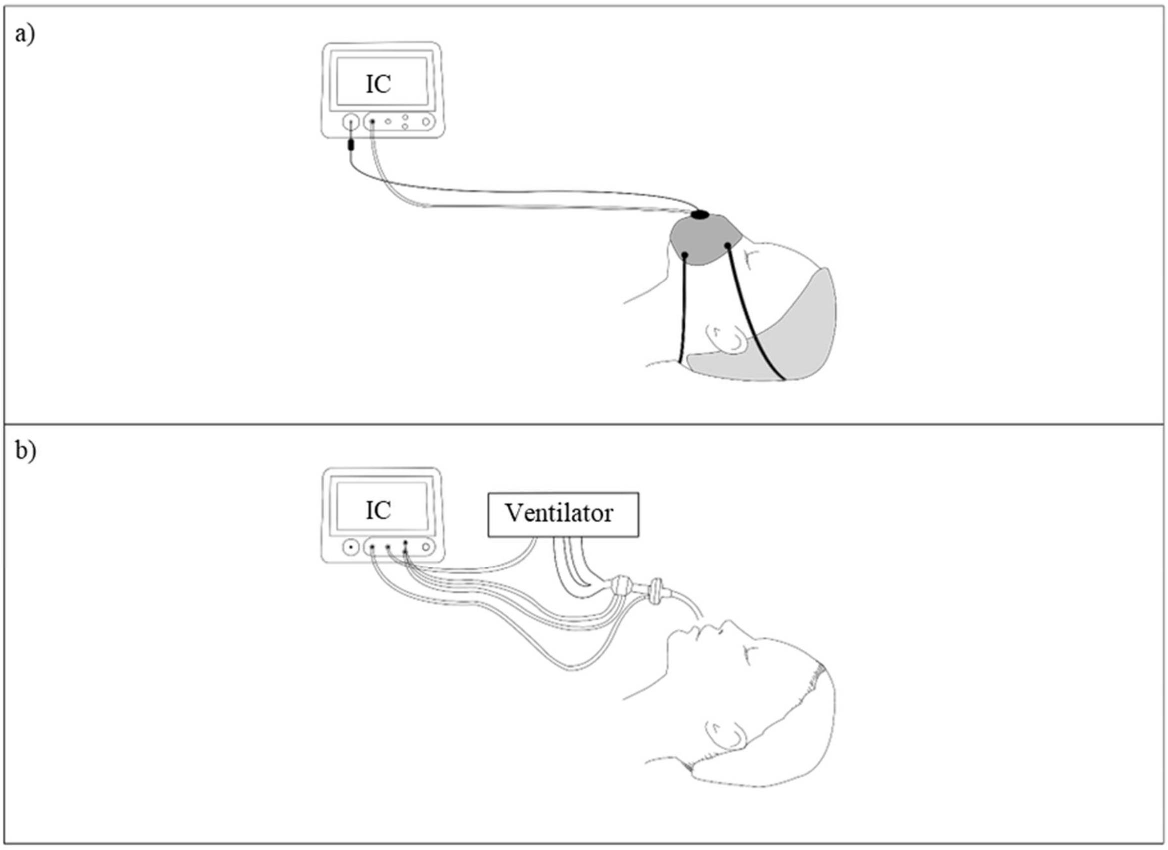

Figure 3: Indirect calorimetry in awake and mechanically ventilated patients
a) Indirect calorimetry performed in an awake, spontaneously breathing patient. Inspired and expired gases are collected with a fitted face mask to assess energy expenditure.
b) Indirect calorimetry performed in a mechanically ventilated patient. Samples of inspired and expired gases are drawn from the circuit linking the endotracheal tube to the ventilator.
IC = indirect calorimeter. Schaade, 2023.

3.5. Alternatives to indirect calorimetry to determine energy expenditure

Energy expenditure varies according to factors like sex, age, body composition, clinical condition, and physical activity (Elizabeth Weekes, 2007). Therefore, it is important to determine the patients' individual energy expenditure as accurate as possible. Since indirect calorimetry used to be expensive, time consuming, and required trained personnel, several predictive equations to determine energy expenditure have been proposed in the literature (Ocagli et al., 2021). These equations most commonly consider the patients' age, sex, ethnicity, height, weight, fat-free mass, fat mass, organ tissue mass, and in some cases specific data like diabetes markers (Ocagli et al., 2021). Not all equations are suitable to the patients' individual situation, making it necessary to clinically evaluate which formula to use (Elizabeth Weekes, 2007).

Studies showed that the values of energy expenditure calculated with these equations to estimate energy expenditure did not correspond to values measured with the gold standard indirect calorimetry (Flancbaum et al., 1999, Delsoglio et al., 2019, Cioffi et al., 2021, Ocagli et al., 2021).

3.5.1. Cardiovascular parameters

We measured cardiac index, mean arterial blood pressure, and heart rate using pulse wave analysis with the non-invasive finger-cuff technology CNAP (CNSystems Medizintechnik, Graz, Austria). Cardiac index is calculated by dividing cardiac output with the patients' body surface area. This turns cardiac output into a parameter that accounts for the body size of the patient and makes cardiac output comparable for patients of different weight and height. The technology of non-invasive pulse wave analysis is based on the vascular unloading technology. Its principle is the detection of blood volume changes in the finger arteries and transforming these into continuous blood pressure information (Figure 4) (Saugel et al., 2020). For the measurement, the double finger cuff of the device is connected to a pressure transducer and attached to the patients' index and middle finger. Additionally, an arm cuff is attached to the ipsilateral patients' upper arm for oscillometric blood pressure measurements. The system calibrates the blood pressure signal obtained at the finger cuff. The calibration was performed every ten minutes during our measurements. The finger cuff integrates an infrared photodiode and light detector, measuring the diameter of the finger artery. During the cardiac cycle the blood volume in the finger artery changes. To keep the volume in the finger artery at a constant level during the cardiac cycle, the volume clamp in the finger cuff adjusts its pressure continuously (Saugel et al., 2020, Kouz et al., 2021). These pressure adjustments are used to derive an arterial blood pressure waveform. By mathematically analysing the arterial blood pressure waveform, cardiovascular dynamic flow related variables like cardiac output, stroke volume variation, and pulse pressure variation can be derived (Wagner et al., 2018, Saugel et al., 2020, Kouz et al., 2021). Several previous studies showed the accuracy of real time estimated arterial blood pressure by the CNAP technology, compared with invasive blood pressure monitoring (Jeleazcov et al., 2010, Ilies et al., 2012, Smolle et al., 2015).

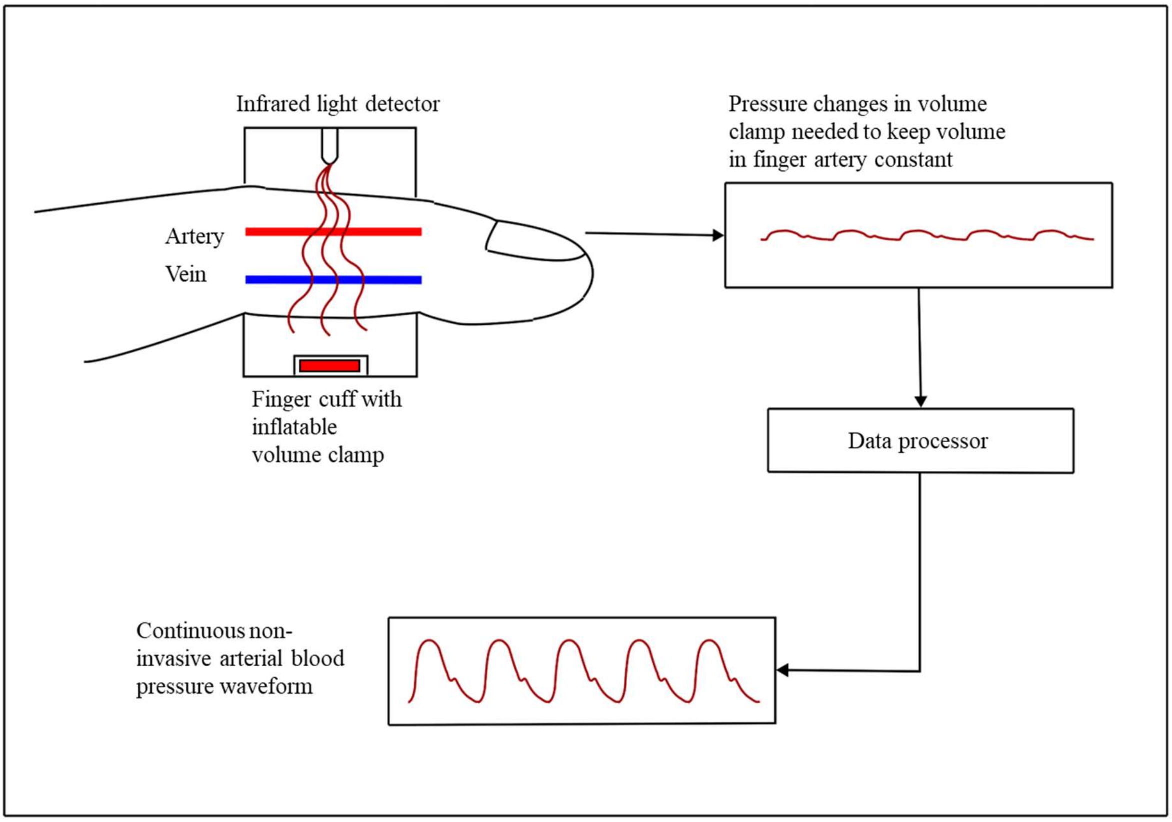

Figure 4: CNAP finger cuff technology with volume clamp method This schema illustrates the non-invasive continuous pulse wave analysis enabled by the finger cuff technology. The changes in volume in the finger artery during the cardiac cycle are registered by an infrared transmission plethysmograph. The volume clamp adjusts its pressure to keep the finger artery at a constant volume. The pressure adjustments are used to derive a continuous non-invasive arterial blood pressure waveform, enabling continuous blood pressure measurements. Adapted with permission from Saugel et al., 2020.

3.6. Additional parameters

The patients' body temperature was measured in awake patients with a sublingual thermometer. In ventilated patients it was assessed with an intra vesical catheter or an intra oesophageal probe. If clinically indicated, a blood gas analysis was performed in abdominal surgery patients with the ABL90 Flex blood gas analyser (Radiometer, Krefeld, Germany). Blood gas analysis was only performed in patients having an arterial access or a central venous catheter. If available, blood gas analysis was assessed simultaneously to each measured time point. If the patient was mechanically ventilated, the ventilator parameters were documented once during the measurement. Cardiovascular parameters were also documented once for each measurement. A detailed overview of the documented parameters during each measurement is shown in Table 1.

Table 1: Additional parameters

Body temperature	[°C]
Blood gas analysis	pH, base excess [mmol L^{-1}], Hb [g dL^{-1}], lactate [mmol L^{-1}], pO_2 [mmHg], pCO_2 [mmHg], sO_2 [%]
Cardiovascular parameters	MAP [mmHg], SAP [mmHg], DAP [mmHg], heart rate [min^{-1}]
Ventilator settings	End tidal CO_2 [mmHg], inspiratory O_2 [%], expiratory O_2 [%], tidal volume [mL], minute ventilation [L min^{-1}], respiratory frequency [min^{-1}], positive end-expiratory pressure [mbar], plateau pressure [mbar]
Volatile anaesthetics	MAC [Vol%], inspiratory and expiratory sevoflurane [Vol%]

CO_2 = carbon dioxide; DAP = diastolic arterial pressure; Hb = haemoglobin; MAC = minimal alveolar concentration; MAP = mean arterial pressure; O_2 = oxygen; pCO_2 = partial carbon dioxide pressure; pO_2 = partial oxygen pressure; SAP = systolic arterial pressure; sO_2 = oxygen saturation.

3.7. Measurements

We performed indirect calorimetry and measurement of cardiovascular parameters simultaneously. Measurements were performed in the patient before surgery, under general anaesthesia, during the course of surgery, and within 24 hours after surgery. The primary outcome was energy expenditure and oxygen consumption under general anaesthesia. Energy expenditure and oxygen consumption during the course of surgery were an exploratory outcome in a group of patients undergoing abdominal surgery.

3.7.1. Preoperative measurement

The preoperative measurement was conducted ≥ 24 hours before surgery (time point: preoperative). Awake resting energy expenditure, awake oxygen consumption, cardiac index, mean arterial blood pressure, and heart rate were assessed in the patient. It was performed either in a separated room in the premedication area or in the patients' room on normal ward. We documented the patients' last food intake and nicotine use. The body temperature was measured sublingually. The patients' weight, hight, age, and sex were entered into the indirect calorimeter and into the CNAP device. The patient was laid down in supine position on an examination couch or the hospital bed, five minutes before and during the measurement.

The finger cuff, used for the non-invasive measurement of cardiovascular parameters, was attached and the hand positioned at the patients' heart level. The arm cuff was attached to the ipsilateral patients' upper arm. Indirect calorimetry was conducted using the mask mode of the indirect calorimeter. The mask was attached over the mouth and nose of the patient and secured by an elastic strap around the patients' head. Air leaks were avoided to secure the accuracy of the measurement. Central venous pressure was set at 5mmHg in CNAP system. The interval of recalibrating the arterial blood pressure with the arm cuff was set at every 10 minutes. At the beginning of the first measurement, both devices were started at the same time. The patient was advised to breathe calmly, without talking or moving. Disturbances were avoided. After ten minutes the recording was stopped and the devices removed from the patient.

3.7.2. At incision measurement

The at incision measurement was conducted under general anaesthesia and was initiated few minutes before surgical incision (time point: at incision). There were no major changes in the patients' position and no major surgical trauma yet. Indirect calorimetry was conducted using the flowmeter mode of the indirect calorimeter. The CNAP was attached in the same way as in the preoperative measurement. Ventilator settings were under the discretion of the responsible anaesthesiologist but were not changed during the measurement. The fraction of inspired oxygen was kept under 60 percent at all times.

3.7.3. Intraoperative measurements

Intraoperative measurements were performed in patients having abdominal surgery. Every 60 minutes after incision, a new measurement was conducted (time point: 60 min, 120 min, etc.). Intraoperative measurements were performed as the at incision measurement.

3.7.4. Postoperative measurement

The postoperative measurement was performed within one to 24 hours after the end of surgery (time point: postoperative). Either in an awake spontaneous breathing patient using the face mask, or in a still intubated patient. The measurement took place in the patients' room on normal ward, on the intensive- or intermediate care unit, or in the post anaesthesia care unit. The last food intake as well as nutrition therapy, if applicable, were documented. If the patient was awake, the measurement was performed as in the preoperative measurement. Patients who were still intubated were measured as in the measurement at incision.

3.8. Procedural and perioperative data

At the end of the surgical procedure of each patient the instrumentalization, cumulative amount of medication given, amount of administrated fluids, amount of blood products, and fluid loss were documented. Additionally, we documented whether anaesthesia was maintained with sevoflurane or propofol. Finally, we documented the duration of surgery and general anaesthesia (Table 2).

Table 2: Perioperative data

Instrumentalization	Epidural catheter, regional anaesthesia, arterial access, central venous catheter
Fluids	Crystalloid fluid [mL], colloid fluid [mL]
Blood products	Fresh frozen plasma [mL], packet red blood cells [mL], platelet concentrates [mL]
Administrated medication	Norepinephrine [µg], atropine [mg], epinephrine [µg], propofol [mg], sufentanil [µg], remifentanil [µg], rocuronium [mg], cisatracurium [mg], mivacurium [mg]
Fluid loss	Blood loss [mL], urine production [mL]
Procedural data	Duration of surgery [min], duration of general anaesthesia [min]

3.9. Follow-Up

The follow up was performed at least 30 days after surgery. We used the patients' digital clinical record to detect postoperative complications, length of hospitalization, intensive care unit, intermediate care unit, and post anaesthesia care unit stay, and death cases.

3.10. Statistics

In parallel to our publication from 2023, medical, demographic, and biometric patient data, as well as procedural data are described (Briesenick et al., 2023). Continuous data is presented as median (interquartile range) and categorical data as absolute frequencies (%). The patients' medical, demographic, and biometric data were extracted from the medical records. Energy expenditure, oxygen consumption, cardiac index, mean arterial blood pressure, and heart rate were averaged for each measured time point.

Median and interquartile range were calculated for each patient at each timepoint. Using median values of each patient we calculated medians and interquartile ranges for each patient group (abdominal-, orthopaedic/trauma-, and head/neck surgery), and for all patients for each time point. To ensure better comparability between patients of different weight and height, energy expenditure and oxygen consumption were indexed for body surface area calculated with the DuBois formula.

$$\mathbf{log(BSA) = -4.93590 + 0.425 \cdot log(weight) + 0.725 \cdot log(height)}$$

DuBois Formula

BSA = body surface area; weight [kg]; height [cm] (Wang et al., 1992).

To test the primary hypothesis that general anaesthesia decreases energy expenditure and oxygen consumption compared to preoperative awake values, a Wilcoxon signed-rank test for paired measurements with corresponding 95%-confidence intervals was performed (Briesenick et al., 2023). We furthermore performed Wilcoxon signed-rank tests to analyse differences between the values of the measured parameters in different timepoints and in different patient groups. Symmetry was checked by plotting boxplots, violin plots, and histograms. No indications of any violation of the assumptions of paired Wilcoxon signed-rank test were found during the visual inspection of these plots. If values were missing, the calculation was based on the number of valid data (Briesenick et al., 2023). A *P* value less than 0.05 was considered statistically significant. The constellations of parameters for which a Wilcoxon signed-rank tests were performed are shown in Table 3.

Table 3: Constellations of parameters for Wilcoxon signed-rank test

Variable	Constellations of parameters for Wilcoxon signed-rank test
Body temperature	Comparison of preoperative values of all patients with at incision and postoperative values. Comparison of at incision with postoperative values.
Blood gas analysis	Comparison of pH, base excess, Hb, lactate, pO_2, pCO_2 and sO_2 at incision with values 180 minutes, and 300 minutes after incision in the group undergoing abdominal surgery.
Energy expenditure and oxygen consumption	Comparison of preoperative values with at incision and postoperative values in all patients and in the different patient groups (abdominal; orthopaedic/trauma; head/neck).
Energy expenditure and oxygen consumption–comparison of groups	Comparison of preoperative, at incision and postoperative values of one patient group (abdominal; orthopaedic/trauma; head/neck) with the corresponding values of a different group. Additionally, comparison of the reduction of energy expenditure and oxygen consumption from preoperative values to values at incision between groups.
Cardiac index, mean arterial blood pressure, and heart rate	Comparison of preoperative values with at incision and postoperative values in all patients.

Hb = haemoglobin; pCO_2 = partial pressure of carbon dioxide; pO_2 = partial pressure of oxygen; sO_2 = oxygen saturation.

Energy expenditure and oxygen consumption in all patients in the preoperative, at incision and postoperative measurement were presented as spaghetti plots (Figure 5 and Figure 7). Energy expenditure and oxygen consumption at three timepoints (preoperative; at incision; postoperative) for the different subgroups (abdominal; orthopaedic/trauma; head/neck) were presented as boxplots (Figure 6 and Figure 8). Perioperative values, including intraoperative values, of energy expenditure and oxygen consumption in abdominal surgery patients were presented as spaghetti plots (Figure 9 and Figure 10). Cardiac index and mean arterial blood pressure in all patients in the preoperative, at incision and postoperative measurement were presented in a line graph (Figure 11). The statistical analyses and figures were performed with GraphPad Prism (Version 9.3.1., GraphPad Software, San Diego, USA).

Since there was no published literature on perioperative energy expenditure when the study was designed, a priori sample size calculation was not performed. Though, we considered that repeated measures in a sample size of 60 patients achieves a power of 80% to detect a small to medium effect (effect size of 0.37) using a paired Wilcoxon signed-rank test, assuming that the actual distribution is uniform and using a significance level of 5% (Briesenick et al., 2023). The justification of sample size was performed with PASS 2008 (Version 08.0.6, Hintze, J. (2008): PASS 2008, NCSS, LLS, Kaysville, Utah).

4. Results

In this study 85 patients were enrolled. We excluded 21 patients because surgery was cancelled or surgical or anaesthetic management changed. Four patients were excluded due to technical problems with indirect calorimetry. Finally, 60 patients were included - 20 patients having abdominal surgery, 20 patients having orthopaedic/trauma surgery, and 20 patients having head/neck surgery.

4.1. Patient characteristics

Median age of all patients was 58. Males represent 63% of the study population. Patients were predominantly assigned for American Society of Anaesthesiologists physical status class II (47%) and III (38%). Further detailed information about the patient groups and patient characteristics are presented in Table 4.

Table 4: Patient characteristics

		Total (n = 60)	Abdominal surgery (n = 20)	Trauma/ orthopaedic surgery (n = 20)	Head/neck surgery (n = 20)
Age, years		58 (43 to 65)	60 (57 to 68)	60 (51 to 67)	40 (32 to 52)
Male sex, n (%)		38 (63)	13 (65)	12 (60)	13 (65)
Height, cm		173 (168 to 182)	173 (170 to 180)	171 (168 to 182)	174 (167 to 181)
Weight, kg		77 (67 to 90)	71 (64 to 81)	81 (71 to 92)	78 (71 to 90)
BMI, kg m^{-2}		25 (22 to 29)	23 (21 to 26)	25 (22 to 31)	25 (24 to 30)
ASA physical status class, n (%)	**I**	9 (15)	0 (0)	3 (15)	6 (30)
	II	28 (47)	6 (30)	10 (50)	12 (60)
	III	23 (38)	14 (70)	7 (35)	2 (10)
Heart disease, n (%)		3 (5)	0 (0)	3 (15)	0 (0)
Arterial hypertension, n (%)		15 (25)	5 (25)	7 (35)	3 (15)
Diabetes mellitus Type II, n (%)		6 (10)	3 (15)	3 (15)	0 (0)
Smoker, n (%)		12 (20)	2 (10)	5 (25)	5 (25)

Categorical variables are presented as absolute number (%), continuous variables are presented as median (25th to 75th percentiles). ASA = American Society of Anaesthesiologists; BMI = body mass index; heart disease = history of ischemic heart disease (myocardial infarction, angina pectoris) (Briesenick et al., 2023).

4.2. Procedural and perioperative data

After each surgical treatment, instrumentalization, the given medication, fluid therapy, blood loss as well as duration of surgery and general anaesthesia were documented. Median duration of all surgical procedures was 100 minutes (60 to 169). Median duration of abdominal surgery was 250 minutes (165 to 336). Orthopaedic/trauma surgery lasted for 80 minutes (65 to 95) and head/neck surgery had the shortest duration with 51 minutes (34 to 111). Median values of each patient subgroup, as well as the types of surgery performed, are shown in Table 5. Median time fastened before induction of general anaesthesia was 16 hours (12 to 19).

Table 5: Procedural and perioperative data

	Total (n = 60)	**Abdominal surgery** (n = 20)	**Trauma/orthopaedic surgery** (n = 20)	**Head/neck surgery** (n = 20)
Type of surgery, n		Hepatic resection, 8	Hip replacement, 3; acetabulum fracture, 1	Ear surgery, 6
		Re-anastomosis, 5	Lower limb fractures, 7	Nose surgery, 3
		Pancreatic surgery, 2	Upper limb fractures, 7	Throat surgery, 4
		Other major abdominal resection, 5	Ruptured tendons, 2	Oral/maxillofacial surgery, 7
Epidural, n (%)	12 (20)	11 (55)	1 (0,5)	0 (0)
Duration surgery [min]	100 (60 to 169)	250 (165 to 336)	80 (65 to 95)	51 (34 to 111)
Duration general anaesthesia	165 (120 to 245)	310 (235 to 420)	140 (125 to 188)	100 (84 to 169)
Inhalational anaesthesia, n (%)	44 (73)	20 (100)	16 (80)	8 (40)
Blood loss [mL]	100 (50 to 425)	450 (200 to 2200)	125 (93 to 325)	20 (20 to 50)

Norepinephrine cumulative [µg]	940 (460 to 830)	4221 (1143 to 5778)	812 (500 to 1365)	110 (55 to 558)
Crystalloid fluid [mL]	1000 (500 to 1500)	2500 (1500 to 4125)	1000 (500 to 1500)	750 (500 to 1000)
Colloid fluid [mL]	1250 (625 to 1902)	1500 (1000 to 2000)	500 n =1	0 (0 to 0)
Packed red blood cells [mL]	1120 (560 to 2100)	1120 (560 to 2100)	0 (0 to 0)	0 (0 to 0)

Categorical variables are presented as absolute number (%), continuous variables are presented as median (interquartile range) (Briesenick et al., 2023).

4.3. Perioperative body temperature

The patients' body temperature was measured at each time point. Median preoperative body temperature was 36.5 (36.3 to 36.7). At incision and postoperative temperature measurements showed similar median values (at incision 36.5 (36.2 to 36); postoperative 36.5 (36.1 to 37)). There was no significant difference between preoperative, at incision, and postoperative temperature values (Table 10).

4.4. Perioperative blood gas analysis

In 18 out of 20 patients in the abdominal surgery group, a blood gas analysis was performed during the at incision and intraoperative measurements. Median values are shown in Table 6. At incision and 60 minutes after incision, data of 18 patients were available. Due to differences in surgery duration, there were fewer data available in the following intraoperative measurements (120 min – 17 patients, 180 min – 13 patients, 240 min – 10 patients, 300 min – 7 patients).

Significant changes between the at incision measurement and the measurement after 180 minutes were found in base excess ($P = 0.0098$), haemoglobin ($P = 0.0205$) and lactate ($P = 0.0352$). Median base excess decreased from -1.5 mmol L^{-1} at incision to -3.9 mmol L^{-1} 180 minutes after incision. Median haemoglobin decreased from 11.8 g dL^{-1} at incision to 11.2 g dL^{-1} 180 minutes after incision. Median lactate increased from 0.7 mmol L^{-1} at incision to 1 mmol L^{-1} 180 minutes after incision. In the remaining parameters, no significant differences were found between the at incision and 180 minutes after incision measurement (Table 10).

Significant changes between the at incision measurement and the measurement at 300 minutes after incision were found in haemoglobin concentration (P = 0.0156) and lactate concentration (P = 0.0156).

Median haemoglobin decreased from 11.8 g dL^{-1} at incision to 8.7 g dL^{-1} 300 minutes after incision. Median lactate values increased from 0.7 mmol L^{-1} at incision to 1.5 mmol L^{-1} 300 minutes after incision. In the remaining parameters, no significant differences were found between the at incision and 300 minutes after incision measurement (Table 10).

Table 6: Perioperative blood gas analysis

Time point	pH	Base excess [mmol L^{-1}]	Hb [g dL^{-1}]	Lactate [mmol L^{-1}]	pO_2 [mmHg]	pCO_2 [mmHg]	sO_2 [%]
At incision	7.37 (7.34 to 7.42)	- 1.5 (-3.6 to 0.0)	11.8 (10.2 to 13.3)	0.7 (0.58 to 0.8)	205.5 (140.5 to 236)	38.4 (36.7 to 42.4)	99.5 (98.8 to 99.6)
60 min	7.37 (7.33 to 7.4)	-1.65 (-4.03 to 0.35)	12.6 (10.95 to 13.63)	0.7 (0.6 to 0.83)	157.5 (126 to 180)	39.8 (39.2 to 43.1)	99.15 (98.2 to 99.3)
120 min	7.38 (7.32 to 7.4)	- 2.0 (- 5.6 to - 0.3)	11.7 (10.05 to 12.4)	0.9 (0.65 to 1)	163 (129 to 199)	40.5 (37.4 to 41.25)	98.9 (98.4 to 99.4)
180 min	7.35 (7.32 to 7.41)	- 3.9 (- 5.9 to - 0.55)	11.2 (9.4 to 11.55)	1 (0.65 to 1.4)	179 (136 to 195)	41.3 (36.1 to 42.5)	99.3 (98.65 to 99.5)
240 min	7.35 (7.32 to 7.4)	- 3.25 (-5.03 to -0.93)	11.5 (10.35 to 12.18)	1.2 (0.78 to 1.68)	157.5 (127 to 186.8)	39.9 (36.9 to 42.6)	99.05 (98.28 to 99.28)
300 min	7.34 (7.3 to 7.39)	-4.3 (-5.3 to -0.5)	8.7 (8.4 to 11.3)	1.5 (1 to 3.9)	166 (140 to 198)	39.8 (38 to 43.5)	99.4 (98.6 to 99.4)

Variables are represented as median (interquartile range). Hb = haemoglobin; pCO_2 = partial carbon dioxide pressure; pO_2 = partial oxygen pressure; sO_2 = oxygen saturation.

4.5. Perioperative energy expenditure

Median preoperative awake resting energy expenditure of awake and spontaneously breathing patients was 960 (837 to 1061) kcal d^{-1} m^{-2}. Median energy expenditure under general anaesthesia measured at incision was 687 (576 to 775) kcal d^{-1} m^{-2}. Preoperative energy expenditure was reduced by 264 kcal d^{-1} m^{-2} (151 to 377) or 26% (18% to 36%) ($P <$ 0.0001). Postoperative median energy expenditure was 888 (758 to 1068) kcal d^{-1} m^{-2} and thus showed no significant difference to preoperative values (Table 10). Perioperative energy expenditure in all patients is shown in Figure 5.

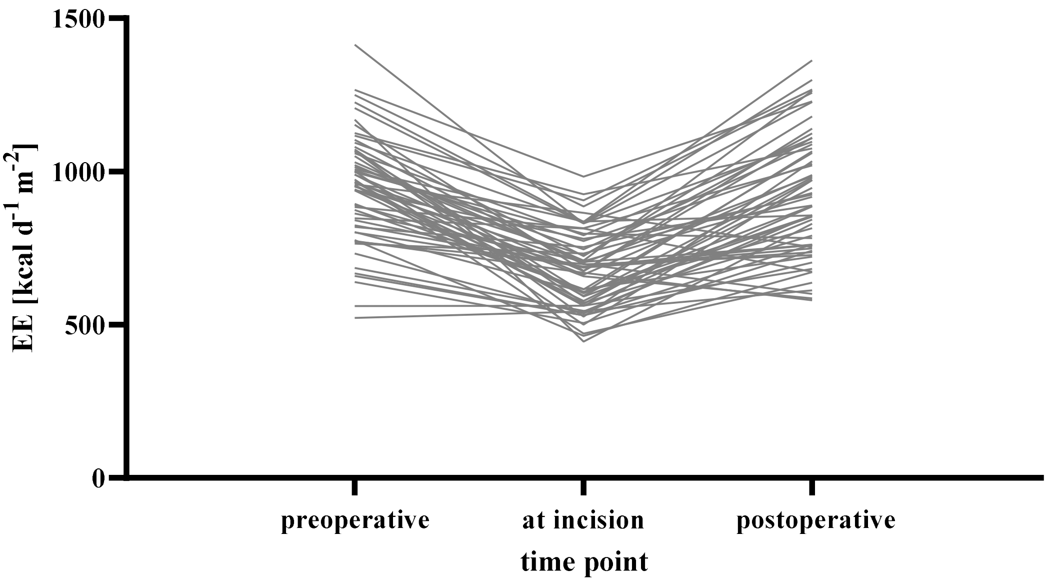

Figure 5: Perioperative energy expenditure
Shown is the median perioperative energy expenditure [kcal d^{-1} m^{-2}] in sixty patients having elective non-cardiac surgery at three measured timepoints: preoperative, at incision and postoperative. Each line represents one patient. EE = energy expenditure. Adapted from Briesenick et al., 2023.

4.5.1. Perioperative energy expenditure in different patient groups

Median preoperative awake energy expenditure in the group of patients having abdominal surgery was 954 kcal d^{-1} m^{-2} (794 to 1061) and showed a reduction of 293 kcal d^{-1} m^{-2} (154 to 377) or 30% (18% to 39%) to 637 kcal d^{-1} m^{-2} (569 to 717) at incision ($P < 0.0001$). Median postoperative energy expenditure of this group was 813 kcal d^{-1} m^{-2} (672 to 1046) which is 10% (0% to 20%) lower than the preoperative energy expenditure in this group (P = 0.0215).

In the orthopaedic/trauma surgery group, median preoperative awake energy expenditure was 995 kcal d^{-1} m^{-2} (897 to 1071). At incision energy expenditure was 635 kcal d^{-1} m^{-2} (533 to 771), which is 315 kcal d^{-1} m^{-2} (198 to 476) or 31% (22% to 42%) lower than preoperative energy expenditure ($P < 0.0001$). Median postoperative energy expenditure was 976 kcal d^{-1} m^{-2} (801 to 1110), showing no significant difference to preoperative values (Table 10).

The group undergoing head/neck surgery showed a median preoperative awake energy expenditure of 946 kcal d^{-1} m^{-2}. Median energy expenditure at incision was 729 kcal d^{-1} m^{-2} (674 to 818) which is 182 kcal d^{-1} m^{-2} (119 to 283) or 21% (15% to 30%) lower than preoperative values ($P < 0.0001$). Median postoperative energy expenditure was 921 kcal d^{-1} m^{-2} (761 to 1082) and thus returned to preoperative levels (Table 10).

The energy expenditure of all patient groups at three different timepoints (preoperative; at incision; postoperative) is shown in Figure 6. There was no significant difference between the preoperative values of awake resting energy expenditure in the different groups as well as the values of energy expenditure at incision (Table 10). There was a significant difference in the reduction of preoperative awake resting energy expenditure to energy expenditure at incision in the group having orthopaedic/trauma surgery and the group undergoing head/neck surgery ($P = 0.0027$). Preoperative awake energy expenditure in the orthopaedic/trauma group was reduced by median 31% at incision, whereas preoperative awake energy expenditure in the head/neck surgery group was only reduced by median 21% at incision. Other significant differences between the groups were not found (Table 10).

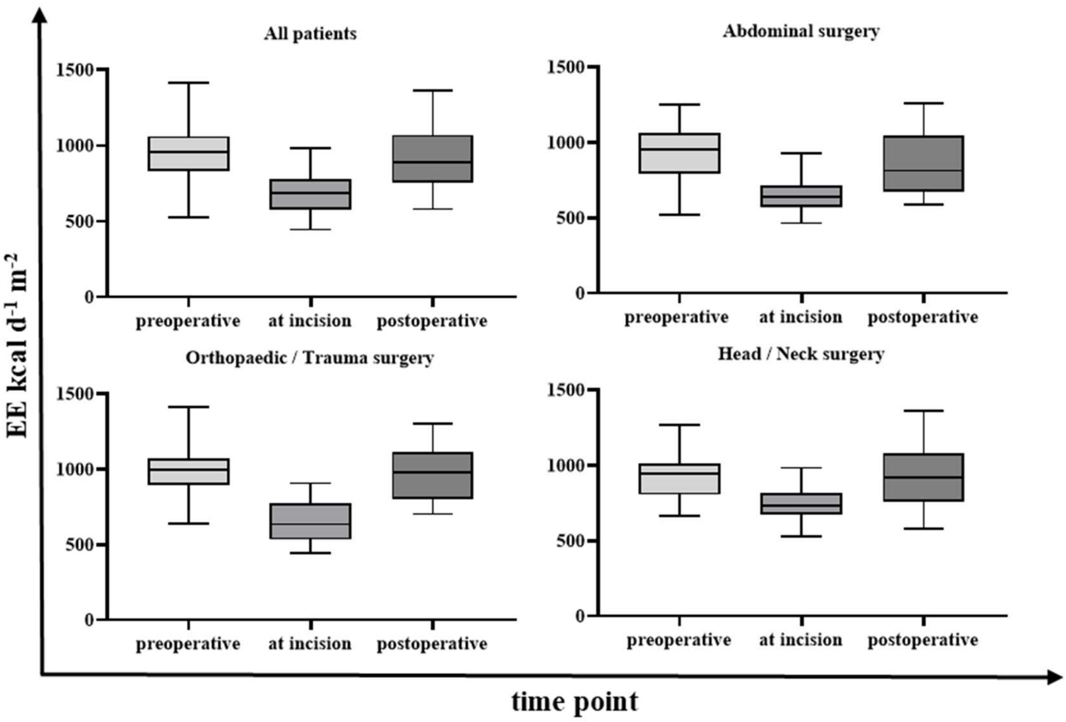

Figure 6: Perioperative energy expenditure in different patient groups Shown is the perioperative energy expenditure [kcal d^{-1} m^{-2}] in all patients, patients having abdominal surgery, patients having orthopaedic/trauma surgery, and patients having head/neck surgery at three different time points (preoperative = light grey, at incision = grey, postoperative = dark grey). Boxes represent 25th and 75th percentiles and the range between them is the inter-quartile range. Bold horizontal lines inside the boxes represent medians. The whiskers (vertical extensions from the box) indicate the lowest and highest value. EE = energy expenditure.

4.6. Perioperative oxygen consumption

Median preoperative awake oxygen consumption of all patients was 139 mL min^{-1} (118 to 151). Median oxygen consumption under general anaesthesia at incision was 99 mL min^{-1} (81 to 115) – a reduction of median 36 mL min^{-1} (21 to 54) or by 27 % (17% to 39%) compared to the preoperative measurement (P < 0.0001). Postoperative median oxygen consumption was 131 mL min^{-1} (110 to 156) and thus returned to preoperative levels (Table 10). Perioperative oxygen consumption in all patients is shown in Figure 7.

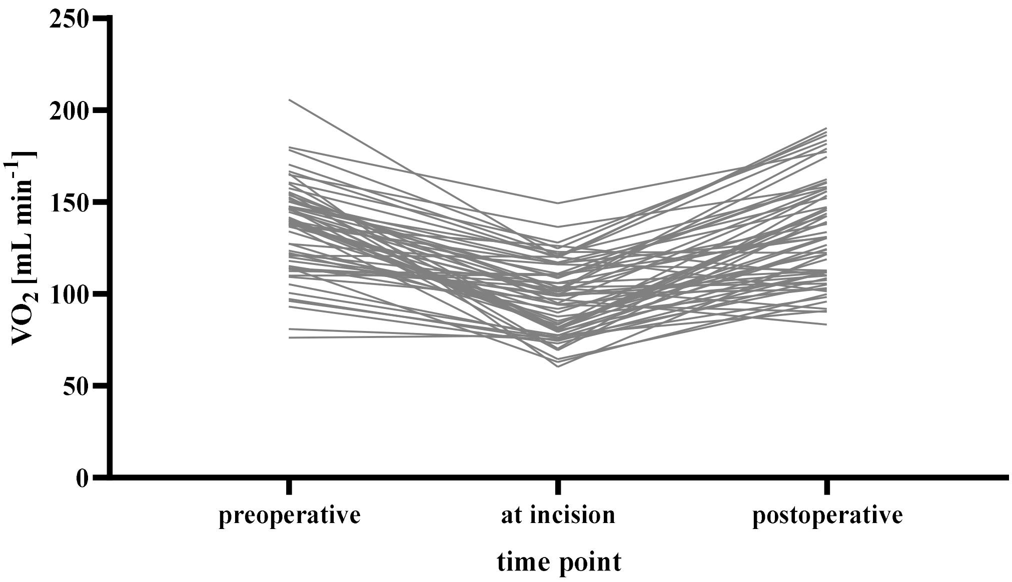

Figure 7: Perioperative oxygen consumption
Shown is the median perioperative oxygen consumption [mL min^{-1}] of sixty patients having elective non-cardiac surgery at three measured timepoints: preoperative, at incision and postoperative. Each line represents one patient. VO_2 = oxygen consumption.

4.6.1. Perioperative oxygen consumption in different patient groups

Median preoperative awake oxygen consumption in the abdominal surgery group was 138 mL min^{-1} (115 to 151). At incision oxygen consumption was significantly reduced by 44 mL min^{-1} (24 to 55) or 31% (18 to 40%) to 89 mL min^{-1} (78 to 103) ($P < 0.0001$). Median postoperative oxygen consumption was 118 mL min^{-1} (99 to 145) and thus returned to preoperative levels (Table 10).

In orthopaedic/trauma surgery patients, median preoperative awake oxygen consumption was 145 mL min^{-1} (130 to 157) and showed a reduction by 43 mL min^{-1} (30 to 74) or 29% (22% to 44%) to 90 mL min^{-1} (76 to 107) at incision ($P < 0.0001$). Postoperative oxygen consumption in this group was 143 mL min^{-1} (114 to 160) and therefore returned to preoperative levels (Table 10), in parallel to the abdominal surgery group.

In patients having head/neck surgery, median preoperative awake oxygen consumption was 138 mL min^{-1} (114 to 180) and significantly decreased to 110 mL min^{-1} (98 to 119) at incision ($P < 0.0001$). This is a reduction by 24 mL min^{-1} (13 to 43) or 19% (12% to 28%). Oxygen consumption was 132 mL min^{-1} (112 to 157) in the postoperative measurement, showing no significant difference to preoperative values (Table 10).

The perioperative oxygen consumption of all patient groups at three different timepoints (preoperative; at incision; postoperative) is shown in Figure 8.

There was no significant difference between preoperative awake oxygen consumption in the different groups (Table 10). At incision there was a significant difference between oxygen consumption in the orthopaedic/trauma surgery (90 mL min^{-1}) and head/neck surgery group (110 mL min^{-1}) (P = 0.0136). In addition, there was a significant difference in the reduction of oxygen consumption from values in the preoperative measurement to oxygen consumption at incision between these two groups (P = 0.0005). In the orthopaedic/trauma surgery group a reduction of 29% was noted, whereas in the head/neck surgery group there was only a reduction of 19%. There were no significant differences between postoperative values of oxygen consumption in the three groups (Table 10).

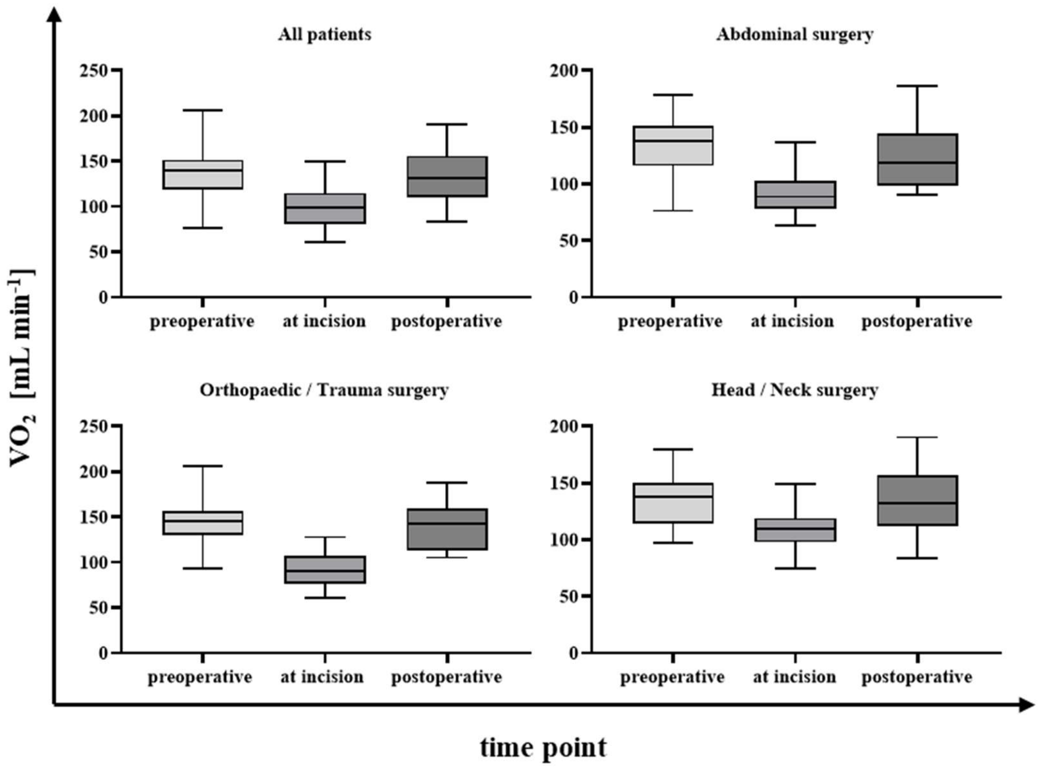

Figure 8: Perioperative oxygen consumption in different patient groups Shown is the perioperative oxygen consumption [mL min^{-1}] of all patients, patients having abdominal surgery, patients having orthopaedic/trauma surgery, and patients having head/neck surgery at three different time points (preoperative = light grey, at incision = grey, postoperative = dark grey). Boxes represent 25th and 75th percentiles and the range between them is the inter-quartile range. Bold horizontal lines inside the boxes represent medians. The whiskers (vertical extensions from the box) indicate the lowest and highest value. VO_2 = oxygen consumption.

4.7. Abdominal surgery patients

To further explore the effect of surgery on perioperative energy expenditure and oxygen consumption – on exploratory basis – we measured intraoperative values in the abdominal surgery patient group.

4.7.1. Perioperative energy expenditure in abdominal surgery patients

Median intraoperative energy expenditure during abdominal surgery was at 20% below the awake resting energy expenditure in 15 out of 20 patients. In 3 patients intraoperative energy expenditure was at least 10% lower than the awake resting energy expenditure. Two out of 20 patients showed an exceeded intraoperative energy expenditure during surgery (in one patient after 300 minutes of surgery by 14% and in the in the other patient during the whole course of surgery) (Briesenick et al., 2023). The values of each measured time point for each patient in the abdominal surgery group are shown in Table 7 and Figure 9.

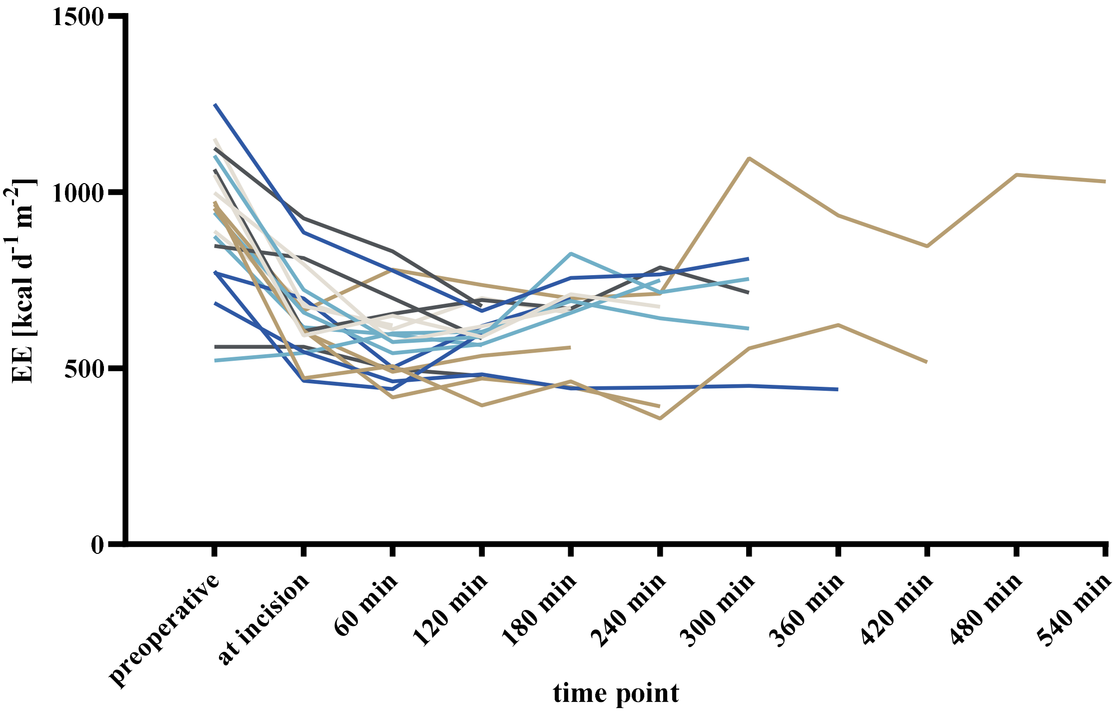

Figure 9: Perioperative energy expenditure in abdominal surgery patients Shown is the perioperative energy expenditure [$kcal^{-1}$ m^{-2}] in 20 patients undergoing abdominal surgery. Each line represents one patient. Measured timepoints included the preoperative awake measurement, measurement at incision, and intraoperative measurements every 60 minutes after incision. EE = energy expenditure. Adapted from Briesenick et al., 2023.

Table 7: Perioperative energy expenditure in 20 abdominal surgery patients

Patient	Preoperative awake resting EE	Intraoperative EE										Postoperative EE
		At incision	60 min	120 min	180 min	240 min	300 min	360 min	420 min	480 min	540 min	
1	1250	885; -29%	778; -38%	663; -47%	757; -39%	767; -39%	811; -35%					1257; +1%
2	974	472; -52%	506; -48%	394; -60%	463; -52%	357; -63%	557; -43%	622; -36%	517; -47%			637; -35%
3	1049	593; -44%	649; -38%	589; -44%	710; -32%	675; -36%						852; -19%
4	1104	723; -34%	574; -48%	589; -47%	826; -25%	715; -35%	754; -32%					1180; +7%
5	1125	926; -18%	832; -26%	676; -40%								1075; -4%
6	685	546; -20%	463; -32%	483; -29%	443; -35%	446; -35%	450; -34%	440; -36%				612; -11%
7	953	607; -36%	418; -56%	471; -51%	447; -53%	391; -59%						856; -10%
8	998	796; -20%	574; -43%	619; -38%	672; -33%							783; -22%
9	848	813; -4%	698; -18%	584; -31%								673; -21%
10	776	465; -40%	442; -43%	601; -23%								672; -13%

Patient	Preoperative awake resting EE	Intraoperative EE										Postoperative EE
		At incision	60 min	120 min	180 min	240 min	300 min	360 min	420 min	480 min	540 min	
11	955	603; -37%	490; -49%	536; -44%	559; -41%							888; -7%
12	965	663; -31%	780; -19%	737; -24%	698; -28%	711; -26%	1097; +14%	934; -3%	847; -12%	1050; +9%	1030; +7%	988; +2%
13	522	543; +4%	599; +15%	603; +16%	690; +32%	641; +23%	612; +17%					843; +61%
14	1152	676; -41%	622; -46%									1139; -1%
15	941	658; -30%	543; -42%	568; -40%	657; -30%	751; -20%						586; -38%
16	1065	605; -43%	654; -39%	693; -35%	669; -37%	787; -26%	714; -33%					1066; 0%
17	771	698; -9%	502; -35%	620; -20%	696; -10%							601; -22%
18	889	687; -23%	611; -31%	698; -21%	656; -26%							749; -16%
19	874	617; -29%	596; -32%	565; -35%								721; -18%
20	561	561; 0%	498; -11%	478; -15%								682; +22%

Perioperative energy expenditure [kcal d^{-1} m^{-2}] in 20 individual patients having abdominal surgery and percentage change of energy expenditure from preoperative awake resting energy expenditure. EE = Energy expenditure (Briesenick et al., 2023).

4.7.2. Perioperative oxygen consumption in abdominal surgery patients

Intraoperative oxygen consumption in the abdominal surgery group showed similar developments as intraoperative energy expenditure, as oxygen consumption is mathematically and physiologically coupled to energy expenditure. In 17 out of 20 patients, median intraoperative oxygen consumption (including measurements at incision and intraoperative timepoints after incision) was 38% lower than preoperative awake oxygen consumption. In two patients, median intraoperative oxygen consumption showed a reduction of the preoperative value by only 17% and 19%. In one patient median intraoperative oxygen consumption was increased by 13% compared to preoperative awake oxygen consumption (Table 8 and Figure 10).

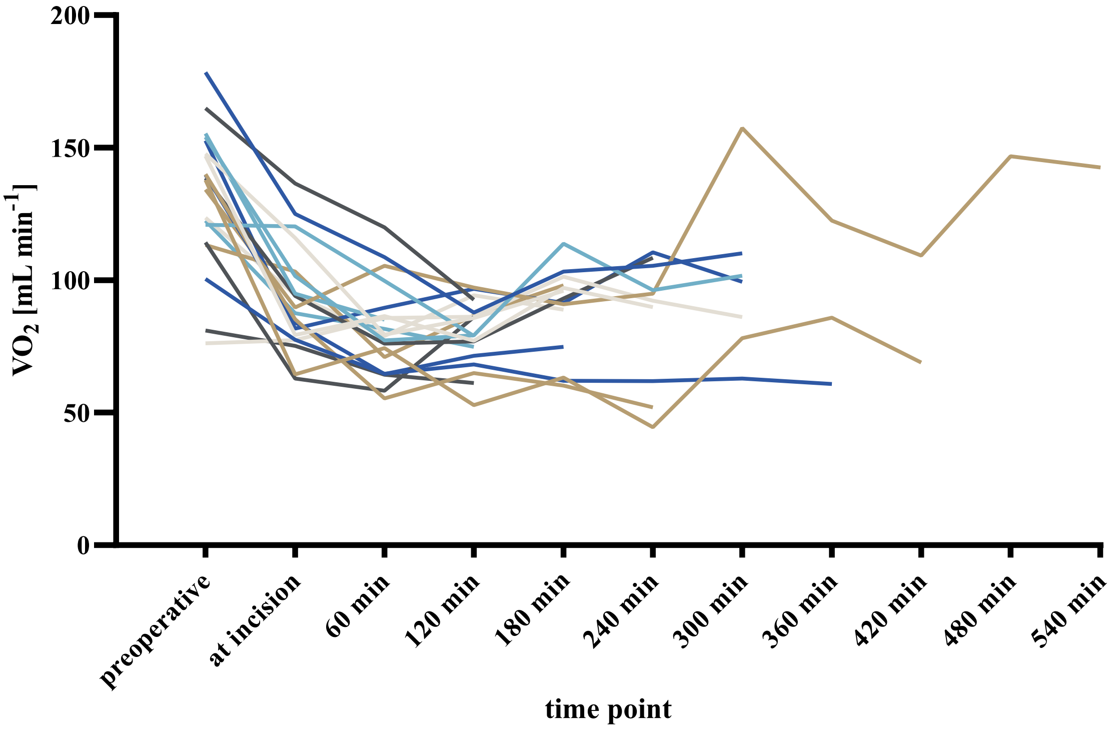

Figure 10: Perioperative oxygen consumption in abdominal surgery patients Shown is the perioperative oxygen consumption [mL min^{-1}] in 20 patients undergoing abdominal surgery. Each line represents one patient. Measured timepoints included the preoperative measurement, measurement at incision, and intraoperative measurements every 60 minutes after incision. VO_2 = oxygen consumption.

Table 8: Perioperative oxygen consumption in 20 abdominal surgery patients

Patient	Preoperative awake VO_2	Intraoperative VO_2										Postoperative VO_2
		At incision	60 min	120 min	180 min	240 min	300 min	360 min	420 min	480 min	540 min	
1	178	125; -30%	109; -39%	88; -51%	103; -42%	105; -41%	110; -38%					186; +4%
2	138	64; -54%	74; -46%	53; -62%	63; -54%	44; -68%	78; -43%	86; -38%	69; -50%			96; -30%
3	147	79; -46%	86; -41%	77; -48%	97; -34%	90; -39%						124; -16%
4	154	102; -34%	77; -50%	79; -49%	114; -26%	96; -38%	102; -34%					175; +14%
5	165	136; -18%	120; -27%	93; -44%								158; -4%
6	100	77; -23%	65; -35%	68; -32%	62; -38%	62; -38%	63; -37%	61; -39%				91; -9%
7	140	85; -39%	55; -61%	65; -54%	60; -57%	52; -63%						124; -11%
8	148	116; -22%	79; -47%	86; -42%	96; -35%							113; -24%
9	121	120; 0%	100; -17%	79; -35%								101; -17%
10	114	63; -45%	58; -49%	86; -25%								100; -12%

Patient	Preoperative awake VO_2	Intraoperative VO_2										Postoperative VO_2
		At incision	60 min	120 min	180 min	240 min	300 min	360 min	420 min	480 min	540 min	
11	140	84; -40%	65; -54%	71; -49%	75; -46%							131; -6%
12	134	90; -33%	105; -22%	97; -28%	91; -32%	95; -29%	157; +17%	122; -9%	109; -19%	147; +10%	142; +6%	139; +4%
13	76	77; -1%	86; +13%	86; +13%	101; +33%	92; +21%	86; +13%					127; +67%
14	155	95; -39%	85; -45%									156; 0%
15	138	94; -32%	76; -45%	77; -44%	93; -33%	108; -22%						90; -35%
16	153	82; -46%	90; -41%	97; -37%	91; -41%	110; -28%	99; -35%					147; -4%
17	113	103; -9%	71; -37%	87; -23%	98; -13%							92; -19%
18	124	94; -24%	79; -36%	94; -24%	88; -29%							108; -13%
19	122	88; -28%	82; -33%	75; -39%								103; -16%
20	81	75; -7%	64; -21%	61; -25%								98; +21%

Perioperative oxygen consumption [$mL\ min^{-1}$] in 20 individual patients having abdominal surgery and percentage change of oxygen consumption from preoperative awake oxygen consumption. VO_2 = oxygen consumption.

4.8. Perioperative cardiovascular parameters

In addition to the patients' perioperative energy expenditure and oxygen consumption, we measured cardiac index, mean arterial blood pressure, and heart rate at each time point. Median values of all patients in the preoperative, at incision and postoperative measurements are shown in 9. Figure 11 shows median cardiac index and mean arterial blood pressure in the three measured time points. Median preoperative cardiac index was reduced by 12% (2% to 19%) at incision compared to preoperative cardiac index ($P < 0.0001$). Median postoperative cardiac index was 7% (6% to 19%) higher than preoperative cardiac index ($P = 0.0021$). Median preoperative mean arterial blood pressure also showed a reduction in the measurement at incision compared to values in the preoperative measurement ($P = 0.0003$). Median values were reduced by 14% (-4% to 25%). Postoperative median mean arterial blood pressure was 12% (-1% to 24%) lower than preoperative mean arterial blood pressure ($P < 0.0001$). Median heart rate was reduced by 16% (6% to 24%) in the measurement at incision, compared to preoperative median heart rate ($P < 0.0001$). Median postoperative heart rate was 9% (1% to 17%) higher than median preoperative heart rate ($P < 0.0001$).

Table 9: Perioperative cardiovascular parameters

	Preoperative (n = 60)	**At incision** (n = 60)	**Postoperative** (n = 60)
Cardiac index [L min^{-1} m^{-2}]	3.0 (2.7 to 3.4)	2.6 (2.3 to 3.1)	3.1 (2.8 to 3.6)
Mean arterial pressure [mmHg]	98 (88 to 108)	86 (73 to 100)	85 (77 to 99)
Heart rate [min^{-1}]	71 (66 to 76)	59 (52 to 65)	76 (67 to 87)

Continuous variables are presented as median (25^{th} to 75^{th} percentiles).

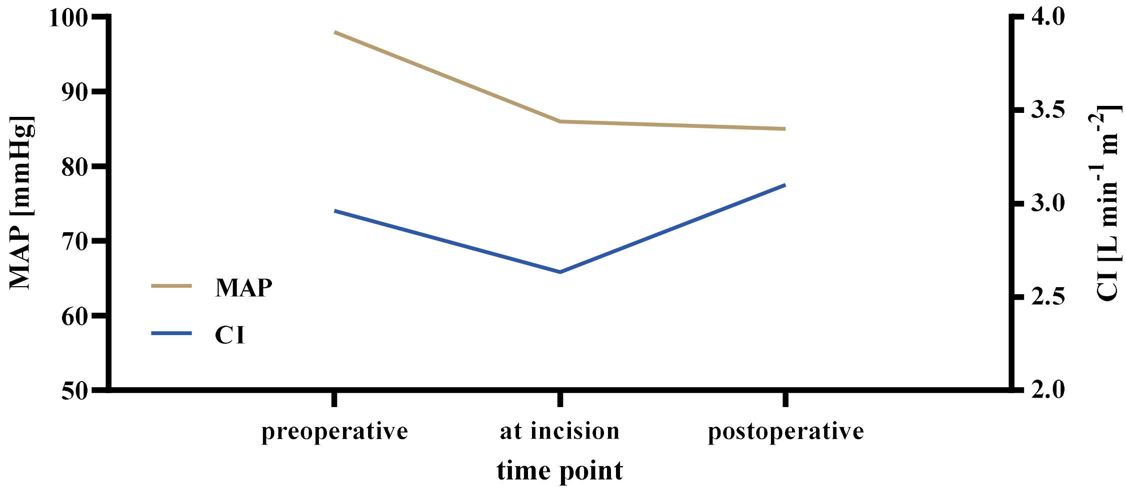

Figure 11: Perioperative cardiac index and mean arterial blood pressure Shown is the median cardiac index [L min^{-1} m^{-2}] and median mean arterial blood pressure [mmHg] in sixty patients having elective non-cardiac surgery at three measured timepoints: preoperative, at incision, and postoperative. Mean arterial pressure is shown on the left y-axis and cardiac index is shown on the right y-axis (MAP = beige; CI = blue). CI = cardiac index; MAP = mean arterial pressure.

4.9. P Values of all performed Wilcoxon signed-rank tests

All Wilcoxon signed-rank tests for paired measurements performed in this study with the associated P Values are shown in Table 10.

Table 10: P Values of Wilcoxon signed-rank tests

	Value 1	Value 2	P Value
Body temperature			
	Preoperative awake	At incision	0.7266
	Preoperative awake	Postoperative	0.3519
	At incision	Postoperative	0.3985
Blood gas analysis			
pH	At incision	180 min	0.8022
Base excess	At incision	180 min	0.0098
Hb	At incision	180 min	0.0205
Lactate	At incision	180 min	0.0352
pO_2	At incision	180 min	0.7490
pCO_2	At incision	180 min	0.7739
sO_2	At incision	180 min	0.9668
pH	At incision	300 min	0.1406
Base excess	At incision	300 min	0.1563
Hb	At incision	300 min	0.0156
Lactate	At incision	300 min	0.0156
pO_2	At incision	300 min	0.3750
pCO_2	At incision	300 min	0.8125
sO_2	At incision	300 min	> 0.9999
Energy expenditure			
All patients	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.1804
Abdominal surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.0215
Orthopaedic/trauma surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.8480
Head/neck surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.8983
Energy expenditure – comparison of groups			
Abdominals surgery and orthopaedic/trauma surgery	Preoperative awake abdominal surgery	Preoperative awake orthopaedic/trauma surgery	0.3884
	At incision abdominal surgery	At incision orthopaedic/trauma surgery	0.8124
	Reduction from preoperative awake value to at incision value abdominal surgery	Reduction from preoperative awake value to at incision value orthopaedic/trauma surgery	0.3300
	Postoperative abdominal surgery	Postoperative orthopaedic/trauma surgery	0.0897

Abdominal surgery and head/neck surgery	Preoperative awake abdominal surgery	Preoperative awake head/neck surgery	0.9563
	At incision abdominal surgery	At incision head/neck surgery	0.1054
	Reduction from preoperative awake value to at incision value abdominal surgery	Reduction from preoperative awake value to at incision value head/neck surgery	0.2024
	Postoperative abdominal surgery	Postoperative head/neck surgery	0.1429
Orthopaedic/trauma surgery and head/neck surgery	Preoperative awake orthopaedic/trauma surgery	Preoperative awake head/neck surgery	0.3488
	At incision orthopaedic/trauma surgery	At incision head/neck surgery	0.0583
	Reduction from preoperative awake value to at incision value orthopaedic/trauma surgery	Reduction from preoperative awake value to at incision value head/neck surgery	0.0027
	Postoperative orthopaedic/trauma surgery	Postoperative head/neck surgery	0.3884
Oxygen consumption			
All patients	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.4315
Abdominal surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.0532
Orthopaedic/trauma surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.6477
Head/neck surgery group	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.9273
Oxygen consumption – comparison of groups			
Abdominal surgery and orthopaedic/trauma surgery	Preoperative awake abdominal surgery	Preoperative awake orthopaedic/trauma surgery	0.2943
	At incision abdominal surgery	At incision orthopaedic/trauma surgery	0.9563
	Reduction from preoperative awake value to at incision value abdominal surgery	Reduction from preoperative awake value to at incision value orthopaedic/trauma surgery	0.4091

	Postoperative abdominal surgery	Postoperative orthopaedic/trauma surgery	0.0897
Abdominal surgery and head/neck surgery	Preoperative awake abdominal surgery	Preoperative awake head/neck surgery	0.9273
	At incision abdominal surgery	At incision head/neck surgery	0.0532
	Reduction from preoperative awake value to at incision value abdominal surgery	Reduction from preoperative awake value to at incision value head/neck surgery	0.0696
	Postoperative abdominal surgery	Postoperative head/neck surgery	0.1650
Orthopaedic/trauma surgery and head/neck surgery	Preoperative awake orthopaedic/trauma surgery	Preoperative awake head/neck surgery	0.1893
	At incision orthopaedic/trauma surgery	At incision head/neck surgery	0.0136
	Reduction from preoperative awake value to at incision value orthopaedic/trauma surgery	Reduction from preoperative awake value to at incision value head/neck surgery	0.0005
	Postoperative orthopaedic/trauma surgery	Postoperative head/neck surgery	0.4091
Cardiac index			
	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	0.0021
Mean arterial pressure			
	Preoperative awake	At incision	0.0003
	Preoperative awake	Postoperative	< 0.0001
Heart rate			
	Preoperative awake	At incision	< 0.0001
	Preoperative awake	Postoperative	< 0.0001

Value = value of a specific parameter at a certain timepoint or in a specific patient group at a certain time point; Hb = haemoglobin; pCO_2 = partial carbon dioxide pressure; pO_2 = partial oxygen pressure; sO_2 = oxygen saturation.

4.10. Follow up

We performed a follow up investigation of the outcome of all patients. It was performed at least 30 days after surgery. We scanned the patients' clinical records for the length of hospital, intensive care unit, intermediate care unit and post anaesthesia care unit stay, typical postoperative complications, and death (Table 11). The most frequent postoperative complications were acute kidney injury (6 out of 60 patients), surgical site infection (organ) (5 out of 60 patients) and pulmonary emboly (4 out of 60 patients). There were no deaths recorded during the time of the follow up investigation. The most postoperative complications were observed in the abdominal surgery group. Median hospital stay in days was 6 (abdominal surgery patients: 13; orthopaedic/trauma surgery patients: 5; head/neck surgery patients: 4). Fourteen out of 60 patients stayed in the intermediate care or intensive care unit after their surgical procedure, all of them were in the abdominal surgery group. Median intensive care unit stay was 4.2 days.

Table 11: Postoperative complications.

Post operative complication	**Total cases** (n=60)	**Abdominal surgery** (n =20)	**Trauma/Orthopaedic surgery** (n =20)	**Head / Neck surgery** (n =20)
Acute kidney injury	6 (60)	6 (20)	0 (20)	0 (20)
Acute respiratory distress syndrome	1 (60)	1 (20)	0 (20)	0 (20)
Anastomotic failure	2 (60)	2 (60)	0 (20)	0 (20)
Delirium	1 (60)	1 (20)	0 (20)	0 (20)
Gastrointestinal bleeding	1 (60)	1 (20)	0 (20)	0 (20)
Infection (source uncertain)	3 (60)	2 (20)	0 (20)	1 (20)
Infection (blood stream)	1 (60)	1 (20)	0 (20)	0 (20)
Paralytic ileus	3 (60)	3 (20)	0 (20)	0 (20)
Pulmonary emboly	4 (60)	4 (20)	0 (20)	0 (20)
Surgical site infection (superficial)	2 (60)	1 (20)	0 (20)	1 (20)

Surgical site infection (organ)	5 (60)	5 (20)	0 (20)	0 (20)
Urinary tract infection	1 (60)	1 (20)	0 (20)	0 (20)
Others: Cardiac arrest, Arrythmia, Cardiogenic pulmonary oedema, Deep vein thrombosis, Myocardial infarction, Myocardial injury after non cardiac surgery, Pneumonia, Stroke, Surgical site infection (deep)	0 (60)	0 (20)	0 (20)	0 (20)
Death	0 (60)	0 (20)	0 (20)	0 (20)

Variables are presented as absolute number (total number of patients in the respective patient group).

5. Discussion

In this single-center observational study we used indirect calorimetry to measure perioperative energy expenditure and oxygen consumption in patients undergoing elective non-cardiac surgery, as presented in our publication from 2023 (Briesenick et al., 2023). We hypothesised that energy expenditure and oxygen consumption would decrease under general anaesthesia. We additionally measured intraoperative energy expenditure and oxygen consumption in patients undergoing abdominal surgery on an exploratory basis. In our study, energy expenditure and oxygen consumption decreased under general anaesthesia by about one quarter, confirming our hypothesis. Additionally, in our study, energy expenditure and oxygen consumption did not increase during the course of abdominal surgery.

The field of perioperative energy expenditure and oxygen consumption is currently underexplored (Briesenick et al., 2023). As shown in a recent meta-analysis of studies on the effect of general anaesthesia on oxygen consumption (Jakobsson et al., 2019), which is closely related to energy expenditure (Delsoglio et al., 2019), there seems to be considerable study heterogeneity and low quality of data on this subject. According to the authors, general anaesthesia seems to reduce oxygen consumption, but the estimate remains uncertain (Jakobsson et al., 2019, Briesenick et al., 2023). Most studies included in this analysis were published more than 20 years ago. Therefore, the findings give little guidance on the effects of general anaesthesia on oxygen consumption and the closely related energy expenditure in the modern older and high-risk patient population (Jakobsson et al., 2019, Briesenick et al., 2023). Having used the gold standard for assessing energy expenditure, indirect calorimetry, we now provide perioperative data on energy expenditure and oxygen consumption in the modern patient population (Briesenick et al., 2023).

5.1. Discussion of methods

In this study, energy expenditure and oxygen consumption were measured using indirect calorimetry. It is considered the gold standard of measuring energy expenditure and oxygen consumption (Delsoglio et al., 2019, Cioffi et al., 2021, Ocagli et al., 2021). Indirect calorimetry showed advantages over the calculation of energy expenditure using formulas to calculate energy expenditure in patients (Delsoglio et al., 2019, Cioffi et al., 2021, Ocagli et al., 2021). Especially in tumor and elderly patients these formulas showed low accuracy (Mazzo et al., 2020, Ocagli et al., 2021).

The accuracy of the indirect calorimeter used in this study to perform indirect calorimetry is well validated (Oshima et al., 2019, Delsoglio et al., 2020, Oshima et al., 2020). It allows real time estimation of energy expenditure and oxygen consumption in awake patients and mechanically ventilated intensive care patients (Oshima et al., 2020). It requires much shorter time than most other indirect calorimetry devices to determine these values in mechanically ventilated patients. Additionally, in 2020 the used indirect calorimeter was the only commercially available device tested against mass spectromy to ensure gas accuracy (Oshima et al., 2020).

Still, there are limitations when performing perioperative indirect calorimetry. In the preoperative measurement, the patients' discomfort while wearing the face mask and possible allergic skin reactions to the mask material limit its use. Limitations to the use of indirect calorimetry under general anaesthesia and surgery were the need of fixed ventilator settings during each measurement, an inspiratory oxygen fraction of under 60% during the measurement, and a maximum inspiratory pressure of 30mbar. In our study these limitations were considered to avoid measurement inaccuracies. According to the manufacturer, the used indirect calorimeter is not suitable for the presence of flammable anaesthetics. However, sevoflurane is not flammable in the concentration used for general anaesthesia and can thus be used in measurements (Wallin et al., 1975). Still, we cannot rule out that the presence of sevoflurane may have affected indirect calorimetry measurements. However, there was no important difference in perioperative energy expenditure changes between patients with balanced or intravenous general anaesthesia (data not shown) (Briesenick et al., 2023).

In the postoperative measurements, the tight fit of the face mask could cause discomfort or pain, especially if surgery was performed in the head/neck area. Postoperative nausea and vomiting could additionally complicate postoperative measurements using the face mask. Furthermore, it is not possible to supplement oxygen while performing the measurement, which some patients may be dependent on before and after surgery. Additionally, the study design required conducting preoperative measurements with a tight fitted face mask, and intraoperative measurements via the endotracheal tube. However, since the indirect calorimeter is well validated for both measurement modes, it seems unlikely that measurement results differ between the two modes (Briesenick et al., 2023). Furthermore, a recent study performing perioperative indirect calorimetry in elderly patients also used the face mask and the endotracheal tube for their measurements, making their results comparable to ours (Jakobsson et al., 2021).

The device used in the named study was the Quark RMR (Quark RMR, COSMED, Rome, Italy). Its accuracy, like the QNRG+, has already been validated in several studies (Sundström et al., 2013, Ashcraft and Frankenfield, 2015, Allingstrup et al., 2017).

The CNAP system used in this study to perform continuous non-invasive estimation of cardiac index, mean arterial pressure, and heart rate, was well validated in former validation studies (Jeleazcov et al., 2010, Ilies et al., 2012, Smolle et al., 2015, Saugel et al., 2020). However, a recent systematic review and meta-analysis showed that there is still substantial study heterogeneity in the validation studies comparing non-invasive techniques to invasive gold standard methods of pulse wave analysis (Saugel et al., 2020). For instance, differences in patient population and device related factors, like different software versions of monitors, complicate the comparability of the studies (Saugel et al., 2020). There are several limitations when performing pulse wave analysis with the non-invasive volume clamp method. Firstly, the general limitations of pulse wave analysis have to be taken into account. The pulse wave analysis depends on an optimal arterial blood pressure waveform signal, which can be disturbed in certain clinical situations like cardiac arrythmia, and can be rapidly invalidated by artefacts (Saugel et al., 2021). In addition, pulse wave analysis cannot be used in patients with non-pulsatile blood flow, which is found in patients with veno-arterial extracorporeal membrane oxygenation or left ventricular assistant devices (Saugel et al., 2021). We have bypassed these limitations by excluding patients with cardiac arrythmia or cardiac assistant devices. Secondly, there are specific limitations to the use of non-invasive pulse wave analysis devices using the volume clamp method. According to the manufacturer, bright light can distort the measurement of the infrared light detector. If the finger clamp is too big or too small for the patient, measurements might be inaccurate. Furthermore, severe vasoconstriction (e.g., caused by circulatory shock or high dose vasopressor therapy), peripheral vascular diseases or distorted fingers (e.g. due to arthritis) complicate obtaining a valid arterial blood pressure waveform (Meidert and Saugel, 2018, Kouz et al., 2021). In addition, the measurements are sensible to the patients' movements and have to be checked for plausibility in awake patients (Meidert and Saugel, 2018).

5.2. Discussion of results

5.2.1. Perioperative energy expenditure

In our study energy expenditure in patients having elective non cardiac surgery decreased by 26% after the induction of general anaesthesia. Oxygen consumption decreased by 27% under general anaesthesia. Oxygen consumption is closely related to energy expenditure (Delsoglio et al., 2019). These findings are in line with the results of a study performed 26 years ago. In this study, general anaesthesia reduced the metabolic heat production of healthy volunteering adults by about 30%, compared to awake measurements before induction of general anaesthesia (Matsukawa et al., 1995). A more recent observational study from 2021 examined oxygen consumption in elderly patients undergoing abdominal surgery, using indirect calorimetry. In this study, the induction of general anaesthesia reduced oxygen consumption by 34%, compared to preoperative awake oxygen consumption (Jakobsson et al., 2021). When comparing the different patient groups (abdominal surgery; orthopaedic/trauma surgery; head/neck surgery), certain differences become apparent. A significant difference in the reduction of energy expenditure from preoperative awake values to values at incision was found between the orthopaedic/trauma (-31%) and head/neck surgery group (-21%). Additionally, at incision, oxygen consumption was significantly higher in the head/neck surgery group compared to the orthopaedic/trauma surgery group. Perioperative anaesthetic management was not standardised due to the observational nature of the study and the number of patients in each group is small. We therefore refrain from speculating on the reasons for the differences between the groups.

Our results showed no significant difference between preoperative awake- and postoperative energy expenditure and oxygen consumption in all patients. These findings are in line with two recent studies measuring energy expenditure respectively oxygen consumption in patients undergoing major abdominal surgery using indirect calorimetry (Jakobsson et al., 2021, Silva et al., 2021). Silva et al. reported no difference between preoperative awake energy expenditure and postoperative energy expenditure on the third and fifth day after surgery (Silva et al., 2021). Jakobsson et al. also reported no difference between preoperative and postoperative values of oxygen consumption (Jakobsson et al., 2021). An earlier observational study from 2001, measuring oxygen consumption and energy expenditure in 17 patients having elective surgery of small-medium scope, also reported no significant difference between preoperative awake- and postoperative energy expenditure and oxygen consumption (Tannus et al., 2001).

In difference to the findings of other studies, the patients of the abdominal surgery group in our study showed a postoperative energy expenditure that was 10% lower than preoperative awake values. A possible explanation could be that 5 out of 20 patients in this group were still intubated and therefore sedated during the postoperative measurement. In contrast, in the two studies from 2021, all patients were awake during the postoperative measurement (Jakobsson et al., 2021, Silva et al., 2021).

5.2.2. Intraoperative energy expenditure and oxygen consumptions in abdominal surgery patients

We had speculated that energy expenditure and oxygen consumption might increase during the course of surgery, due to physiological stress and systemic inflammation induced by the surgical trauma (Weissman, 1990, Gillis and Carli, 2015, Parker et al., 2019). Therefore, on an exploratory basis, we measured perioperative energy expenditure and oxygen consumption in 20 patients having abdominal surgery during the course of surgery (Briesenick et al., 2023). In 18 out of 20 patients, intraoperative energy expenditure was reduced compared to preoperative awake energy expenditure, remaining around surgical incision levels. It is possible that modern anaesthesiologic management may have limited the stress response to the surgical trauma and explain this observation (Briesenick et al., 2023). However, in two patients energy expenditure increased during the surgical procedure compared to preoperative awake energy expenditure. Energy expenditure increased at 300, 480 and 540 minutes after incision in one patient and during the whole course of surgery in the other patient. One patient had surgery lasting for more than 10 hours and required massive blood transfusion. The extensive surgical trauma might have led to systematic inflammation and physiologic stress, resulting in increased cellular metabolic needs reflected by the increase of energy expenditure (Briesenick et al., 2023). The patient showed high levels of lactate concentration suggesting anaerobic metabolism. He additionally developed an acute kidney injury postoperatively. The other patients' preoperative awake resting energy expenditure was not reduced by general anaesthesia. Energy expenditure increased up to 32% during surgery compared to preoperative awake energy expenditure. The patients' preoperative awake energy expenditure was comparable low with 522 kcal d^{-1} m^{-2} (Briesenick et al., 2023). These findings have to be interpreted as processes in single individual patients and should not be generalised. More research on individual changes in energy expenditure during the course of surgery is needed to better understand these processes.

Intraoperative oxygen consumption showed similar changes as energy expenditure during the course of surgery, since it is mathematically and physiologically coupled to energy expenditure (Delsoglio et al., 2019). Intraoperative oxygen consumption was reduced in 18 out of 20 patients in the intraoperative measurements. These findings are in line with Jakobsson et al, reporting in their observational study a decrease of oxygen consumption in abdominal surgery patients by a median of 24%, two hours after incision, compared to preoperative awake values (Jakobsson et al., 2021). In the abdominal surgery group of our patients, intraoperative oxygen consumption was 37% lower two hours after incision, compared to preoperative awake oxygen consumption.

There are several possible explanations for these differences. All patients in the study of Jakobsson et al. received an epidural catheter (Jakobsson et al., 2021). Epidural anaesthesia seems to reduce the amount of sevoflurane required to maintain adequate sedation levels during non-cardiac surgery (Hodgson and Liu, 2001). Therefore, epidurals allow general anaesthesia to be less deep to maintain adequate sedation. An increased depth of sedation seems to be associated with lower oxygen consumption values (Terao et al., 2003). Additionally, the use of epidural catheters seems to lead to an increase of energy expenditure and oxygen consumption (Shichinohe et al., 1993). In our patient group of 20 patients having abdominal surgery, only 12 patients received an epidural catheter. Thus, our patients possibly needed deeper sedation levels than the patient population of Jakobsson et al. (Jakobsson et al., 2021) to maintain adequate anaesthesia. This could explain the greater reduction in median intraoperative oxygen consumption in our patient group undergoing abdominal surgery. We measured higher intraoperative oxygen consumption in patients with epidural catheters than in patients without an epidural catheter (data not shown). Since the number of patients is small, these results are fragile and should not be generalised.

Furthermore, the median age of patients in the study of Jakobsson et al. was 73 years, compared to 58 years in our study. Age is an important factor when evaluating energy expenditure (Hölzel et al., 2021). The different median age of the study populations might have an influence on the differing oxygen consumption values in the intraoperative period, although preoperative awake values of oxygen consumption are similar (135mL min^{-1} vs. 139mL min^{-1}). Moreover, other patient characteristics like sarcopenia or body mass index, and perioperative management could have influenced intraoperative oxygen consumption (Mtaweh et al., 2019).

5.2.3. Perioperative cardiovascular parameters

In addition to energy expenditure and oxygen consumption, we examined the patients' cardiovascular parameters cardiac index, mean arterial blood pressure, and heart rate. All cardiovascular parameters were lower under general anaesthesia than in the awake preoperative measurement. General anaesthesia was induced with propofol. The administration of propofol seems to cause a decrease in cardiac contractility as well as systemic vascular resistance. This results in an decrease of cardiac output, hence cardiac index (Loushin, 2005). However, other studies report no decrease of cardiac output when using propofol (de Wit et al., 2016). Mean arterial blood pressure also appears to be reduced by propofol (de Wit et al., 2016). Heart rate seems to be influenced by propofol due to an inhibition of the sympathetic tone which may lead to significant bradycardia or even asystole (Loushin, 2005, Tramèr et al., 1997, James et al., 1989).

Apart from propofol, most of our patients were anaesthetised with sevoflurane at incision. Volatile anaesthetics appear to influence the cardiovascular system by affecting the myocardium itself or by decreasing systemic vascular resistance (Ciofolo and Reiz, 1999, Brioni et al., 2017). Cardiac output seems to be reduced or unaffected by sevoflurane (Malan et al., 1995, Rivenes et al., 2001, Stachnik, 2006, Brioni et al., 2017). Mean arterial pressure appears to be reduced by sevoflurane depending on the dose administrated (Holaday and Smith, 1981, Loushin, 2005). This is thought to be caused by decreases in myocardial contractility, systemic vascular resistance, sympathetic output, or a combination of these factors (Loushin, 2005). Heart rate also seems to be reduced or unchanged by sevoflurane (Stachnik, 2006).

In the postoperative measurements we observed an increase in cardiac index and heart rate compared to preoperative values, whereas mean arterial blood pressure decreased. Postoperative cardiac index in patients having non-cardiac surgery is scarcely described, making it difficult to compare our results with other studies. Cardiac index is determined by heart rate, myocardial contractility, cardiac pre- and afterload (Vincent, 2008). Since heart rate also increased in the postoperative measurement compared to the preoperative measurement, it might have increased cardiac index. The remaining three parameters influencing cardiac index were not monitored in our measurements, which limits considerations on why cardiac index is increased.

Postoperative mean arterial blood pressure was lower than preoperative mean arterial blood pressure. Postoperative hypotension during the first days after surgery is common and seems to cause postoperative complications like myocardial injury or acute kidney injury (Sessler et al., 2018, Saugel and Sessler, 2021). A feasibility study on the use of the CNAP device to monitor patients undergoing major elective surgery in the postoperative period reports that over 50 percent of the patient population had at least one episode of hypotension in the postoperative period (King et al., 2021). Our patients do not show a postoperative median mean arterial blood pressure which would be defined as hypotension (Sharma et al., 2022). Still, the decrease of mean arterial blood pressure could have the same causes as postoperative hypotension like hypovolemia, due to blood loss or inadequate fluid replacement, and vasodilatation (King et al., 2021).

Postoperative heart rate was higher than preoperative. The patients' heart rate is a highly variable parameter. It varies constantly and depends on the pacemaker activity of the sinoatrial node cells which is influenced by modifiable and nonmodifiable factors (Valentini and Parati, 2009). Postoperative heart rate could have been increased due to postoperative pain, general agitation, or the mean arterial blood pressure, which was low compared to the preoperative measurement (Valentini and Parati, 2009). Overall, since cardiovascular parameters were only measured over a ten-minute time period once after surgery, the measured values do not represent the general state of the patients' cardiovascular system and therefore have to be interpreted with care.

5.3. Energy expenditure in hemodynamic goal-directed therapy protocols

5.3.1. The relationship between energy expenditure and oxygen delivery

To determine whether energy expenditure can be used as a therapy target in hemodynamic goal-directed therapy to improve end organ oxygen delivery, the relationship between oxygen delivery and energy expenditure needs to be further understood. Optimal oxygen delivery is needed to meet cellular metabolic needs (Parker et al., 2019, Molnar et al., 2020). Cellular metabolic needs are reflected by energy expenditure (Weissman, 1990, Leiner et al., 2020). Energy expenditure can be assessed by measuring oxygen consumption and carbon dioxide production using indirect calorimetry (Delsoglio et al., 2019). Thus, energy expenditure is mathematically coupled with oxygen consumption (Weir, 1949). The relationship between oxygen consumption and oxygen delivery was analysed in various animal studies (Vincent and De Backer, 2004).

They suggest that oxygen consumption is independent of oxygen delivery over a wide range of oxygen delivery values. This is due to the rapid adjustment of oxygen extraction when oxygen delivery changes. When oxygen delivery is acutely reduced, for instance due to a decrease in cardiac output, anaemia or hypoxemia, oxygen extraction increases to ensure steady oxygen consumption (Vincent and De Backer, 2004).
However, in case of limited cellular oxygen availability, when oxygen delivery is reduced below a critical value, oxygen extraction compensation is less efficient. Consequently, oxygen consumption can no longer be kept at the physiological level and decreases. Thus, cellular metabolic needs would no longer be satisfied. This is followed by an abrupt increase of lactate concentrations as a sign of anaerobic metabolism (Lugo et al., 1993, Vincent and De Backer, 2004, Vincent, 2005). Especially in severe cases of circulatory shock with significantly reduced blood flow, oxygen consumption seems to become dependent on oxygen delivery (Vincent and De Backer, 2004). Additionally, in the presence of sepsis mediators the critical value below which oxygen consumption becomes dependent on oxygen delivery can be normal or even elevated (Vincent, 2005). However, oxygen consumption is not globally dependent on oxygen delivery in stable and even critically ill patients (Vincent and De Backer, 2004). Oxygen delivery/consumption dependency is rather a hallmark of acute circulatory shock in clearly unstable patients (Vincent, 2005).

To understand how changes in oxygen consumption reflect changes in oxygen delivery, the two parameters should be examined in the same patient. In their study from 2021, Jakobsson et al. measured perioperative oxygen consumption together with oxygen delivery. The authors showed that oxygen delivery decreased in the perioperative measurements in parallel to oxygen consumption. However, the authors warn to interpret these parameters as correlations, because of the previously explained controversial concept of supply dependency of oxygen consumption when oxygen delivery becomes critical (Jakobsson et al., 2021). Due to these clinical controversies, when considering whether oxygen consumption is or is not dependent on oxygen delivery, there might be a limit in drawing conclusions from oxygen consumption to oxygen delivery. In addition, Jakobsson et al. reported that changes of values during surgery of each individual do not indicate a relationship between oxygen delivery and oxygen consumption, only the data of all patients combined do so (Jakobsson et al., 2021).

To further understand the correlations between oxygen delivery and oxygen consumption, as Jakobsson et al. also remarked, it would need a study design with controlled and predefined interventions, as well as standardized conditions to measure oxygen delivery and oxygen consumption in high risk patients (Jakobsson et al., 2021).

5.3.2. Energy expenditure as a therapy target in perioperative hemodynamic goal-directed therapy protocols

As explained in 5.3.1, it is controversial whether oxygen consumption and therefore also energy expenditure are dependent on oxygen delivery. Thus, drawing direct conclusions from energy expenditure to oxygen delivery would be inaccurate. However, in contrast to hemodynamic parameters like cardiac output or blood pressure, energy expenditure does not only give information about oxygen delivery. Energy expenditure reflects cellular metabolic needs (Weissman, 1990, Leiner et al., 2020).

In their randomised controlled study from 1993, Lugo et al. concluded that the intraoperative period can be associated with a decrease in oxygen extraction capacity in high-risk patients, which cannot be compensated by lower oxygen demand during general anaesthesia. Thus, even normal or elevated levels of oxygen delivery could still lead to cellular oxygen dept during surgery and general anaesthesia, due to the low oxygen extraction capacity of the tissue (Lugo et al., 1993). This cellular oxygen dept, despite adequate oxygen delivery, would not be detected by actual hemodynamic monitoring protocols which commonly focus on parameters reflecting oxygen delivery and cardiac output. Yet, by measuring energy expenditure, which reflects cellular metabolic needs, cellular oxygen dept could be registered, filling a blind spot in the hemodynamic monitoring protocols we have today. Therefore, a detailed understanding of perioperative cellular metabolic needs, reflected by energy expenditure, could help tailor perioperative hemodynamic goal-directed therapy protocols to the individual demands of the patient (Briesenick et al., 2023). As also concluded in our publication, the findings of this study, obtained by using indirect calorimetry, the gold standard technology, might lay the foundation to further research and development to improve actual perioperative hemodynamic goal-directed therapy protocols (Briesenick et al., 2023).

5.4. Limitations

This study is a single-center observational study. Therefore, the results found in this study might not be generalisable for other clinical settings (Briesenick et al., 2023). Due to the observational nature of this study, perioperative management was not standardized. Thus, we cannot systematically analyse which potential confounding factors could have affected our measurements (Briesenick et al., 2023). Potential confounding factors of measuring perioperative energy expenditure and oxygen consumption include the exact fasting period, depth of anaesthesia, total intravenous as opposed to a balanced anaesthesia, use of neuraxial anaesthesia, and effects of neuromuscular blocking agents (Shichinohe et al., 1993, Yoshimura et al., 2015, Delsoglio et al., 2019, Mtaweh et al., 2019, Briesenick et al., 2023). Additionally, energy expenditure is influenced by age, sarcopenia, and sepsis (Delsoglio et al., 2019, Mtaweh et al., 2019). Median age of our patients was 58. A recent observational database study reports a decrease in energy expenditure with increasing age, which was significant for patients aged ≥ 80 years compared to younger age groups (Hölzel et al., 2021). Thus, the data from our patient population can be considered safe from distortion due to age. By excluding patients with a body weight under 50kg we aimed to exclude patients with sarcopenia. Moreover, all patients had elective surgery and were not septic according to SEPSIS-3 definition, making a distortion of measured energy expenditure values due to sepsis improbable (Singer et al., 2016). The size of our study population limits drawing general conclusions about all patients. Still, our study has a population with three times more patients (n = 60) than the recent study of Jakobsson et al. (n = 20) on the same matter (Jakobsson et al., 2021).

We aimed to assess energy expenditure and oxygen consumption in a heterogenous modern patient population with 60 patients in three different surgical groups. Thus, our patient group is heterogenic considering age and types of surgery performed. On the one hand this allows to further understand energy expenditure and oxygen consumption in the modern patient population, since the three different groups with small, medium, and major surgical trauma allow to see how different types of traumata influence these parameters. On the other hand, due to the three different groups, each group includes less patients making the results less transferable to all patients with similar traumata.

Furthermore, in the abdominal surgery group, in which we measured intraoperative energy expenditure and oxygen consumption, the length of surgery ranged between two hours to over six hours. Therefore, intraoperative energy expenditure and oxygen consumption might be different for each patient and should be interpreted as individual processes, and not be generalized for all patients undergoing abdominal surgery. Additionally, five out of twenty patients were still intubated during the postoperative measurement, which might have influenced postoperative energy expenditure and oxygen consumption in the abdominal surgery group.

Postoperative measurements were conducted within 24 hours after the end of surgery, meaning that the timing of the postoperative measurement was not standardized. Patients measured within one hour after surgery could possibly have different energy expenditure and oxygen consumption than patients measured 24 hours after the end of surgery. Median time between the end of surgery and the postoperative measurement was 9.7 hours. A shorter time period, in which the postoperative measurement was performed, would have improved the comparability of the measured postoperative values of the patients. This, however, was not feasible due to the observational nature of the study, patient related factors like pain or nausea, and limited availability of personnel to conduct the measurements. Future studies on this matter should ensure standardised anaesthetic management – including exact timing of pre- and postoperative measurements of energy expenditure and oxygen consumption, standardization of food intake, monitoring of the depth of anaesthesia, type of anaesthesia maintenance, timing of repeated neuromuscular blocking agents, use of neuraxial anaesthesia (Briesenick et al., 2023). Additionally, a more homogeneous patient population could avoid confounding factors of different types of surgical interventions.

5.5. Conclusion and outlook

We conducted this study to better understand energy expenditure and oxygen consumption under general anaesthesia and surgery in the modern patient population. In our study, median energy expenditure and oxygen consumption under general anaesthesia were about one quarter lower than preoperative awake values in patients having elective non-cardiac surgery. Even during the course of surgery, in abdominal surgery patients, these parameters did not exceed preoperative awake values.

This knowledge can be used to further understand the complex processes of the body while under the influence of general anaesthesia and surgery. While most hemodynamic goal-directed therapy protocols focus on oxygen delivery and cardiac output, energy expenditure represents cellular metabolic needs (Weissman, 1990, Pearse et al., 2014, Futier et al., 2017, Leiner et al., 2020, Saugel et al., 2020).
At times in the perioperative period, cellular metabolic needs cannot be fulfilled even if oxygen delivery is adequate (Lugo et al., 1993). By monitoring perioperative energy expenditure, unfulfilled cellular metabolic needs could be detected where today's hemodynamic monitoring would not detect a need for intervention. Therefore, the monitoring of energy expenditure could fill a blind spot in hemodynamic monitoring. Energy expenditure could be used as a therapy target during perioperative hemodynamic goal-directed therapy. To enable this, it is crucial to understand how to interpret perioperative energy expenditure, and which interventions should be used to respond to the measured values. Our study demonstrates that performing perioperative indirect calorimetry is feasible (Briesenick et al., 2023). We need further studies on this matter with set hemodynamic monitoring and goal-directed therapy protocols to expand today's knowledge about perioperative energy expenditure.

Besides the new insights our findings can offer on hemodynamic monitoring, they can also be used when improving the patients' nutrition before, during, and after surgery. Since studies suggest that indirect calorimetry guided energy delivery can improve the outcome of critically ill patients in the intensive care unit, it may also help improving a patients' postoperative outcome (Singer et al., 2011, Tatucu-Babet et al., 2020). There are already studies engaging in perioperative nutrition therapy (Yue et al., 2013, Satoh et al., 2018). Future studies could further examine whether indirect calorimetry guided perioperative nutrition therapy could improve the patients' postoperative outcome.

6. Summary

Perioperative hemodynamic goal-directed therapy is an important tool to optimise perioperative end organ oxygen delivery and prevent perioperative morbidity, especially in high-risk patients. To improve hemodynamic goal-directed therapy, there is a need for an individualised, patient centred approach. Most protocols of perioperative hemodynamic goal-directed therapy focus on the monitoring and optimisation of oxygen delivery and cardiac output. However, at times in the perioperative period, cellular metabolic needs cannot be fulfilled even if oxygen delivery is adequate. Cellular metabolic needs are reflected by energy expenditure. Thus, perioperative energy expenditure could give better guidance about the actual individual cellular metabolic needs of the patient. By monitoring perioperative energy expenditure, unfulfilled cellular metabolic needs could be detected where actual hemodynamic monitoring would not detect a need for intervention. Still, perioperative energy expenditure has yet scarcely been described. In this single-center observational study, we measured perioperative energy expenditure and oxygen consumption, which is mathematically and physiologically coupled with energy expenditure, in 60 patients undergoing elective non-cardiac surgery. Our patient population includes patients of different age and surgical intervention, representing our modern patient population. We measured energy expenditure and oxygen consumption using the gold standard, indirect calorimetry. All patients were measured preoperatively while awake, under general anaesthesia, and postoperatively within the first 24 hours after the end of surgery. Additionally, on an exploratory basis, we measured intraoperative energy expenditure and oxygen consumption in 20 patients undergoing abdominal surgery. In our study, energy expenditure decreased by 26% and oxygen consumption by 27% under general anaesthesia, compared to preoperative awake values. Postoperative values showed no difference to preoperative awake values. Overall intraoperative energy expenditure and oxygen consumption in the abdominal surgery group did not exceed preoperative values. Perioperative measuring of energy expenditure using indirect calorimetry is feasible. It remains to understand how perioperative energy expenditure should be interpreted and which interventions should be used to respond to the measured values. Further studies are needed with set hemodynamic monitoring and goal-directed therapy protocols to expand today’s knowledge about perioperative energy expenditure.

7. Zusammenfassung

Die perioperative zielgerichtete hämodynamische Therapie ist ein wichtiges Instrument um die Sauerstoffzufuhr der Zellen zu optimieren und die perioperative Morbidität zu verringern. Dies gilt insbesondere für Hochrisikopatienten. Um die zielgerichtete hämodynamische Therapie zu verbessern braucht es einen auf die Bedürfnisse des Patienten zugeschnittenen Ansatz. Die meisten Konzepte fokussieren sich auf das Überwachen und Optimieren der Sauerstoffzufuhr und des Herzzeitvolumens. Während der perioperativen Phase kann es jedoch dazu kommen, dass der zelluläre Sauerstoffbedarf trotz optimaler Sauerstoffzufuhr nicht gedeckt wird. Der individuelle zelluläre Sauerstoffbedarf spiegelt sich direkt im Energiebedarf wider. Somit könnte durch die Überwachung des perioperativen Energiebedarfs ein möglicher Sauerstoffmangel in den Zellen erkannt werden, obwohl aktuelle Therapiekonzepte noch keinen Handlungsbedarf aufzeigen würden. Trotz dieses Wissens ist der perioperative Energiebedarf bisher kaum untersucht. In dieser monozentrischen Beobachtungsstudie haben wir den perioperativen Energiebedarf und Sauerstoffverbrauch, welcher mathematisch und physiologisch mit dem Energiebedarf verbunden ist, gemessen. Bei der Studienpopulation handelte es sich um 60 Patienten, welche sich einer elektiven nicht-herzchirurgischen Operation unterzogen. Die Patienten waren unterschiedlichen Alters und bekamen verschiedenen chirurgischen Eingriffe und repräsentieren somit die moderne Patientenpopulation. Um den Energiebedarf und den Sauerstoffverbrauch zu messen benutzten wir das Goldstandard Verfahren, die indirekte Kalorimetrie. Wir haben den Energiebedarf und Sauerstoffverbrauch aller Patienten präoperativ im Wachzustand, unter Vollnarkose, sowie postoperativ innerhalb der ersten 24 Stunden nach Beendigung der Operation gemessen. Zusätzlich haben wir bei 20 Patienten, die sich einer abdominalen Operation unterzogen haben, auch den intraoperativen Energiebedarf und Sauerstoffverbrauch gemessen. In unserer Studie sank der Energiebedarf unter Vollnarkose um 26 % und der Sauerstoffverbrauch um 27 % im Vergleich zu den präoperativen Werten im Wachzustand. Die postoperativen Werte zeigten keinen Unterschied zu denen der präoperativen Messung. Insgesamt stiegen die intraoperativ gemessenen Werte nicht über das Level der präoperativen Messung hinaus an. Es bleibt zu klären, wie der perioperative Energiebedarf zu interpretieren ist und welche Maßnahmen auf die gemessenen Werte folgend eingeleitet werden sollten. Weitere Studien mit festgelegten hämodynamischen Überwachungskonzepten und Konzepten der zielgerichteten hämodynamischen Therapie sind nötig um den heutigen Kenntnisstand über den perioperativen Energiebedarf zu erweitern.

8. References

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11. List of abbreviations

ASA	American Society of Anaesthesiologists
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CI	Cardiac index
CO	Cardiac output
CO_2	Carbon dioxide
CVP	Central venous pressure
DAP	Diastolic arterial pressure
DO_2	Oxygen delivery
EE	Energy expenditure
Hb	Haemoglobin
IC	Indirect calorimeter
MAC	Minimal alveolar concentration
MAP	Mean arterial pressure
O_2	Oxygen
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
PPV	Pulse pressure variation
SAP	Systolic arterial pressure
$ScvO_2$	Central venous oxygen saturation
sO_2	Oxygen saturation
SV	Stroke volume
SVV	Stroke volume variation
VCO_2	Carbon dioxide production
VO_2	Oxygen consumption

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13. Curriculum Vitae

Der Lebenslauf entfällt aus datenschutzrechtlichen Gründen.

14. Eidesstattliche Versicherung

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 Dissertation 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 Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift: Schaade

Annika Schaade, Hamburg, 08.09.2023