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**THE NEW OLD NORMAL:
REASSESSING PERIOPERATIVE OXYGEN
CONSUMPTION AND HAEMODYNAMICS
IN THE ELDERLY**

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The new old normal: Reassessing perioperative oxygen consumption and haemodynamics in the elderly

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“Dissents speak to a future age.”

Ruth Bader Ginsburg

ABSTRACT

Perioperative haemodynamic instability and disturbances of global oxygen transport are associated with complications and organ injury after surgery. The continuously growing population of elderly in surgical care are at higher risk due to age-related cardiovascular alterations and increased prevalence of comorbidities. Optimised and tailored haemodynamic interventions may improve outcomes, but goals to aim for and responses to expect are not adjusted for elderly. Hypotension and changes in oxygen consumption (VO₂) induced by anaesthesia are potentially very relevant in the elderly and reassessment is needed in modern perioperative care with current methodologies. In this thesis, cardiac output and haemodynamic changes related to hypotension after spinal anaesthesia (SPA) are outlined in the first study. VO₂ after general anaesthesia (GA) and surgery is investigated in three studies with different approaches; by meta-analysis, prospectively during major surgery and by method comparison.

Study I (prospective observational): 20 ASA II-IV patients (mean age 72 years) were monitored with LiDCO™plus prior to and 45 minutes after injection of SPA. Stroke volume and cardiac index, and consequently oxygen delivery index, decreased before the intrathecal injection and this decrease progressed after SPA in those who developed hypotension. In contrast, the non-hypotensive demonstrated an initial increase in cardiac index after SPA. Logistic regression analyses demonstrated that pre-anaesthetic changes of cardiac index could predict post-spinal hypotension (OR 0.79, 95% CI: 0.60, 0.91) with high discriminative ability (AUC 0.91).

Study II (systematic review and meta-analysis): Cochrane Library, MEDLINE and EMBASE databases were searched for studies with measurements of VO₂ before and after induction of GA. 24 studies with 453 patients were identified, published 1969-2000. Cochrane and NIH quality assessment tools revealed general high risk of bias in the majority of studies. However, measurements and interventions were described in great detail. A random-effects meta-analysis estimated the reduction of VO₂ to -33 (95% CI: -38, -28) ml min⁻¹ m⁻² during GA but with uncertainty of the estimate due to very low quality as indicated in a GRADE evidence profile. A sample size calculation for study III was performed based on this data.

Study III (prospective observational): VO₂ was measured by indirect calorimetry (QuarkRMR), before, during and after major upper abdominal surgery in 20 ASA II-IV patients (mean age 73 years). VO₂ decreased by a mean of -46 (95% CI: -55, -38) ml min⁻¹ m⁻² after induction of GA and increased during surgery. Simultaneous calculations of oxygen delivery (DO₂) and estimated oxygen extraction ratio (O₂ER) from LiDCO™plus monitoring and arterial-central venous blood gas content showed low intraoperative levels of extraction and delivery. Mixed effect models of relative changes of intraoperative VO₂ compared to DO₂ and estimated O₂ER indicated that these parameters changed in parallel.

Study IV (method comparison): Estimations of VO₂ by LiDCO™plus-derived cardiac output and arterial-central venous oxygen content difference were compared to 85 simultaneous measurements by indirect calorimetry from study III. Intraclass correlation, Bland-Altman and mixed models analyses for relative changes over time indicated systematic underestimation and poor absolute agreement by this method compared to indirect calorimetry. It may be possible to construct methods for estimation or trending of VO₂ from routine monitoring, but further adjustments and assessment in larger populations are needed.

In summary, these studies characterise and demonstrate that peri-anaesthetic cardiac output and oxygen consumption undergo changes in elderly patients important to haemodynamic stability and oxygen transport. Mechanistic approaches, with feasible and reliable methods for monitoring or estimation of these changes, are suggested when investigating haemodynamic interventions in elderly.

LIST OF SCIENTIFIC PAPERS

- I. **Is postspinal hypotension a sign of impaired cardiac performance in the elderly? An observational mechanistic study**
Jakobsson J, Kalman, SH, Lindeberg-Lindvet M, Bartha E
Br J Anaesth 2017; 119 (6): 1178-1185.
- II. **The effects of general anaesthesia on oxygen consumption: A meta-analysis guiding future studies on perioperative oxygen transport**
Jakobsson, J, Vadman, S, Hagel, E, Kalman, S, Bartha, E
Acta Anaesthesiol Scand 2019; 63: 144-53. E-pub Sept 20, 2018
- III. **Perioperative oxygen consumption revisited: An observational study in elderly undergoing major abdominal surgery**
Jakobsson J, Norén C, Hagel E, Kalman S, Bartha E
Manuscript submitted for publication
- IV. **Estimated oxygen consumption by minimal-invasive cardiac output and central venous sampling in major abdominal surgery: secondary outcomes of a prospective observational study in elderly**
Jakobsson J, Norén C, Hagel E, Backheden M, Kalman S, Bartha E
Manuscript

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LIST OF ABBREVIATIONS

AF	Atrial fibrillation
ANOVA	Analysis of variance
ANS	Autonomous nervous system
ASA	American Society of Anesthesiologists' physical status
AUC	Area under curve
B-A	Bland-Altman analysis
BA	Before-after study
CaO ₂	Arterial oxygen content
CcvO ₂	Central venous oxygen content
CI	Cardiac index
CO	Cardiac output
CVC	Central venous catheter
CvO ₂	Mixed venous oxygen content
CVP	Central venous pressure
DAP	Diastolic arterial pressure
DO ₂	Oxygen delivery
EDA	Epidural anaesthesia
EDV	End-diastolic volume
EO ₂ ER	Estimated oxygen extraction
ESV	End-systolic volume
EVO ₂	Estimated oxygen consumption
FeO ₂	Expired oxygen fraction
FiO ₂	Inspired oxygen fraction
GA	General anaesthesia
GDHT	Goal-directed haemodynamic therapy
GVO ₂	Gas-derived oxygen consumption
Hb	Haemoglobin
HR	Heart rate
...I or i	Indexed for body surface area
ICC	Intraclass correlation

L	Lumbar level
LA	Left atrium
LoA	Limits of agreement
LSM	Least square means
LV	Left ventricle
MAP	Mean arterial pressure
mDO ₂	Myocardial oxygen delivery
mVO ₂	Myocardial oxygen consumption
NMB	Neuromuscular block
O ₂ ER	Oxygen extraction
PAC	Pulmonary artery catheter
PaO ₂	Partial pressure of oxygen in arterial blood
PcvO ₂	Partial pressure of oxygen in central venous blood
POD	Postoperative day
Q	Flow
QA	Quality assessment
RA	Right atrium
RCT	Randomised controlled trial
REML	Restricted maximum likelihood
RM-ANOVA	Repeated measures analysis of variance
ROC	Receiver operating characteristics
RV	Right ventricle
SAP	Systolic arterial pressure
ScvO ₂	Central venous oxygen saturation
SMD	Standardised mean difference
SPA	Spinal anaesthesia
SV	Stroke volume
SvO ₂	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
Th	Thoracic level
VO ₂	Oxygen consumption

1 INTRODUCTION

Surgery is safe, but not for all. In the elderly patient, ageing and disease in cardiovascular and other organ systems increase the risk of developing complications. Many complications and observations of organ injury are associated with perioperative haemodynamic instability and disturbances of the relationship between oxygen consumption and delivery. The elderly are particularly exposed to these effects of anaesthesia and surgery. Perioperative hypotension and oxygen consumption changes have been demonstrated to impact on postoperative outcomes. However, detailed assessments of these changes during anaesthesia and underlying haemodynamic mechanisms have mainly been described in older publications. Those studies were mostly conducted in younger populations and care settings different from today's, with monitoring and analysis methods no longer commonly used. With increasing life expectancy, improvements of surgical and anaesthetic techniques and changing patient demands, the elderly may in a near future form the major part of the surgical population. Reassessment is therefore needed, in modern perioperative care with current methodological approaches. This thesis specifically addresses the effects of spinal anaesthesia on haemodynamic changes and the effects of general anaesthesia on oxygen consumption in older patients. The 'new old normal' not only refers to the older patient as 'the new normal' in surgical care, but also to the difficulties in distinguishing the 'new' from the 'old normal' in perioperative haemodynamic and oxygen transport in changing surgical populations.

1.1 THE ELDERLY SURGICAL PATIENT

Increasing age a major risk factor for complications and death following surgery.^{1,2} Perioperative care has improved substantially over the last decades, but morbidity and mortality estimates continue to vary between nations, patients and procedures.^{3,4} Reports have indicated that postoperative outcomes in elderly can be greatly improved.^{5,6} Surgical volumes are expected to grow globally and increased life expectancy correlate with surgical rates.⁷ As elderly form a larger part of the population, age-related conditions for which surgical treatment is beneficial will increase as well as conditions associated with surgical risk.⁸ It is also known that procedures carried out in elderly have increased more than expected from the demographics.⁹ In fact, nearly every second surgical procedure in Sweden is today performed in a patient over 60 years of age.¹⁰ Surgery is also common at the end of life, up to 30% undergo an in-patient procedure in the last year before their death.¹¹ The elderly patient is indeed becoming the 'the new normal' in perioperative medicine.

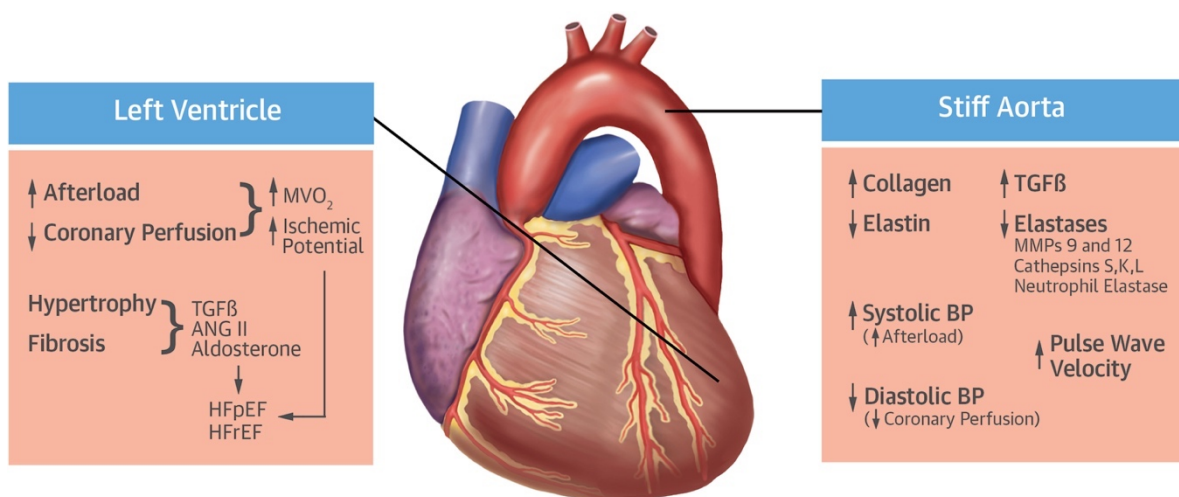


Figure 1. Aortic-left ventricle pathophysiology and dynamics in the ageing cardiovascular system. Ang II = angiotensin II; BP = blood pressure; CV = cardiovascular; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricular; MMP = matrix metalloproteinase; MVO₂ = myocardial oxygen consumption; TGF = transforming growth factor. From Paneni et al. The aging cardiovascular system: understanding it at the cellular and clinical levels. *JACC*:2017; 69 (15):1952-67 ©2017 Elsevier. Reprinted with permission.

1.1.1 Perioperative implications of cardiovascular and respiratory ageing

Ageing of cardiovascular and respiratory systems added to high prevalence of disease processes and polypharmacy render the elderly patient particularly vulnerable to the haemodynamic and respiratory changes induced by anaesthesia and surgical trauma.

Cardiovascular ageing can be divided into different interdependent processes: 1. decline in cardiac performance with diastolic dysfunction and preload sensitivity; 2. autonomous dysfunction with elevated sympathetic tone, β -adrenergic and baroreceptor insensitivity; 3. vascular stiffening with elevated systolic arterial pressure and left ventricular hypertrophy.^{12,13} The adaptations and consequences of these processes are described in *Fig. 1- 3*.

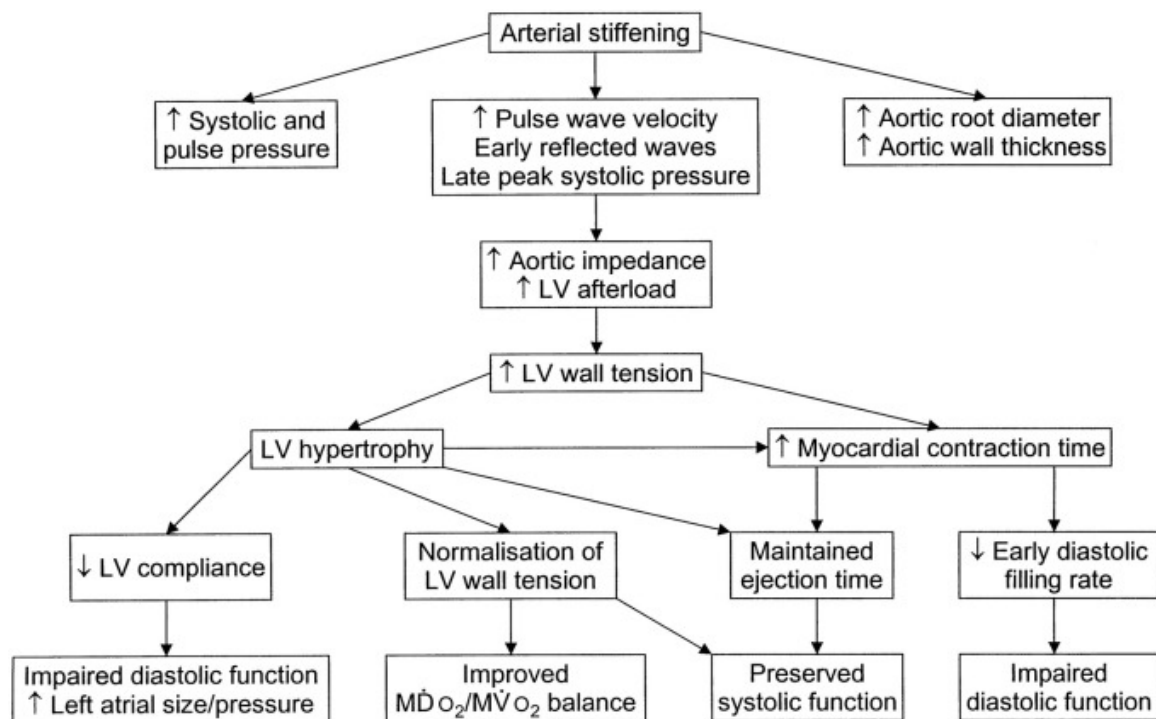


Figure 2. Cardiac adaptations to vascular stiffening. From (13) ©2000 Elsevier. Reprinted with permission.

Myocyte degeneration and vascular stiffness induce left ventricular hypertrophy leading to increased reliance of preload to maintain cardiac output. Early reflected pulse pressure waves increase afterload and wall tension, which prolong myocardial contraction time for ejection but reduce early diastolic filling time. Impaired ventricular relaxation makes the ventricular filling more dependent on atrial contraction, and preservation of sinus rhythm becomes important perioperatively. Degeneration of pacemaker cells and conduction system increase the prevalence of arrhythmias. The blunted β -adrenergic response together with baroreceptor insensitivity limit heart rate and sympathetic responses resulting in profound cardiodepressive and hypotensive effects of anaesthesia.^{12,13}

Diastolic dysfunction is associated with advancing age and hypertension, and the diagnosis is based on echocardiographic criteria.¹⁴ At the early stage, ventricular relaxation is impaired whereas the later stages are characterised by elevated filling pressures. Prevalence have been reported to range 15-27% in elderly populations depending on diagnostic criteria and age-adjustments.¹⁵⁻¹⁷ Both diastolic dysfunction and the related condition HFpEF (heart failure with preserved ejection fraction) are gaining interest in anaesthetic and critical care.¹⁸ In non-cardiac surgery, diastolic dysfunction has been associated with postoperative cardiopulmonary complications.¹⁹

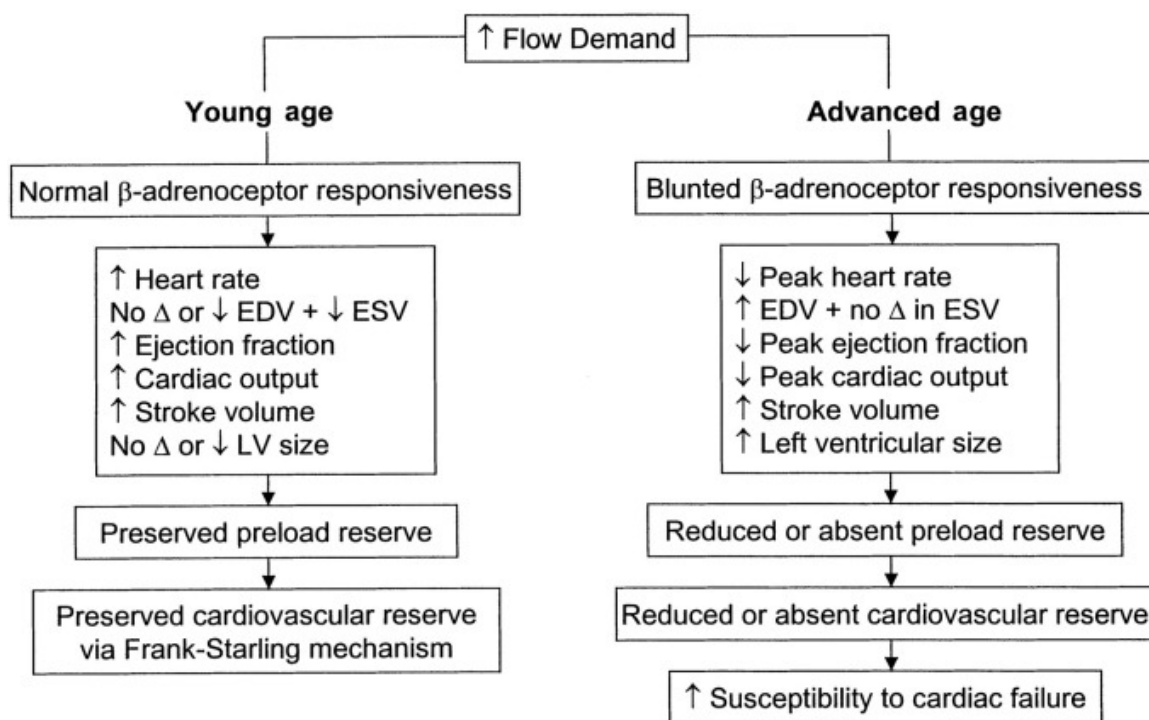


Figure 3. Consequences of reduced β -adrenergic sensitivity in response to flow demand in younger and elderly subjects. From (13) ©2000 Elsevier. Reprinted with permission.

The reserve capacity of the respiratory system is also declining with advancing age. Both pulmonary function and extrinsic features such chest wall compliance, respiratory muscle strength and control of breathing are decreased in the elderly. The increase in closing capacity and residual volume leads to ventilation-perfusion mismatch and increased alveolar-arterial PO₂ gradient. This impairs gas exchange, increases work of breathing and decreases ventilatory response to stress. As a consequence, the elderly patient is prone to respiratory failure with hypoventilation, hypoxemia and hypercarbia in the postoperative period.²⁰

1.1.2 Surgical outcomes in elderly

In a large UK cohort, a high-risk surgical population was identified in which 80% of all surgical deaths occurred despite only accounting for 12.5% of all admissions.² These patients had significantly higher median age compared to a standard surgical population [75 (IQR, 63-83) vs. 54 (IQR, 38-69) years;]. The results were reported similar in a national follow-up five years later.⁵ In Sweden, 30-day mortality after surgery is around 2 % for patients over 70 years, increasing up to 11.5% for those over 90 years.¹⁰ Cohort studies in patients over 80 years have reported mortality rates 3-8% and major complication rates in elderly of 12-25%.^{1,21-23} Geriatric frailty²⁴ assessed by different scores has demonstrated better prediction of poor surgical outcomes than ASA classification alone.^{25,26} It is included in perioperative comprehensive geriatric (CGA) interventions which have shown to reduce complications.²⁷ The major determinant for surgical outcomes in the elderly is the development of postoperative complications.^{22,28} Preoperative cardiopulmonary co-morbidity^{29,30} are well known risk factors and cardiac complications are highly associated with postoperative mortality.³¹⁻³³ Furthermore, intraoperative cardiovascular events such as tachycardia and need for vasoactive agents have been associated with postoperative mortality in elderly.^{23,34} Major abdominal procedures, often in conjunction with malignant disease, are among those with the highest risk in frail elderly.³⁵

1.2 PERIOPERATIVE HAEMODYNAMIC INSTABILITY AND GLOBAL OXYGEN TRANSPORT DISTURBANCES

1.2.1 Principles of global oxygen transport

Supporting adequate gas exchange and blood flow to maintain vital functions and avoid organ injury is essential to anaesthetic and perioperative care. Normal cell metabolism relies on the efficient transport of oxygen from the inspired air to the mitochondria in the oxygen cascade. Effectively, the process has two components: a macrocirculatory, i.e. convective transport, which is active and energy-consuming; and a microcirculatory, i.e. diffusive transport, which is passive down a concentration gradient.³⁶

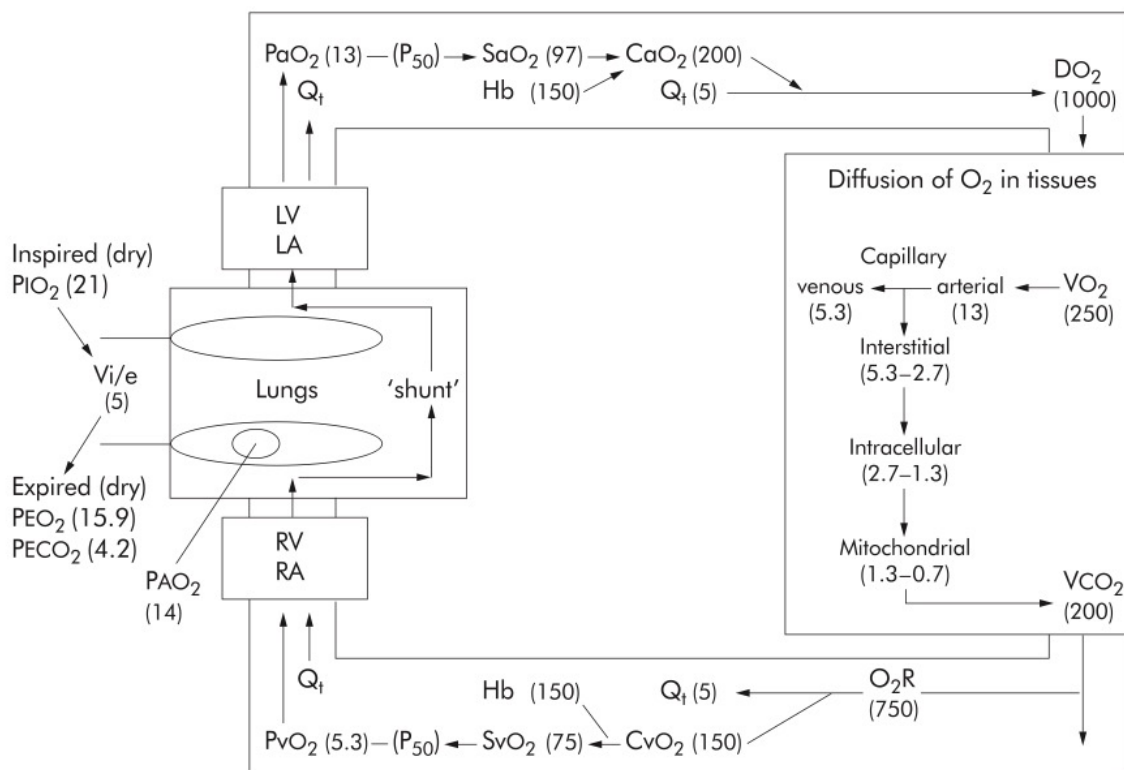


Figure 4. Oxygen transport from atmosphere to mitochondria. Values in parentheses for a normal 75 kg individual (BSA 1.7 m²) breathing air (FiO₂ 0.21) at standard atmospheric pressure (101 kPa). Partial pressures of O₂ and CO₂ (PO₂, PCO₂) in kPa; saturation in %; contents (CaO₂, CvO₂) in ml/l; Hb in g/l; blood/gas flows (Q_t, Vi/e) in l/min. P₅₀ = position of oxygen haemoglobin dissociation curve; it is PO₂ at which 50% of haemoglobin is saturated (normally 3.5 kPa). DO₂ = oxygen delivery; VO₂ = oxygen consumption, VCO₂ = carbon dioxide production in ml/min. PiO₂, PeO₂ = inspired and mixed expired PO₂; PeCO₂ = mixed expired PCO₂; PaO₂ = alveolar PO₂. From Leach and Treacher, *The pulmonary physician in critical care* • 2: Oxygen delivery and consumption in the critically ill, *Thorax* 2002; 50(2):170-77. © 2002 BMJ Publishing group. Reprinted with permission.

After diffusion over the pulmonary capillary membrane, oxygen is transported bound to haemoglobin and, to a smaller extent, dissolved in plasma. The dissolved oxygen is dependent on partial pressure of oxygen (PO₂) and the temperature-dependent oxygen solubility coefficient (0.023 ml O₂ 100 ml⁻¹ plasma kPa⁻¹ at 37°C).³⁷ The amount of oxygen that can bind to haemoglobin is known as the Hüfner constant. It has a theoretical³⁸ maximum of 1.39 ml g⁻¹ Hb but due to the presence of abnormal Hb species, the normal value is 1.31 ml g⁻¹ Hb.³⁹ Haemoglobin saturation (SO₂) is the percentage of occupied oxygen binding sites in relation to the maximum. These variables are used in the calculation of oxygen content, which in arterial blood is:

$$CaO_2 = (Hb \cdot 1.31 \cdot SaO_2 \cdot 0.01) + (0.0225 \cdot PaO_2)$$

Oxygen is delivered to the tissues by the convective flow of cardiac output (CO; L min⁻¹). As a result, oxygen delivery (DO₂; ml min⁻¹) is calculated as:

$$DO_2 = CO \cdot CaO_2$$

In the tissues, oxygen is consumed and the resulting oxygen consumption (VO₂; ml min⁻¹) can be calculated from the arterial and mixed venous oxygen content difference by the *reverse Fick principle*:

$$VO_2 = CO \cdot (CaO_2 - CvO_2)$$

This calculation requires pulmonary artery catheter measurements. Oxygen consumption can also be measured directly through breathing gas analysis, i.e. not derived from cardiac output measurements. These methods are described in further detail below. The ratio between oxygen consumption and delivery is the oxygen extraction (O₂ER):

$$O_2ER = \frac{VO_2}{DO_2} = \frac{CO \cdot (CaO_2 - CvO_2)}{CO \cdot CaO_2} = \frac{CaO_2 - CvO_2}{CaO_2}$$

The O₂ER is normally <0.3, i.e. less than 30% of the oxygen is utilised by the tissues. Regional oxygen extraction varies, the myocardium extracts as much 55% and the kidney only 10% under normal conditions.⁴⁰ Global oxygen extraction can increase up to 0.6-0.8.³⁶ Oxygen delivery is influenced by the levels of the constituting variables of the equation, but is also subject to complex autoregulation processes to match supply to metabolic demands.⁴¹ Oxygen consumption in turn, is affected by several factors, as presented in *Table 1*.³⁹

↑ VO₂

↓ VO₂

<p>Exercise, trauma/surgery/burns, inflammation/sepsis/pyrexia, shivering, seizures, agitation/anxiety/pain, adrenergic drugs, weaning from ventilation</p>	<p>Sedation/analgesia, muscle paralysis, severe shock/hypovolemia, hypothermia/cooling, mechanical ventilation, antipyretics, starvation/hyponutrition</p>
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Table 1. Factors affecting oxygen consumption. From (39) © 2004 Elsevier. Adapted with permission.

Tissue blood flow is determined by local peripheral resistance and the driving arterio-venous pressure gradient in an autoregulated process to match the needs. The relationship between mean arterial (MAP) and central venous pressure (CVP), flow (CO) and systemic vascular resistance (SVR) is described as: $MAP - CVP = CO \cdot SVR$. Cardiac output, a determinant of oxygen delivery, is a product of heart rate and stroke volume. The stroke volume, the difference between end-diastolic (EDV) and end-systolic volume (ESV), is dependent on preload, afterload and contractility during ejection into the circulation. In perioperative haemodynamic support, these three are regulated indirectly by administration of fluids and inotropic drugs, together with maintenance of balanced anaesthesia, adequate oxygen content and blood pressure.

1.2.2 The oxygen consumption-delivery relationship

As stated, global oxygen delivery is surplus to consumption under normal conditions. Falling oxygen delivery is accompanied by increased oxygen extraction, until a critical level at which consumption is thought to become supply-dependent (*Fig. 5*). As of today, the existence of supply-dependency in non-extreme situations is debated as well as the level of critical DO₂ and whether this level is altered in critical illness.⁴² Several methodological problems have been addressed when investigating global changes in relationship between global oxygen consumption, extraction and delivery. These include the possibility of biased conclusions based on static analyses of mathematically coupled data, as both variables are derived from the same cardiac output measurements (i.e. using the Fick equation) and the common use of catecholamines in these clinical studies that increases both consumption and delivery.⁴³

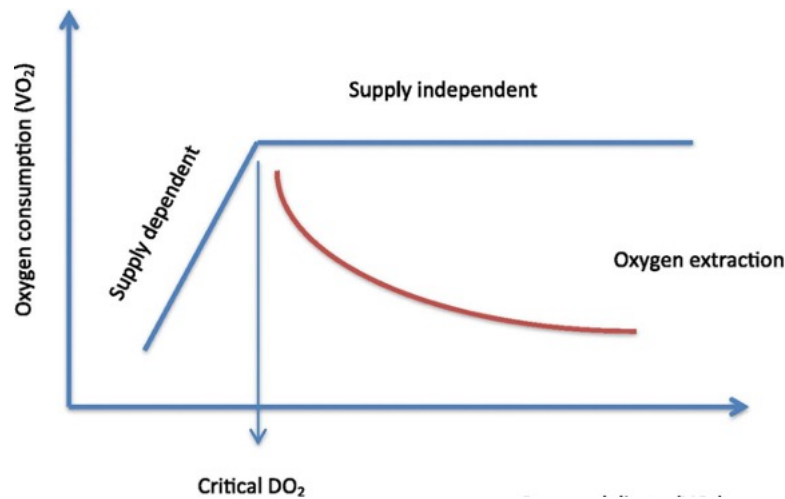


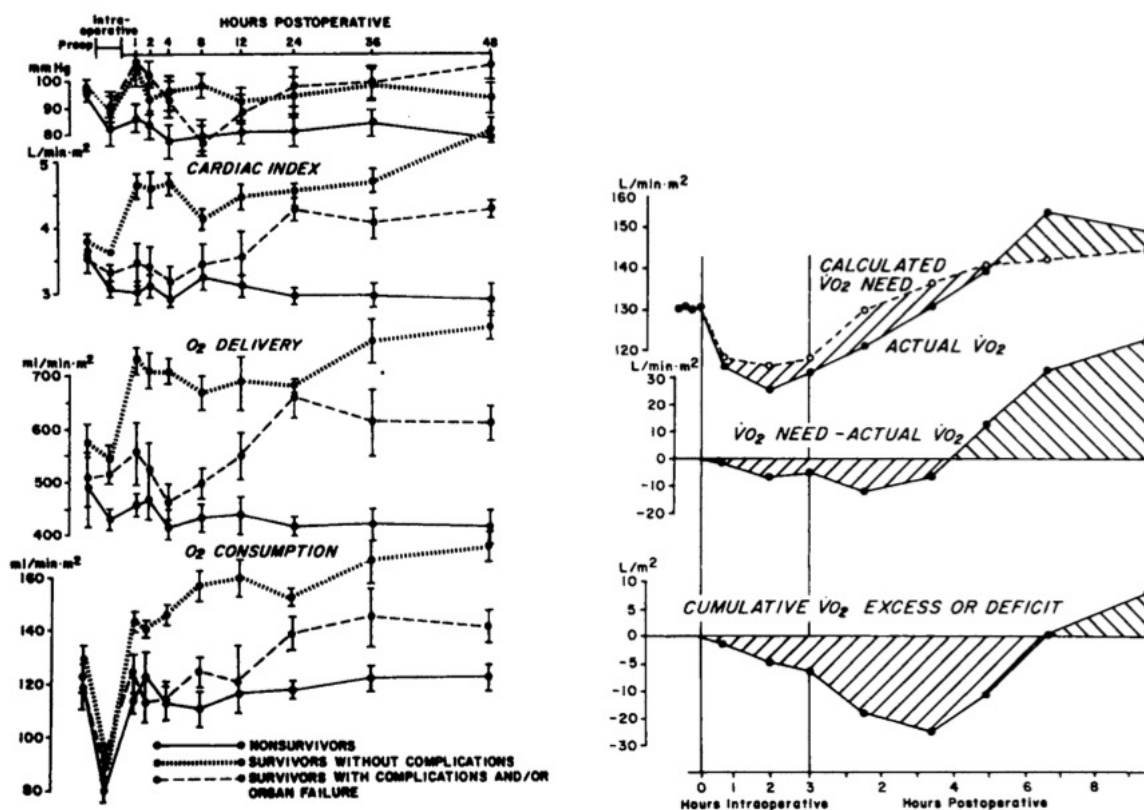
Figure 5. Schematic illustration of the relationship between oxygen consumption, extraction and delivery. From Chan et al. *Pediatrics* 2017;139(4); e20161117 ©2017 AAP. Reprinted with permission.

The concept of supply-dependency of oxygen consumption is therefore controversial and studies using independently obtained oxygen consumption, i.e. simultaneous but different methods of consumption and delivery measurement, have not been able to demonstrate such conditions.⁴⁴⁻⁴⁶ Presumably, the critical level oxygen delivery is individual both on a global and regional level.⁴⁷ Critical level of oxygen delivery during anaesthesia has traditionally been suggested to range 330 to 390 ml min⁻¹ m⁻².^{48,49} However, these suggested values were obtained in studies using mathematically coupled measurements of delivery and consumption derived from the same cardiac output measurements (PAC). Nevertheless, decreases in central venous saturation (ScvO₂) and oxygen extraction ratio (O₂ER) have been associated with development of postoperative complications.⁵⁰⁻⁵² Such observations indicate that VO₂/DO₂-relationship is indeed relevant also under normal clinical conditions.

1.2.3 Haemodynamic optimisation

Goal-directed haemodynamic therapy (GDHT) apply algorithms to monitor and target pre-specified haemodynamic parameters by fluids with inotropes and vasopressors. It has been the subject of a vast number of trials and meta-analyses, since the early landmark studies demonstrated favourable outcomes.^{53,54} Although mortality benefits from GDHT in high-risk surgery has faded over the years, postoperative morbidity outcomes still favour the intervention in meta-analyses.⁵⁵⁻⁵⁹ However, the diversity of patients, interventions and outcomes are a major obstacle in these meta-analyses.⁶⁰ Recent trials and meta-analysis on intraoperative goal directed haemodynamic therapy in hip fractured elderly have not demonstrated clear benefits in terms of postoperative complications.⁶¹⁻⁶³ In a secondary

analysis of haemodynamic responses in one trial, oxygen delivery decreased from baseline in a majority of patients during anaesthesia and surgery regardless of intervention.⁶⁴



Figures 6 a-b. (a, left) Oxygen transport observations in survivors and non-survivors of high risk-surgery and (b, right) calculations of oxygen consumption deficit. From Shoemaker WC, Appel PL and Kram HB. Role of oxygen debt in the development of organ failure, sepsis and death in surgical patients. *Chest* 1992;102 (1): 208-15). ©1992 Reprinted with permission from Elsevier.

Early observations of different oxygen transport patterns in survivors and non-survivors after high-risk surgery have influenced the development of GDHT strategies (Fig 6a).^{53,65} Survival benefits were associated with high levels of oxygen delivery *and* consumption.⁵³ Increased postoperative oxygen extraction due to failure of increasing delivery in response to increased consumption was observed in non-survivors.⁶⁶ Also, failure to increase oxygen consumption in response to goal-directed haemodynamic interventions has been associated with mortality in critically ill.^{67,68} Global oxygen consumption measurements were often reported in haemodynamic optimisation studies conducted when pulmonary artery catheters were still common.^{54,69} In more recent trials in non-cardiac surgery, cardiac output-related parameters are almost exclusively reported.⁶⁰

Shoemaker et al. presented calculations to demonstrate that an *oxygen debt* (Fig. 6b) started to develop already intraoperatively and that could it be reduced by targeting supranormal (>600 ml min⁻¹ m⁻²) goals of oxygen delivery. It is worth noticing that this oxygen debt was

calculated from estimations of anaesthesia-induced reductions of oxygen consumption in closed breathing circuits using a modified Brody equation^{i 70} The concept of a developing oxygen debt has been questioned in cardiac surgery.⁷¹ However, it is plausible that the benefits of high DO₂ levels to prevent tissue oxygen debt are executed at a microcirculatory level.⁴¹ Minimal-invasive monitoring and supranormal oxygen delivery targeting with fluids and inotropes were associated with a reduced risk of cardiovascular complications in a meta-analysis but these results were not age-adjusted.⁷² Concerns regarding risks with haemodynamic optimisation in those with limited cardiopulmonary reserves have been raised.⁷³ Perioperative fluid overload is a particular risk for patients with cardiac compromise.⁷⁴ Autonomic dysregulation with reduction of parasympathetic activity have been observed during randomised controlled trials involving predominately elderly and attributed to GDHT with inotropic support.⁷⁵ In many perioperative trials of goal-directed haemodynamic support, haemodynamic goals are unadjusted regardless of pre, intra or postoperative timing of intervention.⁶⁰ It is, however, still advocated the GDHT intervention should start intraoperatively to prevent haemodynamic instability.^{76,77} This is supported by beneficial outcomes reported from recent trials in which stroke volume optimisation was followed by intraoperative blood pressure targeting to avoid hypotension.^{78,79} There are observations of less intraoperative hypotension with GDHT in elderly⁶¹ but intraoperative goals and responses need further assessment.

1.2.4 Intraoperative hypotension

Despite the lack of a consensus definition of intraoperative hypotension, the importance of preventing low blood pressure during anaesthesia has become increasingly evident in recent years.⁸⁰ The risk of developing hypotension-related organ injury is both *dose* and *time*-dependent but thresholds differ.⁸⁰⁻⁸⁵ Some studies suggest that MAP <55 mmHg or >30% decrease from baseline is associated with increased risk^{82,84} whereas other state <65mmHg.^{81,83} Cardiovascular medication such as angiotensin converting enzyme inhibitors⁸⁶ and beta-blockers⁸⁷ has also been associated with perioperative hypotension in non-cardiac surgery. Elderly are particularly exposed to adverse postoperative outcomes. Associations like the AAGBI (Anaesthetists of Great Britain and Ireland) have recommended to avoid decreases in systolic pressure of > 20% from pre-induction baseline and suggest

ⁱ Brody equation: $VO_2 = w^{0.75} \cdot VO_2$; basal oxygen consumption in ml min⁻¹; w; weight in kilogram. Adapted from Arndt et al. A linear approximation of Brody's equation to predict oxygen consumption in adult humans. J Clin Monit Comput 1995; 11:165–167

intra-arterial blood pressure monitoring to be considered in elderly, especially during major or emergency surgery, to early detect and treat hypotension.⁸⁸ Using this definition in a multicentre prospective audit in patients over 65 years, intraoperative hypotensive episodes occurred in 83% and 1 in 4 had <70 mmHg for >20 min.⁸⁹ In a prospective cohort of >11.000 elderly with hip fractures, decreasing levels of intraoperative blood pressure were associated with increasing mortality at 5 and 30 days after surgery.⁹⁰ Targeted strategies aimed at maintaining blood-pressure close to individual baseline have been associated with better postoperative outcomes compared to standard treatment in elderly during high-risk surgery,⁷⁸ but more trials are needed.

1.3 HAEMODYNAMIC AND OXYGEN CONSUMPTION CHANGES INDUCED BY SPINAL AND GENERAL ANAESTHESIA AND THEIR ASSESSMENT

1.3.1 Haemodynamic effects of spinal anaesthesia

The sympathetic block induced by spinal anaesthesia is largely responsible for the haemodynamic effects. This results in arterial vasodilation and venous pooling caudal to the block level.⁹¹ The sympathetic block often extends further cranially compared to the somatic sensory level.⁹² As a result, systemic vascular resistance is reduced and venous return decreases with possible profound impact on maintenance of blood pressure and cardiac output. Bradycardia can occur due to block extending above Th5,⁹³ impairing cardio-accelerator fibre function (Th1-Th4), but is more commonly caused by reduced venous return due to the reverse Bainbridge reflex.⁹⁴ Spinal anaesthesia has been extensively studied in obstetric patients during caesarean section.^{95,96} As late pregnancy is characterised by marked alterations in cardiovascular physiology, it is potentially deceitful to generalise these haemodynamic responses to other populations. Known risk factors for hypotension include ASA physical status classification, sensory block height, age and hypertension.^{93,97,98} The balance between sympathetic and parasympathetic activity is suggested to play a central role,⁹³ supported by observations in children that rarely exhibit cardiovascular disturbance after spinal anaesthesia at young ages and as they become older (and sympathetic function matures) show similar haemodynamic effects to adults.⁹⁹ In the elderly, the elevated sympathetic tone can induce more pronounced decreases in systematic vascular resistance making the patient more prone to hypotension and decreased venous return.⁹⁷ In addition, the decreased sensitivity of β -adrenergic and baroreceptors impairs regulatory responses. The role of ANS dysregulation has been indicated by the association of heart-rate and blood-pressure variability with post-spinal hypotension in elderly.^{100,101} Pre-emptive fluid loading before spinal anaesthesia has not been demonstrated to prevent hypotension.¹⁰² Smaller doses of local anaesthetic^{90,103} or continuous/titrated spinal anaesthesia can potentially provide better blood pressure control.^{104,105} Earlier studies on haemodynamic changes induced by spinal anaesthesia in elderly have used different methods including thoracic bioimpedance,^{103,106} pulmonary artery catheter¹⁰⁷⁻¹⁰⁹ or transthoracic echocardiography.^{110,111} Minimal-invasive monitoring using calibrated intra-arterial waveform analysis have high-time resolution and has demonstrated good trending accuracy,¹¹² making it suitable for characterisation of haemodynamic effects of spinal anaesthesia in awake subjects.

1.3.2 Perioperative oxygen consumption

Oxygen consumption is markedly reduced during general anaesthesia as seen in *Figs. 6*. Several mechanisms contribute to this reduction of global or whole-body oxygen consumption. Global oxygen consumption is decreased by around 10% during deep natural sleep,^{113,114} presumably due to changes cerebral metabolic rate of oxygen (CMRO₂).¹¹⁵ As intravenous and inhalational anaesthetic agents generally exhibit CNS depressing effects reducing CMRO₂, this contributes to the decrease seen in anaesthesia.¹¹⁶ In paediatric cardiac surgery patients, non-depolarising muscular blocking agents have been demonstrated to decrease oxygen consumption,^{117,118} but results in mechanically ventilated and sedated adults have been conflicting.¹¹⁹ Spinal anaesthesia has been shown to reduce whole-body oxygen consumption in awake subjects by approximately 25%, presumably due to loss of muscle tone.^{108,120} Studies on epidural anaesthesia also support an independent reduction of oxygen consumption^{121,122} and postoperative epidural analgesia inhibit the oxygen consumption increase after surgery.¹²³ Furthermore, anaesthesia and surgery induce *regional* alterations in oxygen consumption. Postoperative hepatosplanchnic oxygen extraction has been demonstrated to differ substantially from global measurements.¹²⁴ Myocardial oxygen consumption and supply-demand relationship are subject to well-known changes induced by anaesthesia, catecholamine therapy and surgical stress.¹²⁵ In addition, the use of vasopressors have demonstrated significant effects on both renal and splanchnic oxygen extraction.^{126,127}

1.3.3 Assessment of perioperative oxygen consumption

Monitoring of oxygen consumption is described and discussed in greater detail in Methods and in the separate papers (III-IV). This section presents an overview of the general aspects of assessment.

Respiratory versus Fick-derived techniques

Principally, oxygen consumption can be determined by analysis of inspiratory and expiratory gases or by the reverse Fick equation (see 1.2.1). Respiratory gas analysis can be performed by different techniques such as indirect calorimetry¹²⁸ mass spectrometry¹²⁹ or in closed anaesthetic breathing circuits.¹³⁰ The latter is theoretically appealing for feasible intraoperative measurements, but has not shown good reliability compared to Fick- or other gas derived techniques.^{131,132} The reverse Fick method does not include pulmonary oxygen consumption and this physiological difference have been used to estimate it using both methodologies simultaneously.¹³³⁻¹³⁶

Mixed versus central venous sampling

In order to calculate oxygen consumption by the reverse Fick equation or to determine oxygen extraction, mixed venous blood need to be sampled from the pulmonary artery. Routine pulmonary artery catheterisation (PAC) is declining¹³⁷ and has not shown outcome benefits in major surgery.¹³⁸ This method is therefore decreasing in use. In contrast, central venous catheters are routinely placed in many major surgical procedures. Blood is then either sampled from the superior and inferior vena cava, presumably reflecting venous oxygen content from either the lower or upper body. Mixed and central venous oxygen saturation have not shown to be interchangeable.¹³⁹⁻¹⁴¹ but trending ability has been demonstrated.¹⁴²⁻¹⁴⁴

Indirect assessments

Central venous saturation (ScvO₂), indirectly reflecting the oxygen consumption-delivery relationship, has been associated with postoperative morbidity in abdominal surgery but target levels remain unclear.^{52,145} In addition, ScvO₂ levels are often consistently high intraoperatively due to supplemental oxygen. Increased lactate level as a marker of anaerobic metabolism and tissue oxygen deficit, has been associated with postoperative morbidity and mortality following major abdominal surgery.¹⁴⁶⁻¹⁴⁸ However, lactate metabolism is complex and responses are unpredictable.^{149,150} Studies on the ratio index of veno-arterial carbon dioxide tension difference to arterio-venous oxygen content difference ($\Delta\text{PCO}_2/\text{C}(\text{a-v})\text{O}_2$) have suggested that it is a reliable marker of anaerobic metabolism¹⁵¹ and possibly better reflect oxygen consumption changes than central venous saturation (ScvO₂)¹⁵² but recent results have been conflicting.¹⁵³

In summary, the current limitations of perioperative assessments of oxygen consumption include technical demands (indirect calorimetry, mass spectrometry), low precision (closed-circuit anaesthesia) and invasiveness (reverse Fick calculations using PAC). Very few studies have used minimal-invasive cardiac output monitors with central venous sampling to estimate oxygen consumption and have not shown good agreement with PAC¹⁵⁴ and indirect calorimetry.¹⁵⁵

2 AIMS

The overall aim of this thesis was to systematically describe certain haemodynamic and global oxygen transport changes during anaesthesia and surgery in elderly surgical patients using different methodological approaches.

The specific aims of the studies (I-IV) were to:

- I.
 - A. Characterise cardiac output and haemodynamic changes before and after spinal anaesthesia and their association with post-spinal hypotension
 - B. Identify potential pre-anaesthetic haemodynamic predictors of post-spinal hypotension

- II.
 - A. Conduct a systematic literature review to estimate the oxygen consumption change after induction of general anaesthesia
 - B. Evaluate the quality of evidence
 - C. Investigate the impact of patient and perioperative characteristics on the effect estimate

- III.
 - A. Estimate the oxygen consumption change after induction of general anaesthesia in elderly undergoing major abdominal surgery
 - B. Estimate the oxygen consumption changes during surgery and in the postoperative period
 - C. Investigate the perioperative oxygen consumption changes in relation to oxygen delivery and extraction obtained by routine monitoring

- IV.
 - A. Compare perioperative oxygen consumption estimated from routine monitoring in major surgery with measurements by indirect calorimetry

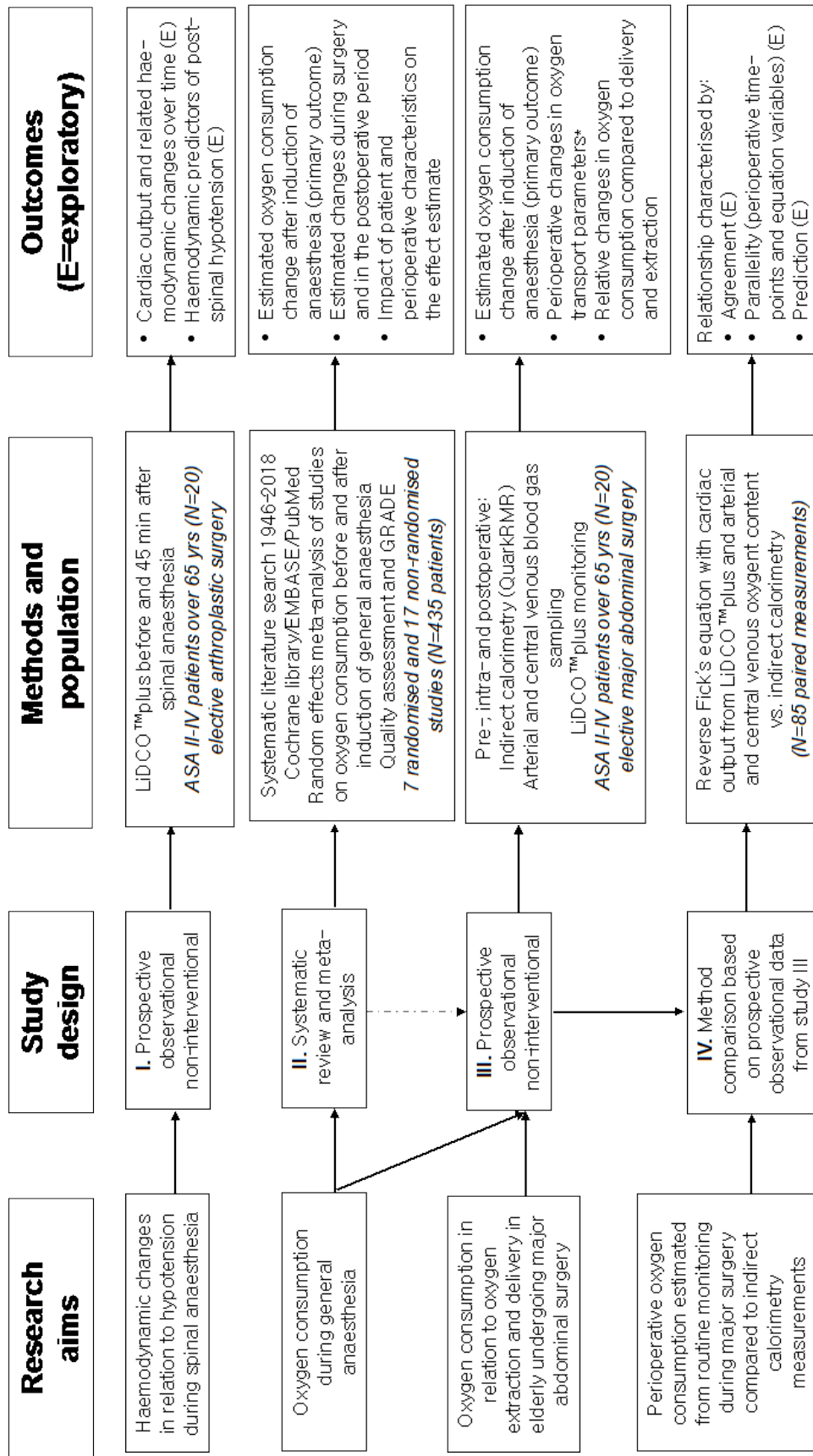


Figure 7. Overview of study designs, populations, methods and outcomes. Abbreviations: ASA; American Society of Anesthesiology classification; GRADE (Grading of Recommendations Assessment, Development and Evaluation www.gradeworkinggroup.org)

* measured oxygen consumption; calculated oxygen extraction ratio from arterial central venous oxygen content difference to arterial oxygen content; ratio index of veno-arterial carbon dioxide tension difference to arterio-venous oxygen content difference ($\Delta PCO_2/C(a-v)O_2$); central venous saturation

3 METHODS

An overview of the study designs, methods and outcomes of the separate studies is presented in *Fig. 7*.

3.1 MONITORING TECHNOLOGY

3.1.1 Minimal-invasive haemodynamic monitoring

The LiDCO™plus (LiDCO Ltd, Cambridge, UK) monitor were used for haemodynamic measurements in the clinical studies (I and III-IV). The algorithm for the continuous cardiac output calculation uses the arterial pulse waveform, but it is not a strict pulse-contour analysis such as the PICCO™ and the FloTrac/Vigileo systems.¹⁵⁶ Instead of a morphology-based approach, the LiDCO monitor applies a *pulse power analysis* assuming that the net power change of a heart beat is linear to net flow after calibrating and correcting for compliance.¹⁵⁷ The calibration and correction for arterial tree compliance is achieved in separate steps. First, an actual cardiac output is determined through lithium indicator dilution. This is carried out by injecting a small bolus dose of lithium chloride in a central (or large peripheral) vein and arterial blood is then drawn through a lithium sensor attached to the arterial line. From the resulting dilution curve, the actual CO is calculated using a modified Stuart-Hamilton equation.ⁱⁱ¹⁵⁸ The next step is autocorrelation, during which the arterial waveform is analysed applying a compliance algorithmⁱⁱⁱ to determine a standardised (stroke volume) waveform. Finally, this standardised stroke volume is scaled to the individual patient's stroke volume determined by the indicator dilution. The *calibration factor* obtained reflects the maximum volume of the arterial tree of the individual. This technique theoretically attenuates the impact of damping and variations in waveform appearance as it renders the analysis less dependent on morphology. The LiDCO system has shown good agreement both with pulmonary artery catheter measurements^{159,160} and other cardiac output monitors in cross-comparisons.¹¹² It has been validated in a wide range of settings,^{161,162} and haemodynamic situations.^{163,164} In addition to cardiac output, different blood pressure data (systolic, diastolic, mean arterial and pulse pressures) is collected. Continuous output of systemic vascular resistance and oxygen delivery is calculated by entering updated values of CVP and arterial haemoglobin oxygen saturation and haemoglobin, respectively. Limitations include those common to all pulse

ⁱⁱ *Modified Stuart Hamilton equation for lithium dilution cardiac output:* $CO = ((Li \times 60)) / [AUC \times (1 - PCV)]$ Li, lithium dose; AUC, area under indicator dilution curve; PCV, packed red cell volume

ⁱⁱⁱ *Compliance algorithm:* $\Delta V / \Delta bp = \text{calibration} \times 250 \times e^{-(k \text{ bp})}$ V, volume; bp, blood pressure; 250, maximum distending volume of the aorta/arterial tree; k, curve coefficient

contour methods, such as arrhythmias and distortion of the arterial waveform (extreme damping, severe aortic regurgitation etc.) and those related to lithium dilution calibration, such as low weight (< 40kg) and lithium medication.^{165,166} In hemodynamically unstable or changing situations, concerns regarding trending ability¹⁶⁷ and underestimation of cardiac output¹⁶⁸ have been raised.

The LiDCO monitor was used due to its feasibility for perioperative monitoring both during general anaesthesia (study III-IV) and in awake subjects, i.e. during spinal anaesthesia (study I) and postoperatively (study III-IV). It was calibrated and re-calibrated according to manufacturer's instructions. Alternative well validated monitoring techniques such as the PiCCO™ system^{169,170} and the oesophageal doppler (OED) recommended in the NICE guidelines¹⁷¹ were not considered suitable for the study settings. The OED cannot be used in awake subjects and the PiCCO requires a femoral artery catheter, which is impractical during surgery.

Data collected by LiDCO™plus were transferred from the monitor to LiDCOviewPRO (LiDCO Ltd, Cambridge, UK) software. Linear interpolation was performed for missing values in the data synthesis.

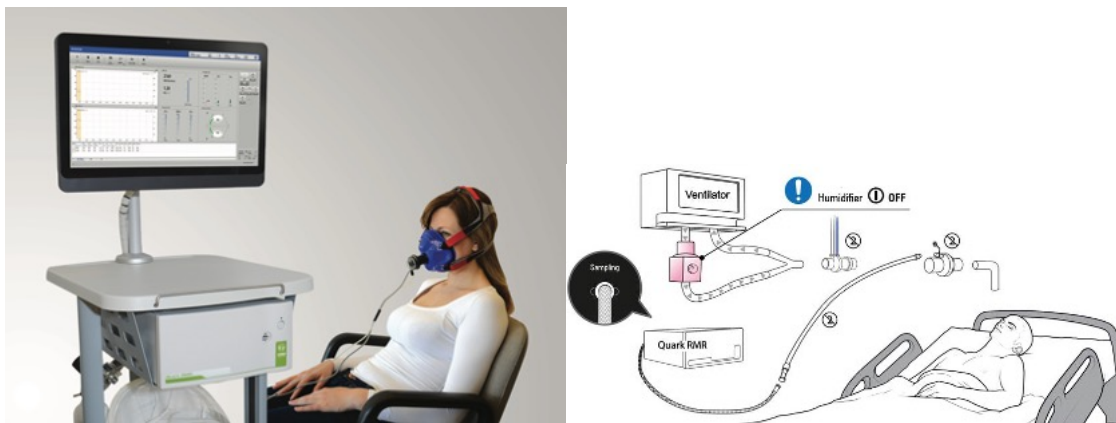
3.1.2 Oxygen consumption measurements by indirect calorimetry

Oxygen consumption was measured by indirect calorimetry in Study III-IV. The QuarkRMR (Cosmed srl, Rome, Italy) monitor uses a breath-by-breath technique based on measurements of flow and gas concentration to analyse the pulmonary gas exchange for energy expenditure calculations. This is achieved through face mask breathing (*Fig. 8a*) or through the breathing circuit during mechanical ventilation (*Fig. 8b*). Gas concentrations of O₂ and CO₂ are determined from side-stream sampling and flow from pneumotachographic measurements of pressure drop across a turbulent flow restrictor. The spirometric and gas analyses are then synchronised by data processing algorithms and the Haldane transformation^{iv} is used to calculate the oxygen consumption.¹⁷² The technique is validated in semi-closed breathing circuits¹⁷³ and the QuarkRMR monitor has been used in previously in this set up.¹⁷⁴ The monitor is calibrated before each measurement by a standardised gas mixture (16% O₂ and 5% CO₂) and the flowmeter (turbine or single-use FlowREE) by a 3L-syringe. No

^{iv} Haldane transformation:

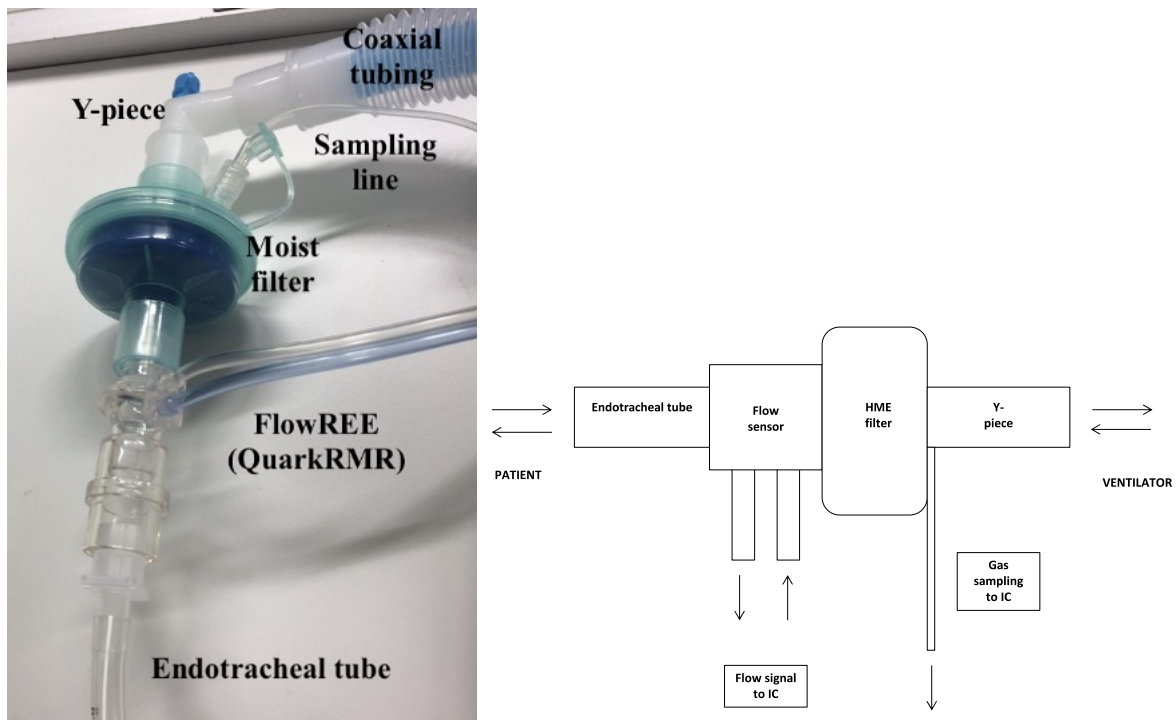
$$VO_2 = [(1 - FeO_2 - FeCO_2)x(FiO_2 - FeO_2)Ve]/(1 - FiO_2)$$

supplemental oxygen is administered during face mask measurements. During mechanical ventilation, no adjustments of ventilator settings are allowed in order to avoid interference of differences in $FeCO_2$ on determinations of VCO_2 . An inherent limitation of any method that applies the Haldane transformation is the error in calculations that occurs with high FiO_2 (due to $1-FiO_2$ as the denominator in the equation).¹⁷⁵ This poses a problem in critically ill but less so in mechanical ventilation during routine anaesthesia where FiO_2 is usually kept well below 0.7. The Deltatrac II monitor (Datex-Ohmeda, Helsinki, Finland), to which most other monitors are compared, uses a mixing chamber instead of a breath-by-breath technique but is no longer in production.¹²⁸ In comparison studies with mixing chamber techniques as reference methods, the QuarkRMR has compared well or better than similar monitors but varying degrees of overestimation of oxygen consumption and energy expenditure have been demonstrated.^{174,176,177}



Figures 8 a-b. (a, left) The QuarkRMR metabolic monitor and face mask with turbine flowmeter and gas sampling. The person depicted did not participate in the studies. (b, right) Schematic set up of QuarkRMR and FlowREE (Cosmed srl, Rome, Italy) in mechanically ventilated patients (not in anaesthetic breathing circuit). ©Cosmed. Published with permission.

In accordance with the LiDCO™plus used for haemodynamic monitoring, the QuarkRMR enabled measurements with the same monitor in awake and anaesthetised subjects. Other metabolic carts such as the E-sCOVX® (GE Healthcare, Helsinki, Finland) have been reported less accurate and would require change of monitoring technique for pre- and postoperative measurements.¹⁷⁸ In the protocol (study III-IV), FiO_2 was set to 0.5 and the fresh gas flow to 2 L to allow for gas sampling during measurements in the anaesthetic breathing circuit. Oxygen consumption data was collected during 20 minute-periods and averaged the minute-to-minute readings. Shorter periods of 10-20 minutes were accepted if measurements were stable. *Figs. 9* demonstrates the connection of the flowmeter (FlowREE) and gas sampling line of the QuarkRMR to the anaesthetic breathing circuit.



Figures 9 a-b. Photograph (a, left) and schematic illustration (b, right) of the connection of the endotracheal tube and anaesthetic breathing circuit to the flowmeter (FlowREE) and gas sampling line of the QuarkRMR (IC). The gas sampling line of the ventilator is not connected to the Y-piece in the photograph (a).

3.1.3 Oxygen content analyses and calculations

Blood samples were collected in Study I (arterial) and III-IV (arterial and central venous). Samples were analysed immediately in ABL800 Flex or ABL90 Flex (Radiometer Medical ApS, Copenhagen, Denmark), accredited by the Karolinska University Laboratory. In study I, baseline values of Hb and SaO₂ were entered in the LiDCO monitor for oxygen delivery output. In study III-IV, blood gas analyses were used for the calculation of oxygen delivery and estimation of oxygen extraction and consumption. In addition, the ratio of veno-arterial carbon dioxide tension difference to arterio-venous oxygen content was obtained in study III. *Table 2* summarises the parameters/variables and calculations. In the calculations of oxygen delivery in study III, cardiac output data was extracted as mean over 20 minute-periods corresponding to simultaneous indirect calorimetry measurements. Oxygen extraction was estimated from mean of two arterial and central venous blood samples drawn simultaneously at 5 and 15 minutes into the period.

Variable (unit)	Equation
Arterial oxygen content (ml 100ml ⁻¹)	$CaO_2 = (Hb \cdot 1.31 \cdot SaO_2 \cdot 0.01) + (0.0225 \cdot PaO_2)$
Central venous oxygen content (ml 100ml ⁻¹)	$CcvO_2 = (Hb \cdot 1.31 \cdot ScvO_2 \cdot 0.01) + (0.0225 \cdot PcvO_2)$
Oxygen delivery (ml min ⁻¹)	$DO_2 = CO \cdot CaO_2 \cdot 10$
Estimated oxygen extraction (ratio; values in ml 100ml ⁻¹)	$estO_2ER = (CaO_2 - CcvO_2)/CaO_2$
Ratio of veno-arterial carbon dioxide tension difference to arterio-venous oxygen content difference (ratio; values converted to mmHg)	$\Delta PCO_2/C(a - cv)O_2 = (PaCO_2 - PcvCO_2)/(CaO_2 - CcvO_2)$

Table 2. Blood gas-derived parameters and equations. Abbreviations: Hb, haemoglobin (g dl⁻¹); 1.31, Hüfner constant corrected for abnormal Hb species (ml O₂ g⁻¹ Hb); SaO₂ and ScvO₂, arterial and central venous haemoglobin saturation (%); PaO₂ and PcvO₂, arterial and central venous oxygen partial pressure (kPa); 0.0225, solubility coefficient for O₂ at body temperature (ml O₂ 100ml⁻¹ plasma kPa⁻¹); 0.01, conversion factor for saturation in %; CO, cardiac output (L min⁻¹); 10, conversion factor for CO in L; PaCO₂ and PcvCO₂, arterial and central venous carbon dioxide partial pressure (kPa)

3.1.4 Estimation of oxygen consumption by minimal-invasive cardiac output and arterial-central venous oxygen content difference

Study IV evaluated a method of estimating perioperative oxygen consumption based on the reverse Fick principle by using LiDCO-derived cardiac output and replacing mixed venous with central venous oxygen content in the original equation (see 1.2.1):

$$\text{Estimated oxygen consumption (ml min}^{-1}\text{)} \quad estVO_2 = CO \cdot (CaO_2 - CcvO_2) \cdot 10$$

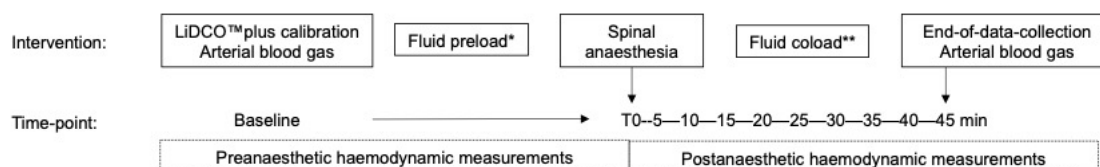
The estimation calculations (EVO₂) used the mean cardiac output and oxygen content data from study III. These results were simultaneous measurements of measured oxygen consumption (GVO₂). 10 is a conversion factor for CO in L min⁻¹.

3.2 GENERAL STUDY INFORMATION

An overview of study parameters (*Table 3*), registration and the clinical protocols are presented here. The protocol of study II is described in the systematic review and meta-analysis section.

3.2.1 Study protocols, time-points and definitions

Study I: An overview of study I is presented in *Fig. 10*. Baseline haemodynamic values were defined as means of monitor readings over 180 seconds at steady state. Continuous monitoring then commenced at arrival to the operating theatre. Time-point T0 was defined as means over 180 seconds just prior to anaesthesia. Data for time-points T5-45 were extracted as means over 60 seconds at 5 minute-intervals. Post-spinal hypotension was defined as a decrease in systolic blood pressure >30% from baseline or <100mmHg occurring at any time from intrathecal injection to end-of data collection at 45 minutes. This definition was in accordance with a previous randomised trial on GDHT in elderly hip fractured patients.⁶¹ Hypotensive events were identified by applying the hypotension criteria on the individual blood pressure data sets.



*Figure 10. Study I protocol overview. *Fluid preload; Ringer's acetate 0-500 ml as decided by the attending anaesthetist: **Fluid coload; Buffered glucose 2.5 mg ml⁻¹ at 1 ml kg⁻¹ h⁻¹ and Ringer's acetate at 2 ml kg⁻¹ h⁻¹*

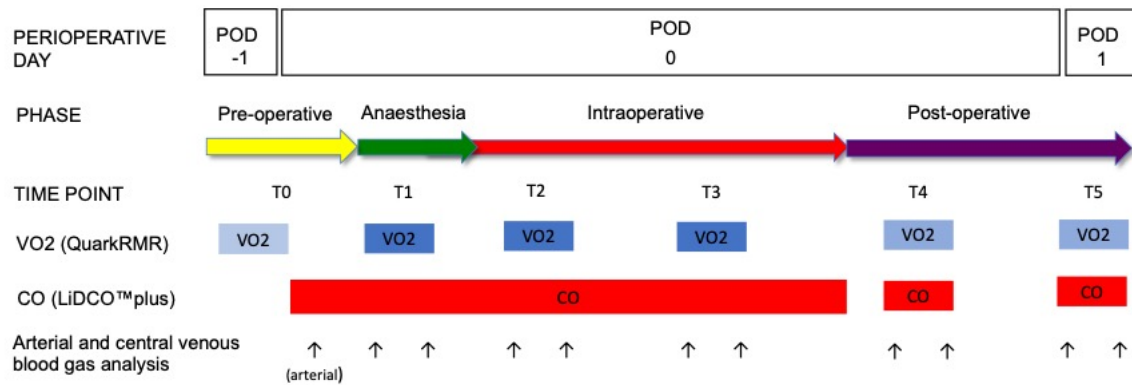


Figure 11. Study III-IV protocol overview. Abbreviations: see List of Abbreviations.

Study III-IV: An overview of study III-IV is illustrated in Fig. 11. Prior to initiation, feasibility of the study protocol was evaluated in awake postoperative patients (N=6) and in intubated anaesthetised patients (N=6) in two separate pilot studies. Baseline measurements (T0) of oxygen consumption were undertaken at rest the evening before surgery (non-fasted). Calorimetric measurements started after intubation but the time-point Anaesthesia (T1) was defined as 20 minutes just prior to surgical incision to ensure stable measurements. Early surgery (T2) was defined as 20-minutes from surgical incision and Late Surgery (T3) was > 2 hours of surgery (not during liver resection). Postoperative measurements were performed at two times: Early postop (T4) on the day of surgery > 60 minutes after extubation but before midnight; and Late postop (T5) on day after surgery > 12 hrs after extubation but before noon. The calorimetric oxygen consumption values at each time-points (T0-T5) were defined as mean over a 20-minute period. The cardiac output measurements for oxygen delivery were performed at baseline (T0) in the preoperative ward calculated as means over 180 seconds at steady state and then continuously during anaesthesia and surgery. Output data was extracted to exactly match the time-periods of the calorimetric measurements. As stated above, blood gas samples for the oxygen content calculation were taken simultaneously from arterial and central venous lines at two times during each 20-minute period, at 5 and 15 minutes.

3.2.2 Study parameters

Study	Patient-, study- and perioperative characteristics	Haemodynamic and oxygen transport parameters
I	Sex; age; ASA-class; BMI; P-POSSUM score; organ dysfunction; cardiovascular medication and perioperative data; type of surgery, fluid preload, sedative premedication, body position at intrathecal injection, anaesthetic technique, level of intrathecal injection, dose of intrathecal bupivacaine and opiates, fluid coload, sensory block level at 15, 30 and 45 minutes, vasopressor administration dosage and timing.	Oxygen delivery index (DO2I); Cardiac index (CI); Stroke volume index (SVI); Systemic vascular resistance index (SVRI); Heart rate (HR); Mean arterial pressure (MAP); Systolic arterial pressure (SAP); Diastolic arterial pressure (DAP); Pulse pressure (PP)
II	Study characteristics (author names, publication year, design, study groups and number of participants), participant and perioperative characteristics (mean age, sex distribution, type of surgery, anaesthetic technique, use of neuromuscular blockers or premedication), oxygen consumption monitoring (technique used, output unit, timing of measurements).	Oxygen consumption in ml min^{-1} (VO_2) or $\text{ml min}^{-1} \text{m}^{-2}$ (VO_2I) at the different time-points: awake baseline; >10 minutes after anaesthesia induction (before surgical incision); during surgery; postoperatively >60 minutes after extubation.
III	Age, sex, BMI, ASA-classification, type of surgery and diagnosis, organ dysfunction, medication, perioperative characteristics (epidural and anaesthetic regimens, duration of anaesthesia and surgery, use of goal-directed haemodynamic therapy, fluid administration and fluid balance at end of surgery, at midnight and at 6 a.m. on postoperative day 1) and measurement specific information (ventilator settings, SpO ₂ , body temperature, haemodynamic interventions i.e. vasopressor dose and fluids).	Measured oxygen consumption (GVO_2) and indexed for body surface area (GVO_2I); calculated oxygen delivery (DO_2) and indexed (DO_2I); estimated oxygen extraction ratio from arterial central venous oxygen content difference to arterial oxygen content (EO_2ER); ratio index of veno-arterial carbon dioxide tension difference to arterio-venous oxygen content difference ($\Delta\text{PCO}_2/\text{C}(\text{a-v})\text{O}_2$); central venous saturation (ScvO_2)
IV	See study III.	Measured oxygen consumption (GVO_2) incl. indexed for body surface area (GVO_2I); estimated oxygen consumption (EVO_2) and indexed (EVO_2I); cardiac output (CO) and index (CI); arterial-central venous oxygen content difference ($\text{C}(\text{a-v})\text{O}_2$).

Table 3. Study parameters. For abbreviations not explained in the table, please see List of abbreviations.

3.2.3 Study registration

The clinical studies were registered at clinicaltrials.gov (U.S. National Library of Medicine) with registration numbers NCT02978066 (study I) and NCT03355118 (study III-IV). Study II was registered in the PROSPERO International Prospective Register for Systematic Reviews (U.K. National Institute for Health Research) at crd.york.ac.uk/PROSPERO with registration number CRD42017078910.

3.3 PATIENT AND STUDY SELECTION

The inclusion and exclusion criteria are summarised here (*Table 4*) together with the patient and study selection flow diagrams for study I-II (*Fig. 12 and 13*)

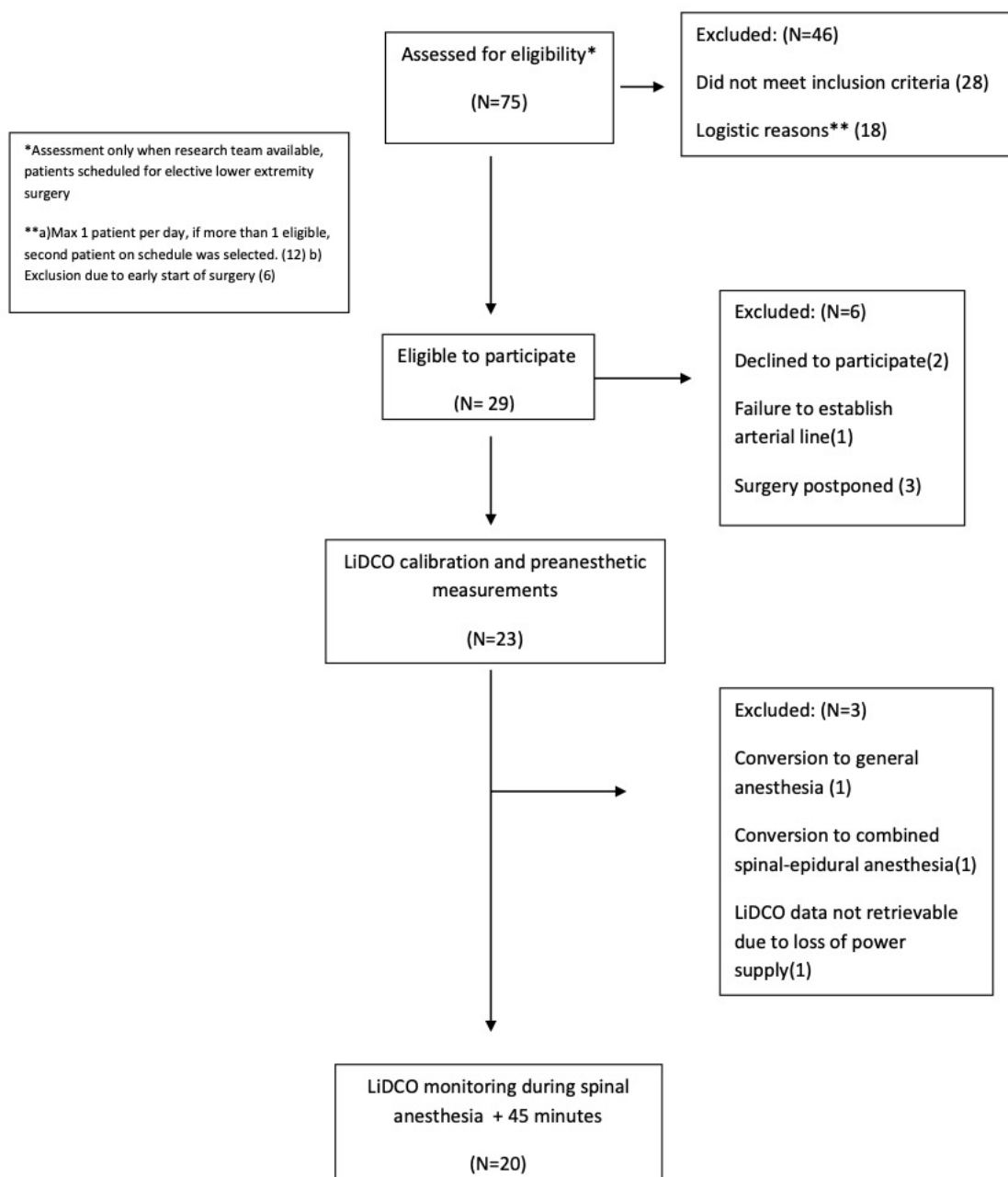
3.3.1 Inclusion and exclusion criteria

Study	Inclusion	Exclusion
I	65 years or older; scheduled for elective lower limb surgery; planned for spinal anaesthesia	Combined spinal and epidural anaesthesia; procedure scheduled as "early start" (i.e. before 8 a.m.); weight <40kg, lithium medication; rescheduled surgery; research team not available; arterial line failure
II	Studies (or groups within studies) in adults (18 years or over) with clear reports of oxygen consumption measurements (gas analysis or central circulation) in the awake state before induction of general anaesthesia and >10 minutes after induction with no surgical manipulation	Pregnancy, trauma, burns, critical conditions or severe comorbidities such as congenital heart diseases; risk of hypothermia; data collection during cardiopulmonary by-pass or other forms of extracorporeal circulation; no full-text in English available. Data extraction from graphs not possible with <5 % error margin.
III-IV	65 years or older; scheduled for major or complex surgery according to AXA specialist procedure codes,* planned insertion of central and arterial lines	Planned short stay at the postoperative unit (less than 12 hours), procedures involving open thoracic cavity or carbon dioxide insufflation (laparoscopies or certain endoscopies) lithium medication, weight <40 kg; rescheduled surgery; research team not available; arterial line failure

*Table 4. Study inclusion and exclusion criteria. *AXA PPP Healthcare. Specialist Procedure Codes. <https://online.axapphealthcare.co.uk/SpecialistForms/SpecialistCode.mvc>*

3.3.2 Patient and study selection flow diagrams

Patient selection of study I is presented in *Fig. 12* and the selection of studies for meta-analysis (study II) in *Fig. 13*. The patient selection process of study III-IV is not presented in this summary chapter due to publication reasons and can be found as a supplementary file to the manuscript (study III).



*Figure 12. Patient selection process of study I. *Assessment only when research team available, patients scheduled for lower extremity surgery. ** a) Maximum 1 patient per day, if >1 eligible, second patient was selected (N=12), b) Exclusion due to early start of surgery (N=6). © 2017 Elsevier. Reprinted with permission from the publisher.*

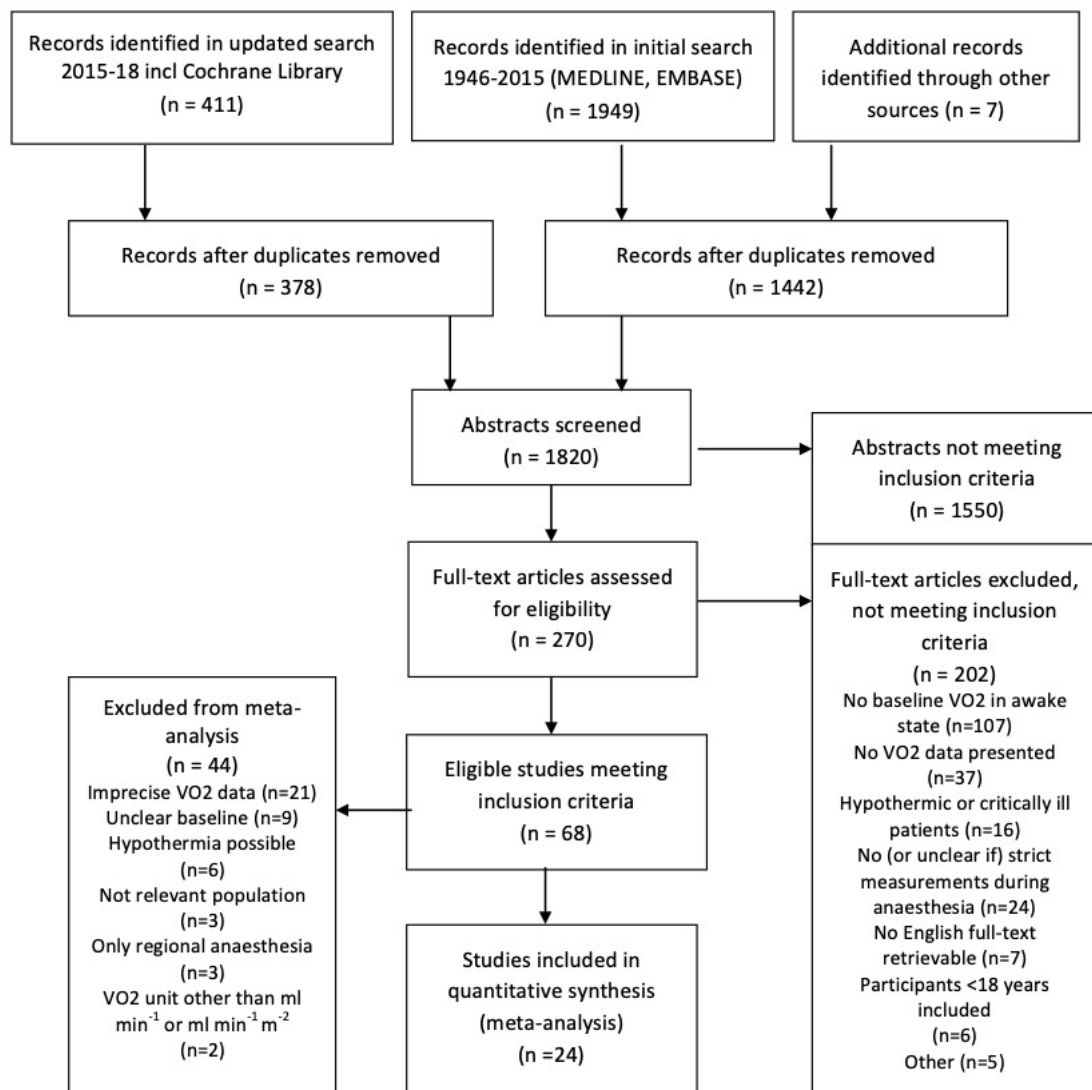


Figure 13. PRISMA flow diagram of study II. © 2019 Wiley. Reprinted with permission from the publisher.

3.3.3 Sample size estimations

Study I was planned as a prospective exploratory follow-up of a randomised controlled trial and a sample size of 20 patients was estimated as adequate for such as study. In study II individual data demonstrated an effect size of 0.95, corresponding to a 20% reduction of oxygen consumption after induction of anaesthesia. This yielded a sample size of 14 patients with a power of 0.9 and a type I error rate of 0.05. As meta-regression analyses in study II had indicated less reduction in elderly and the pilot studies had demonstrated that data loss could be expected, a sample size of 20 patients was planned for study III. This would result in a total of 100 paired measurements of estimated and measured oxygen consumption (time points T1-T5) for study IV which was considered adequate compared to earlier similar studies.^{155,173,179}

3.4 PERIOPERATIVE AND ANAESTHETIC MANAGEMENT

Given the non-interventional and observational design of the clinical studies, all patients were managed at the discretion of the attending anaesthesia teams. Measurement procedures were designed to minimise interference with the routine care of the patients and results were not communicated to patients and personnel. This approach had the purpose of obtaining data that reflected common clinical practice to the highest extent possible. This section describes the routine care procedures during the measurements.

3.4.1 Study I

Patients were transferred to the preoperative ward 1 to 2 hours in advance for preparation and baseline haemodynamic measurements. Prior to arrival, premedication with acetaminophen 1-2 g and modified release oxycodone 5-10 mg was given. ACE-inhibitors or angiotensin-II-receptor blockers had been discontinued on this day, while calcium channel and beta blockers were continued. After establishing venous (antecubital) and arterial (radial) access, LiDCO™plus was calibrated according to the manufacturer's instructions and baseline measurements performed. The patient was then transferred to the operating theatre. All clinical management was handled by the attending anaesthetic team. Pre-anaesthetic fluid loading of 0-500 ml of Ringer's acetate was administered. Local anaesthesia was injected intrathecally by a 25- or 27 G cannula at the lumbar level containing isobaric bupivacaine 12-20 mg with morphine 0.1-0.2 mg. During injection, the patient was either sat up or in a lateral position. Perioperative goals were SpO₂ >95%, MAP 70-100 mmHg and haemoglobin >10 g dL⁻¹. Spinal anaesthesia injection volumes, additional sedatives or administration of fluids or vasopressors after spinal anaesthesia were decided by the attending anaesthetist.

3.4.2 Study III-IV

Baseline measurements of oxygen consumption by indirect calorimetry were performed at rest the day before surgery. As in study I, baseline haemodynamic measurements were performed at the preoperative ward before transfer to the operation theatre where measurements continued throughout surgery. Thoracic epidural anaesthesia was introduced at Th8-Th11, a test dose of 15-20 mg bupivacaine and a bolus of 20 mg morphine was injected but continuous infusion was not activated until after induction of anaesthesia. General anaesthesia was induced by fentanyl and propofol followed by atracurium before tracheal intubation. Flow meter and sampling lines for indirect calorimetry were connected to the anaesthetic breathing circle directly after intubation and disconnected after measurements finished. Anaesthesia was maintained throughout surgery with sevoflurane to 0.8-1.0 MAC

and with continuous epidural infusion of bupivacaine 2.5 mg ml⁻¹ or bupivacaine-fentanyl-adrenaline. Before surgery started, the internal jugular vein was cannulated for central venous access. Postoperative chest radiograph confirmed correct positioning in the superior vena cava. General perioperative goals included haemoglobin > 80 g L⁻¹, SaO₂ of >95% and core temperature (by urine catheter) 36-37°C. Infusion of noradrenaline was used to maintain mean arterial pressure over 65 mmHg (or at other level as decided by the attending anaesthetist) and no patient was given inotropic support. Patients were extubated at the operation theatre and then transferred to the postoperative ward with a continuous epidural infusion of bupivacaine-fentanyl-adrenaline. Buffered glucose with electrolytes 25-50 mg ml⁻¹ at 1 ml kg⁻¹ h⁻¹ was administered as maintenance fluid intra- and postoperatively. A minimum of Ringer's acetate of 2 ml kg⁻¹ h⁻¹ was infused intraoperatively except during liver surgery (10 ml h⁻¹ until the resection was completed according low CVP anaesthesia guidelines). Additional crystalloid or colloids were administered by stroke volume optimisation or continuously. Fluid balance were calculated hourly. Insensible losses were calculated as 3 to 5 ml kg⁻¹ h⁻¹ intraoperatively according to magnitude of surgery and as 0.5 ml kg⁻¹ h⁻¹ postoperatively.

3.5 ETHICAL CONSIDERATIONS

All studies, except study II (meta-analysis), were approved by the Ethics Review Board of the Stockholm Region. Efforts were made to assert that all patient involvement complied with the Declaration of Helsinki.¹⁸⁰ Oral and written informed consent was obtained from all participants including those in the pilot studies of study III-IV. A summary of some important aspects of ethical principles are presented in *Table 5*.

Study	Autonomy	Beneficence	Justice	Non-maleficence
I	+Informed consent +Withdrawal at any time -Exposed situation	+Intensified monitoring (invasive blood pressure)	+/- Obtain data in elderly patients -Only selected procedures	+Minimal-invasive measurements -Arterial line not routine care
II	-Unclear informed consent in some of the included studies	+ Synthesis of available evidence to be used in future study designs	+Evaluation of impact of patient and perioperative features	+Minimise sample size in future clinical studies -No involvement of new patients
III-IV	+Informed consent +Withdrawal at any moment -Exposed situation	+Research team accompanied patients perioperatively	+/- Obtain data in elderly patients -Only selected procedures	+ Studies designed to minimise interference with routine care. -Discomfort during indirect calorimetry

Table 5. Ethical considerations applied to four ethical principles, from Beauchamp TL, Childress JF. Principles of biomedical ethics. 6th ed. New York: Oxford University Press; 2008. +/-: positive/negative aspects.

Study I was initially approved in 2010 as a descriptive pilot study investigating the haemodynamic responses to a goal-directed haemodynamic therapy algorithm in elderly undergoing elective orthopaedic surgery (ID 2010/2042-31/1). However, a planned secondary analysis from a previous randomised trial applying the algorithm showed unexpected results on the haemodynamic responses in both the intervention and in the standard care group.⁶⁴ For this reason, it was decided to only study a standard care cohort, i.e. rendering the study non-interventional. With this approach, arterial line placement and minimal-invasive haemodynamic measurements were the only procedures deviating from routine care. An amendment was made to the Ethics Review Board and approved (ID 2012-1992-32).

Study III-IV was approved in 2017 (ID 2017/291-31/4) for inclusion of a total of 60 patients. An analysis of oxygen consumption data was planned after 20 patients, constituting the results presented in this thesis. The study design was non-interventional but the protocol involved pre-operative calorimetric measurements by face mask breathing for 20 minutes and arterial line-placement with lithium dilution calibration and measurements before anaesthesia induction. In the postoperative period, face mask measurements were performed at two

occasions. To ensure patient comfort during the measurements, feasibility of the protocol and to minimise interference with demanding routine care procedures, two separate pilot studies were conducted in postoperative (n=6) and intraoperative settings (n=6). All measurements were performed and supervised by an anaesthetist from the research team familiar with all clinical procedures but not directly involved in patient care. If a patient experienced discomfort or if saturation decreased below 93%, the measurement was discontinued. The participants had almost exclusively malignant disease with varying prognosis which required awareness and sensibility in all ethical aspects. Given the highly specialised nature of the procedures performed at a university hospital regional cancer centre, many patients met inclusion criteria for participation in several research studies. Patients were informed by specialised research personnel well in time before surgery with 1-3 weeks time to reflect and ask questions before providing the written consent to participate. Patients who were already included or met inclusion criteria in another study involving several intra- and postoperative measurements were not approached. If metastases or carcinosis were diagnosed after laparotomy and the procedure could not be performed as planned, the patient was excluded from the subsequent oxygen transport measurements as we did not consider it correct to encourage participation under such circumstances.

3.6 SYSTEMATIC REVIEW AND META-ANALYSIS METHODOLOGY

The protocol for the systematic review and meta-analysis (study II) was constructed according to the recommendations stated in the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.¹⁸¹ The process was guided by the Cochrane Handbook of Systematic Reviews of Interventions versions 5.1.0 (2011) and 5.2.0 (2017).¹⁸² Results were reported using the PRISMA 2009 checklist¹⁸³ and MOOSE guidelines for observational studies.¹⁸⁴

3.6.1 Search strategies and screening process

Search strategies were developed in collaboration with a search specialist librarian following a PICOS structure with the primary objective to assess, in adults (Population) receiving general anaesthesia (Intervention) with baseline measurements in the awake state (Comparison), the changes in oxygen consumption after induction of general anaesthesia (Outcome) in studies with all types of design (Study design). Searches were performed in MEDLINE, EMBASE and Cochrane Library 1946-2017 based on variants of the terms anaesthesia AND oxygen consumption OR uptake with filters excluding animal studies. The search strategy can be found as an online supplement to paper II. Preliminary searches had

been conducted in 2015 and the search was updated before submission of the manuscript in 2018. The search terms were broad with the purpose of finding studies which reported oxygen consumption changes after induction of anaesthesia regardless if this was the primary outcome. Records were screened, first at a title and abstract level and then at a full-text level. This was done independently by two reviewers at each level, a third reviewer was consulted if agreement was not reached. Only abstracts in English were screened, but non-English fulltexts were assessed and translated if eligible and retrievable. Reference lists of the full-text records were also screened. Eligible full-texts meeting inclusion criteria were quality-assessed and discussed in the review team for inclusion in the final synthesis, i.e. the meta-analysis. The screening process is presented in a PRISMA flow diagram (*Fig 13*).

3.6.2 Risk of bias assessment

The selection process identified 7 randomised studies and 17 non-randomised studies with a before-after design. Randomised studies were assessed by the Cochrane Risk of Bias tool for randomized studies¹⁸⁵ The non-randomised studies were evaluated using the NIH quality assessment tool for before-after (pre-post) studies with no control group.¹⁸⁶ The Cochrane Handbook versions 5.1.0 (2011) and 5.2.0 (2017) did not recommend the use of a specified tool for non-randomised studies.¹⁸² All quality assessment requires a multidimensional approach based on principles of internal and external validity.¹⁸⁷ A major concern in non-randomised studies is the internal validity, which is evaluated in bias domains of selection, performance, detection and attrition. The external validity or generalisability, features patients, settings, interventions and outcomes. Tools for evaluating non-randomised studies are often developed for epidemiological studies such as the Reisch's tool,¹⁸² MINORS,¹⁸⁸ or The Newcastle-Ottawa-Scale, the latter well validated but has also been demonstrated as arbitrary.¹⁸⁹ Some tools have been adapted for before-after studies such as the QUADAS.¹⁹⁰ As this tool is primarily designed for diagnostic test accuracy where a reference standard is used, it could only be applied to some studies comparing different methods of oxygen consumption monitoring in anaesthetised subjects. In summary, the NIH tool for before-after studies¹⁸⁶ were found most suitable as it not only reflected the general domains of internal and external validity in this type of studies, but also allowed to focus on the quality of the before-after change as a primary outcome.

3.6.3 Synthesis of results

From the selected studies, information pre-specified in the protocol was extracted by one reviewer and confirmed by another one. With the purpose of finding a pooled estimate of the oxygen consumption change after induction of anaesthesia, it was decided to proceed with meta-analysis if the included studies clearly reported measurements and interventions despite the quality assessment resulting general high risk of bias or poor study quality. The quality of evidence of the primary outcome was summarised using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology.¹⁹¹

3.7 STATISTICAL METHODOLOGY

An overview of the statistical methodology used is presented in *Table 6*. All data was tested for normal distribution and statistical tests applied accordingly. In the manuscripts, continuous data is presented as median (range) or mean (95% CI), categorical data as numbers (%) or otherwise specified. *P*-values of <0.05 were considered statistically significant. Details on the statistical software used can be found in the separate papers.

Study	Descriptive statistics	Inferential statistics	Other
I	-Median (range) -Mean (SD)	-Uni- and multivariate logistic regression -Repeated measures analysis of variance (one- and two-way RM-ANOVA) -Receiver operating characteristics	-Dunnett's test for multiple comparisons -Bonferroni correction -Hosmer-Lemeshow goodness of fit
II	-Mean (SD) -Weighted standardised mean difference (95%CI) -Forest plot	-Random effects meta-analysis -Meta-regression analysis	-Heterogeneity by Q, tau ² , I ²
III	-Median (range) -Mean (95% CI)	-Student <i>t</i> -test -Linear mixed models -Mixed models (REML) -Two-way mixed effect models	-Dunnett's test for multiple comparisons -Tukey post-hoc test -Holm correction
IV	-Mean difference (95% CI) -Bland-Altman plot -Intraclass correlation	Linear mixed models Mixed models (REML) Random coefficient models	-Dunnett's test for multiple comparisons

Table 6. Statistical methodology overview. Abbreviations: RM-ANOVA; repeated measures analysis of variance: REML; restricted maximum likelihood

3.7.1 Study I

Uni- and multivariate logistic regression models were used with pre-anaesthetic haemodynamic changes as continuous predictors and post-spinal hypotension (y/n) as a categorical outcome. The resulting odds ratios (OR, 95% CI) were evaluated for discriminative ability by receiver operating characteristics (ROC) if significant. In addition, univariate logistic regressions were used to test other factors associated with hypotension (i.e. use of sedatives, bupivacaine dose, antihypertensive medication etc.) and included these in multivariate models for the haemodynamic predictors if found significant. The haemodynamic changes over time were analysed by one- and two-way repeated-measures analysis of variance with Dunnett's test for multiple comparisons and Bonferroni correction.

3.7.2 Study II

Random effects meta-analyses were used to pool means with variances of oxygen consumption changes between each of specified time-points (preoperative, anaesthesia, surgery and postoperatively) with the results presented in Forest plots. Given the anticipated differences between studies in participants and anaesthetic techniques, fixed effects models were not considered suitable.¹⁹² Individual data was used for calculation of correlation coefficients. Results were expressed as standardised mean differences (95% CI) and converted to weighted transformed mean estimates of VO₂ (ml min⁻¹) and indexed VO₂(i) (ml min⁻¹ m⁻²). Heterogeneity was assessed by Q, τ^2 and I² statistics. Meta-regression analyses were performed to assess the impact of the moderators: mean age and gender (distribution) of participants; use of pre-medication; type of anaesthesia; type of surgery; length of observation; number of measurements; monitoring technology; use of muscle relaxants. The contribution to heterogeneity on the effect estimate by the suggested moderators was investigated in these analyses. Meta-regression plots illustrated the impact of continuous moderators with studies weighted by the inverse sampling standard deviation.

3.7.3 Study III

The primary outcome, the absolute and relative change in oxygen consumption after induction of anaesthesia compared to awake baseline measurements, was assessed with Student *t*-test. Changes over time in oxygen consumption and in the other oxygen transport variables (see *Table 3*) more were analysed by linear mixed models and results presented as estimates with 95% family-wise confidence levels. Dunnett's multiple comparison with Holm correction was used to compare the different time-points to preoperative baseline or anaesthesia as reference. The relationship between relative perioperative oxygen consumption

changes and simultaneous changes of delivery and estimated extraction were assessed in mixed models using time-point and the respective oxygen transport parameter as fixed effects. Perioperative changes were normalised to individual baseline measurements and expressed as least square means estimates with 95% CI. Two-way mixed effect models with Tukey posthoc-tests were performed to evaluate if intraoperative stroke volume optimisation or type of surgery could influence the results. Normality and homoscedasticity were assessed by residual plots.

3.7.4 Study IV

In this method comparison study, comparing estimations of oxygen consumption to measurements by indirect calorimetry, several statistical approaches were applied. Bland-Altman plots were here constructed for each time-point to avoid violation of assumptions by repeated measurements under changing conditions. The use of linear correlation in method comparison run the risk of introducing a linear relationship that is interpreted as agreement.¹⁹³ Intraclass correlation (ICC) can be applied instead to address agreement and adjust for systematic differences.^{194,195} ICC coefficients with 95% CI at each time-point and in overall, were here yielded by a single score two-way agreement model. A preliminary random coefficient prediction model was constructed based on individual slopes and intercepts of estimated versus measured oxygen consumption values. The relationship over time between estimated and measured oxygen consumption was also analysed. Mean difference between the methods over time were analysed by linear mixed models with Holm-adjusted Tukey post-hoc tests. Mixed models were used to compare the estimation method and its input variables (cardiac index and oxygen content difference) with measured oxygen consumption. In these models, method or input variable and time-point were used as fixed effects. The relative changes were normalised either to the individual baseline measurements or to an overall mean.

4 MAIN RESULTS AND FINDINGS

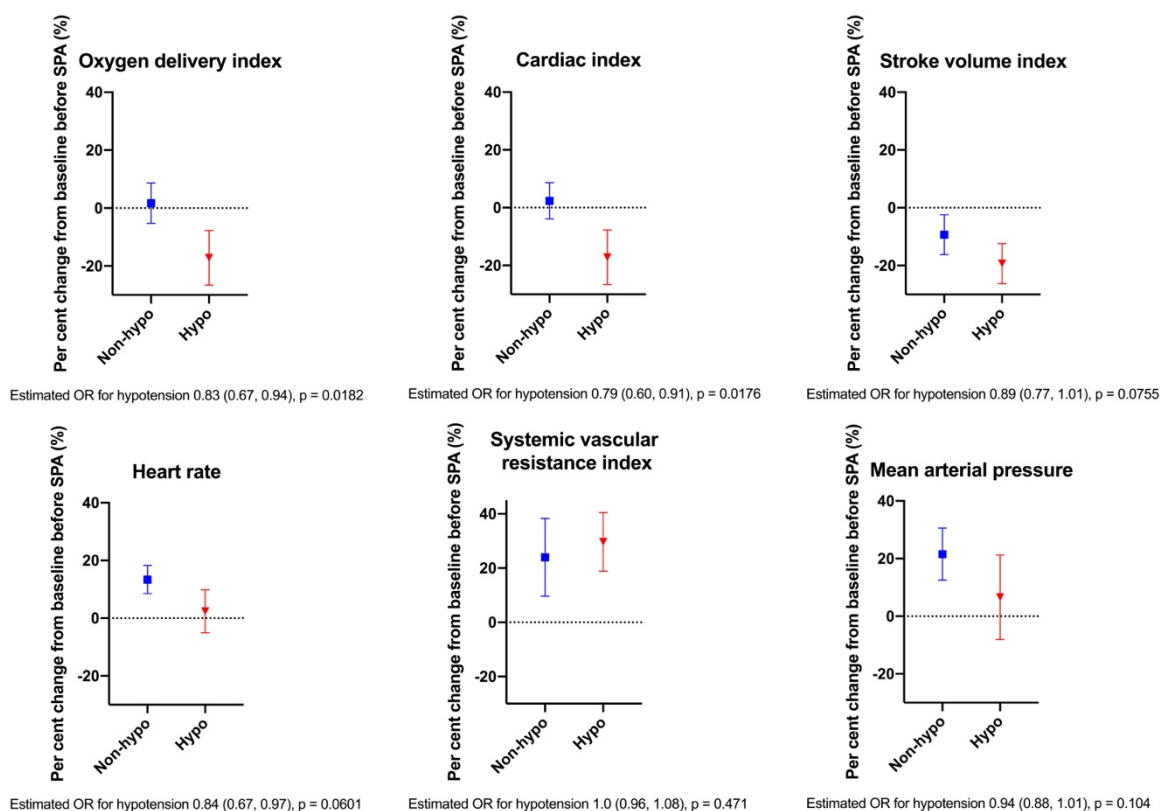
This chapter features the most relevant findings, results are reported in detail in the separate papers. All data is reported as mean (95% CI) or otherwise specified.

4.1 STUDY I

Short summary of findings: Separation of subjects according to development of post-spinal hypotension revealed different profiles of cardiac output responses over time. Furthermore, the relative change in cardiac output detected before spinal anaesthesia was indicated to predict hypotension.

Haemodynamic changes prior to spinal anaesthesia and predictors of hypotension

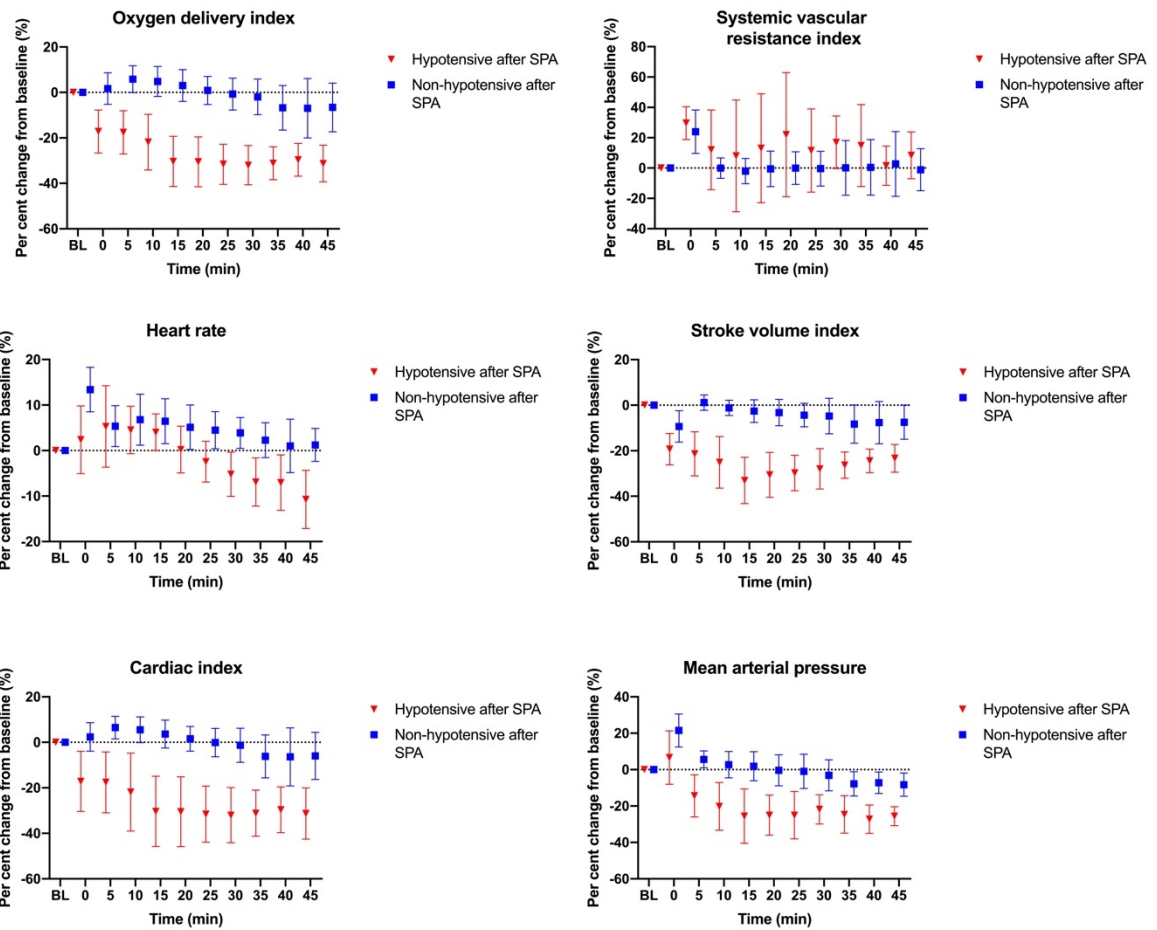
Haemodynamic data was first collected at rest in the pre-operative unit followed by subsequent measurements just before injection of spinal anaesthesia. Overall, increases in mean arterial pressure [MAP; +14 (5.5, 23) %], estimated systemic vascular resistance index [SVRI; +27 (19, 35) %] and heart rate [HR; +7.9 (3.1, 13) %] were demonstrated between these two time-points. At the same time, stroke volume index decreased [SVI; -14 (-19, -9.3) %], along with cardiac index [CI; -7.4 (-14, -0.5) %] and oxygen delivery index [DO₂I; -7.7 (-15, -0.8) %]. Pre-anaesthetic changes in haemodynamic parameters were different in those who developed post-spinal hypotension (N=10) (*Figs. 14*). No differences between the two groups in pre-anaesthetic SVRI changes could be demonstrated. There were no significant interaction effects by age, body position, dose of local anaesthetic, administration of sedatives, betablockers or other cardiovascular medication or by volume of pre- or post-anaesthetic fluid loading. In logistic regression analyses (*Figs. 14*) with post-spinal hypotension (yes/no) as outcome variable, pre-anaesthetic changes of CI and DO₂I were demonstrated as significant predictors (*Figs. 14*). Receiver operating characteristics for these two showed good discriminative ability (AUC 0.91 and 0.88, respectively).



Figures 14. Haemodynamic changes *prior to* injection of spinal anaesthesia in patients developing post-spinal hypotension (Hypo; N=10) and those maintaining blood pressure (Non-hypo; N=10). Results are presented as mean percental change (95% CI) from baseline with the respective estimated OR (95% CI) for development of post-spinal hypotension.

Haemodynamic changes in hypotensive and non-hypotensive after spinal anaesthesia

The changes in MAP and other haemodynamic parameters in hypotensive and non-hypotensive patients to end of data collection are presented in *Figs. 15*. In patients developing post-spinal hypotension, the initial decreases of SVI and CI aggravated over time. In contrast, SVI and CI initially remained unchanged or increased after injection of spinal anaesthesia in patients who maintained their blood pressure. SVRI demonstrated no differences between hypotensive and non-hypotensive patients, an initial decrease by -18 (3.5, 32)% ten minutes after spinal anaesthesia were seen but then remained unchanged. At the end of data collection HR was 12 (2.3, 21; $P<0.01$)% and SVI 15 (3.0, 29; $P<0.01$)% higher in non-hypotensive patients.



Figures 15. Haemodynamic changes **after** spinal anaesthesia (0) relative to baseline measurements (BL) in patients developing post-spinal hypotension (blue quadrant) and those maintaining blood pressure (red triangle). Results are presented as mean percental change (95% CI) from baseline at the different time-points (min) after spinal anaesthesia.

4.2 STUDY II

Short summary of findings: General anaesthesia reduces oxygen consumption, but the effect estimate is uncertain due to low quality of evidence.

Study selection and quality assessment

The study selection process is presented *Fig. 13* (chapter 3), 24 studies reported results that could be synthesised in the meta-analysis. Reported subsequent changes during surgery and in the postoperative period were also analysed. Results from a total of 453 patients in 32 study groups (with separately reported results) were pooled in a random effects meta-analysis. All studies were published before the year 2000 with mean ages of study subjects ranging 28 to 70 years. All randomised studies (N=7) demonstrated an overall high risk of bias assessed by Cochrane risk of bias tool. Quality rating of the observational studies (N=17) with the NIH QA tool for before-after studies with no control group showed fair quality in only 4 of these. The high risk of bias originated mainly from selection and attrition domains. Measurement protocols and interventions were clearly reported in the majority of studies.

The effects of general anaesthesia and surgery on oxygen consumption

Baseline values were calculated as weighted means, separating studies reporting results indexed for body surface area, resulting in a VO₂ of 263 (SD, 54) ml min⁻¹ and a VO₂I of 117 (SD, 28) ml min⁻¹ m⁻². After induction of anaesthesia, VO₂ decreased by -65 (-75, -55) ml min⁻¹ and VO₂I by -33 (-38, -28) ml min⁻¹ m⁻². Subsequent relative changes after induction of general anaesthesia were pooled presented as standardised mean differences (SMD) in random-effects meta-analyses (*Fig. 16*). Overall study heterogeneity was moderate (I²= 61%). Surgery increased VO₂ by 10 (4.4, 17) ml min⁻¹ and VO₂I by 5.1 (2.1, 8.0) ml min⁻¹ m⁻² (316 patients in 15 studies) compared to general anaesthesia alone. Heterogeneity was high (I²=77%) for the 8 studies (including 158 patients) reporting additional postoperative measurements (>60 minutes after extubation). Transformed estimates of postoperative VO₂ change compared to preoperative baseline was 21 (-3.5, 46) ml min⁻¹ and 11 (-1.8, 23) ml min⁻¹ m⁻² for VO₂I. Meta-regression analyses did not show any significant impact of publication year, mean age, gender, study design (randomised or before-after design), monitoring technique (Fick's or gas-derived), severity of surgery, intravenous or inhalational for maintenance of general anaesthesia, use of muscle relaxants and sedative premedication.

Relative oxygen consumption change at different perioperative stages

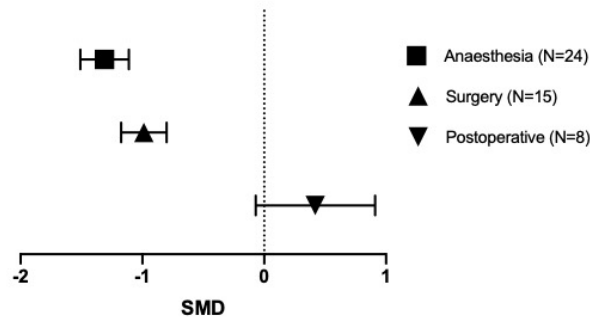


Figure 16. Results from random effects meta-analyses on changes of oxygen consumption at different perioperative stages (anaesthesia, surgery and postoperative period) expressed as standardised mean difference (SMD) with 95% CI compared to pre-operative baseline measurements in the awake state. N; number of studies included in the analysis. Test for overall effect of anaesthesia (primary outcome): $Z = -12.891$ $P < 0.001$ Heterogeneity: Q ($df = 31$) = 70.54, $P < 0.001$, $\tau^2 = 0.172$, $I^2 = 61\%$. N patients = 453.

Summary of findings

A clear direction and large magnitude of effect of the anaesthesia-induced reduction of oxygen consumption were evident in the GRADE summary profile. However, the overall quality of evidence was deemed very low. This resulted from the high risk of bias, large heterogeneity and also indirectness due to differences in populations, interventions and outcomes of the included studies. Table 7 summarises the findings of study II.

Study Groups N (N pat)	Publication years	Design (N)	Monitoring (N)	Anaesthesia (N)	Type of surgery (N)	Effect estimate SMD (95% CI)	GRADE summary profile
32 (453)	1969-2000	BA (20) RCT (12)	PAC (19) PAC/MS (3) PAC/other (1) IC (2) MS (2) CVKRV (5)	INH (23) IV nla (6) IV ket (1) IVopiatemd (2)	Vascular (9) Abdominal (10) Gynaecological (4) Orthopaedic (1) Cardiac (2) Various (2) No surgery (4)	BL-ANE: -1.31(1.51, -1.11) ANE-SUR: 0.32(0.14, 0.51) BL-POP: 0.42(-0.07, 0.91)	⊕○○○ Very low

Table 7. Summary of the systematic review and meta-analysis on oxygen consumption changes after induction of general anaesthesia. Abbreviations: SMD; standardised mean difference, GRADE; grade evidence profile www.gradeworkinggroup.org, GAS MS; mass spectrometric gas analysis, GAS IC; indirect calorimetry, PA; pulmonary artery catheter, CVKRV; central vein catheter in right ventricle, BA; before-after study design, RAND; randomised study design, IV; intravenous, INH; inhalational, nla; neuroleptanaesthesia, ket; ketamine, suf; sufentanil, opiatemd; opiate +midazolam, BL; awake baseline, ANE; anaesthesia, POP; postoperative.

4.3 STUDY III

Short summary of findings: General anaesthesia reduced oxygen consumption by approximately a third. The intraoperative changes were parallel to decreases in oxygen delivery and extraction.

Perioperative oxygen consumption changes

Mean preoperative VO₂I was 135 (127, 144) ml min⁻¹ m⁻² and decreased by a mean of -46 (-55 to -38, $P<0.0001$) ml min⁻¹ m⁻² after induction of general anaesthesia representing a percental decrease of 34 (28, 39, $P<0.0001$) %. After skin incision, VO₂I increased by 8 (-0.4, 17, $P=0.016$) and after >2hrs of surgery by 15 (6, 24, $P<0.0001$) ml min⁻¹ m⁻² relative to general anaesthesia alone. At the surgical and postoperative stages, the patients were also receiving continuous infusion of epidural anaesthesia. Postoperatively, mean VO₂I increased compared to the general anaesthesia by 38 (28, 48; $P<0.0001$) after extubation and by 47 (38, 57, $P<0.0001$) ml min⁻¹ m⁻² on postoperative day 1. No significant differences were seen between the pre- and postoperative values of VO₂I. As seen, the overall perioperative change of VO₂I were highly significant in a linear mixed effect model [$F(5, 81.8)=65.5, P<0.0001$]. The individual perioperative oxygen consumption measurements are presented in *Fig. 17*.

Perioperative oxygen consumption

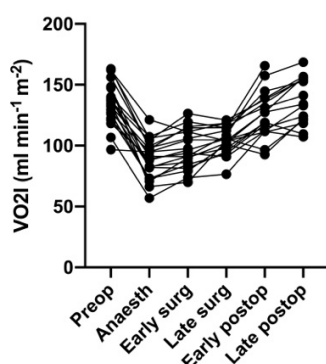
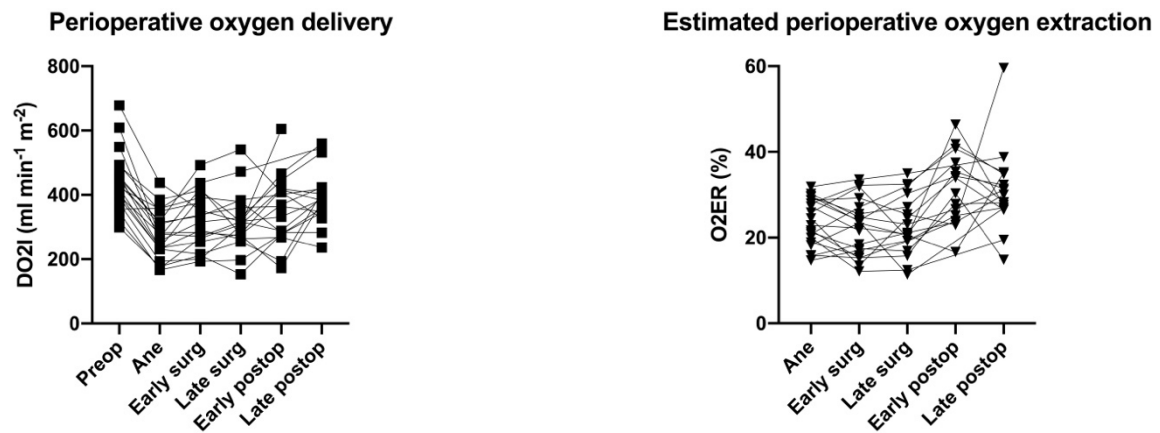


Figure 17. Individual oxygen consumption in ml min⁻¹ m⁻² at different perioperative time-points. Preoperative; (N=20); Anaesthesia; (N=20); Early surgery; (N=20); Late surgery; (N=18); Early postoperative; (N=13); Late postoperative; (N=15). See text for details.

Perioperative calculated oxygen delivery and estimated oxygen extraction

The product of oxygen content calculated from an arterial blood gas sample and the cardiac index data from the LiDCO™plus monitor yielded mean indexed oxygen delivery (DO₂I) of 440 (396, 483) ml min⁻¹ m⁻² preoperatively. After induction of anaesthesia, it decreased to 278 (242, 313; $P<0.0001$) ml min⁻¹ m⁻² and mean DO₂I remained lower than the preoperative at all time-points except at the last measurement on postoperative day 1, the overall model demonstrating highly significant perioperative changes [$F(5, 86.3)=12.7, P<0.0001$]. Mean estimated oxygen extraction (O₂ER), calculated from simultaneous arterial and central

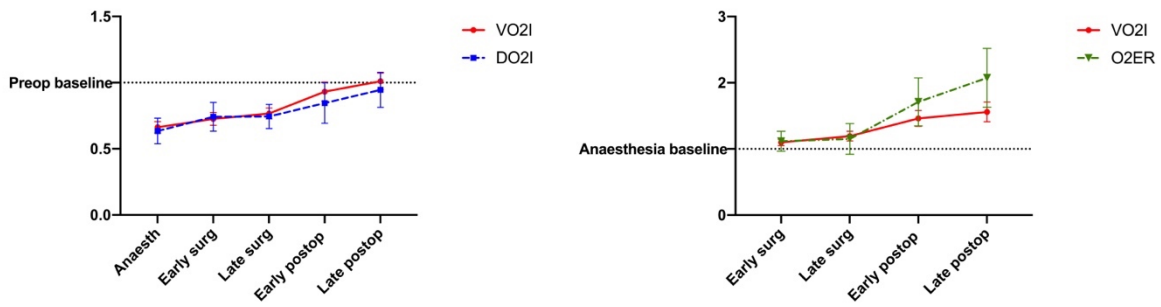
venous samples, increased from the intra- to the postoperative period [$F(4, 67.4) = 9.5, P < 0.0001$]. Mean O2ER was 24 (21, 26) % during anaesthesia (T1), increasing postoperatively (T4-T5) to 31 (27, 36) %. No preoperative baseline was obtained for the estimated O2ER as the central venous line was placed after induction of anaesthesia. The individual changes of DO2I and estimated O2ER are presented in *Figs. 18 a-b*.



Figures 18 a-b. Individual oxygen delivery (left, a) and estimated extraction (right, b) at different perioperative time-points. Preoperative; (N=20): Anaesthesia; (N=20): Early surgery; (N=20): Late surgery; (N=18); Early postoperative; (N=15): Late postoperative; (N=17). See text for details.

Relative changes of oxygen consumption, delivery and extraction

The relative changes in oxygen consumption were compared to the simultaneously obtained calculations of oxygen delivery and estimated extraction in mixed models with time and parameter as fixed effects. The mean changes of each parameter at the different time-points expressed as least square means (95% CI) were obtained by normalising to individual baseline measurements (*Figs. 19 a-b*). Baseline for the VO2I and DO2I comparison were set to preoperative measurements. For the VO2I and O2ER comparison, as no preoperative O2ER was obtained, baseline was set to anaesthesia. DO2I changed in parallel with VO2I at all time-points [$F(4, 21.8)=1.03, P=0.416$]. In the postoperative period, the changes of O2ER were indicated to deviate from VO2I but this was not statistically significant in the overall model [$F(3, 20.4)=2.60, P=0.0802$]. Early postoperatively, oxygen extraction was higher in patients undergoing liver resections and in those had not received stroke volume guided fluid therapy, but no differences were found at the other time-points. Oxygen consumption and delivery did not differ at any time-point when compared by different types of surgery and fluid regimens.



Figures 19 a-b. Results from the mixed effect model on perioperative changes (LSM estimates with 95% CI) normalised to individual baseline measurements: VO2I and DO2I (left, a), VO2I and O2ER (right, b).

4.4 STUDY IV

Short summary of findings: Estimations of oxygen consumption from routine monitoring (obtained by reverse Fick calculation from LiDCO™plus-derived cardiac output and oxygen content difference from arterial and central venous sampling) showed poor absolute agreement compared to indirect calorimetry but trending and systematic differences were indicated.

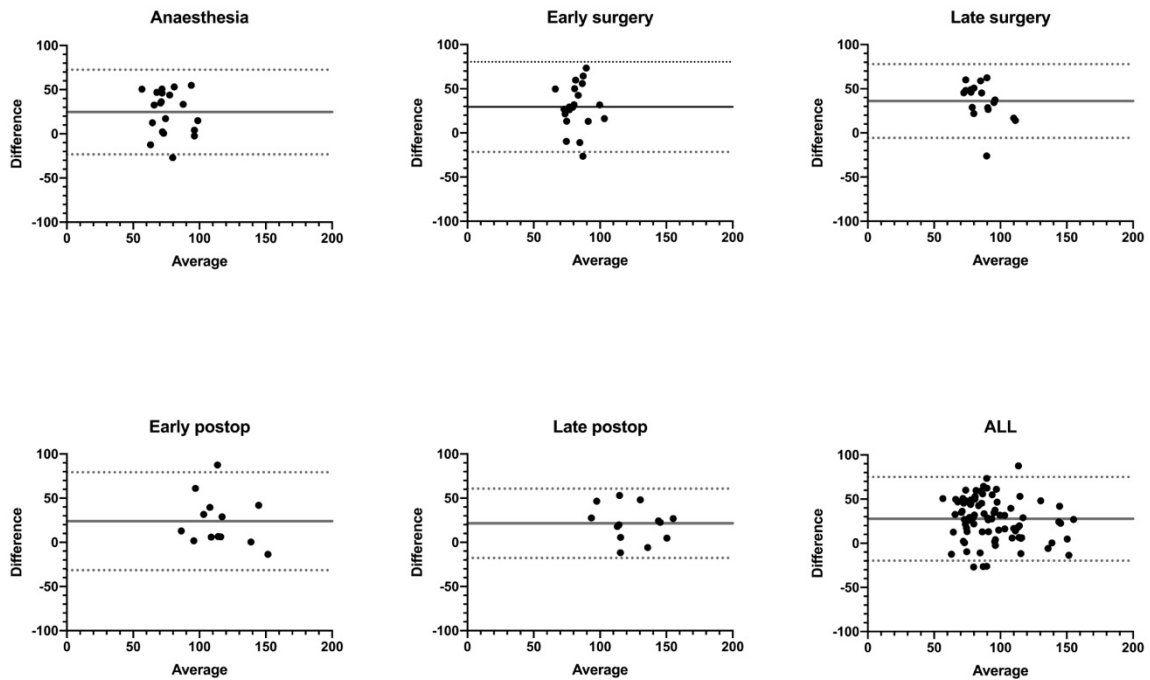
Mean difference over time

A total of 85 paired measurements by both methods from study III were analysed, 27 of these in awake subjects postoperatively and 58 during anaesthesia and surgery. There was an overall difference between EVO2I (estimated) and GVO2I (gas-derived) when each individual's paired measurements at all time-points were compared a linear mixed model [F(1, 167)=72.8, $P<0.0001$]. The mean difference between paired measurements of EVO2I and GVO2I was estimated to -26 (-20, -32) ml min⁻¹m⁻² and this model did not demonstrate significant deviations between the different time-points [F(4, 168)=1.39, $P=0.241$].

Agreement and prediction

Two-way single score intraclass correlation (ICC) analysis showed poor absolute agreement, ICC (A,1) = 0.37 (0.34, 0.65), [F(84, 10.2)= 3.07, $P=0.0266$]. When the analysis was adjusted for consistently lower values of EVO2I the model improved to moderate, ICC(A,1)=0.51 (0.34, 0.65), [F(84, 84)=3.07, $P<0.001$]. The Bland-Altman plots with bias and the limits of agreement (LoA) separated for each time-point are presented in *Figs. 20*. The overall bias was 28 (23, 29) with 95% LoA -20 to 75 ml min⁻¹m⁻². This overall estimate was unadjusted for repeated measurements as these were taken at different at different perioperative states. A preliminary random coefficient mixed model based on the individual subjects' paired measurements at the different time-points, showed a significant association

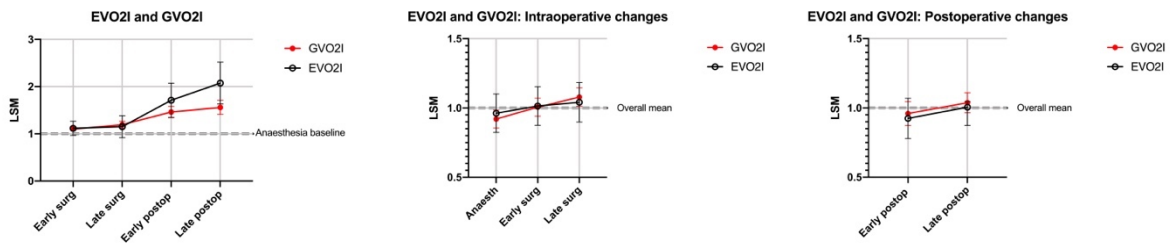
between the two methods but with uncertainty of prediction estimates due to wide confidence intervals of intercept and slope coefficient (see paper IV).



Figures 20. Bland-Altman plots demonstrating difference GVO2I - EVO2I vs average of GVO2I and EVO2I in $ml\ min^{-1}m^{-2}$ at different perioperative time-points: Anaesthesia (T1, N=20); Early surgery (T2, N=20); Late surgery (T3, N=18); Early postop (T4, N=13); Late postop (T5, N=14) including overall (unadjusted). Bias; continuous line: Upper and lower 95% limits of agreement: dotted lines.

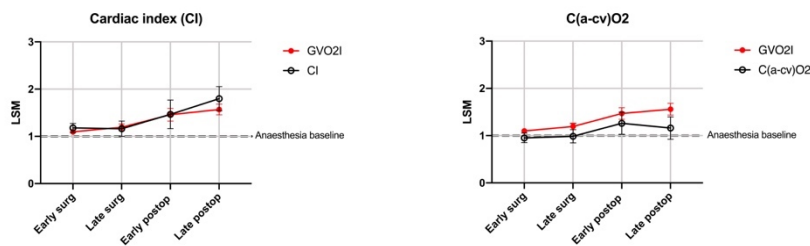
Relative changes over time

Relative changes at the different time-points of EVO2I and its constituting variables (CI and Ca-cvO₂), were compared with GVO2I. Post-hoc tests for GVO2I and EVO2I revealed that increases over time for both methods occurred intraoperatively [$F(2, 42.6)=7.43, P<0.0017$] but not postoperatively [$F(1, 17.1)=3.00, P=0.1013$]. GVO2I and EVO2I changed in parallel when separated to the anaesthetised intraoperative state [$F(2, 49.9)=0.57, P=0.5669$] or the awake postoperative state [$F(1, 22)=0.00, P=0.9604$] as seen in Figs. 21.



Figures 21 a-c. Results from the mixed effect models on perioperative changes (LSM estimates with 95% CI) of EVO2I (black) and GVO2I (red). Left, a: All perioperative changes normalised to individual baseline measurements during anaesthesia. Middle, b: Changes normalised to intraoperative overall mean for each method. Right, c: Changes normalised to postoperative overall mean for each method: LSM; Least square means.

In Figs.22 a-b the two variables of the product EVO2I, cardiac index (CI) and oxygen content difference (Ca-cvO₂), were analysed separately and compared with changes of GVO2I. Variance of EVO2I and its input variables were larger than the variances of GVO2I at all time-points.



Figures 22 a-b. Results from the mixed effect models on perioperative changes (LSM estimates with 95% CI) of EVO2I variables: cardiac index (black) and oxygen content difference (black), compared with GVO2I (red). Left, a: Cardiac index (CI) changes normalised to individual baseline measurements during anaesthesia. Right, b: Oxygen content difference (Ca-cvO₂) changes normalised to individual baseline measurements during anaesthesia: LSM; Least square means.

5 DISCUSSION

The papers included in this thesis describe in detail certain haemodynamic and oxygen transport changes during anaesthesia and surgery in predominately elderly subjects. This chapter discuss the results in relation to other studies and underlying mechanisms. The methodological strengths and limitations are discussed first in general, and then separately for each study.

5.1 GENERAL METHODOLOGICAL CONSIDERATIONS AND LIMITATIONS

The conceptual framework of this thesis is the reappraisal of earlier physiological observations and assumptions in clinical anaesthesia by modern methodological approaches. The findings presented are based on observational data, prospectively collected with detailed protocols and monitoring techniques with high-time resolution. In order to reflect common practice, the clinical studies were designed and conducted to minimise interference with standard care. Systematic review and meta-analysis preceded prospective data collection on perioperative oxygen consumption. Several statistical methods not previously used in the field were applied in the data analysis.

However, there are several general limitations to these study designs. First, spurious associations of physiological relationships can arise from data collected in uncontrolled dynamic clinical settings. The observational design and the multitude of clinical interventions introduced possible patient- and care-related confounders. This concerns both the clinical studies in the thesis and those included in the systematic review and meta-analysis. In addition, detailed protocols involving different monitors are practically demanding. This increases the risk of data loss and limits the number of measurements and participants. The small sample sizes render the studies underpowered for many outcomes and impair subgroup analyses. Measurement errors, both random and systematic, can occur despite meticulous calibration and perhaps more so with minimal-invasive techniques that rely on data processing algorithms, i.e. the indirect calorimetry and arterial wave form analysis used in these studies. Last, and most important, data was collected in elderly patients over 65 years and no comparisons were made with matched younger controls. As a consequence, the explorative findings are first and foremost hypothesis-generating. Estimates and their variabilities can be used in the design of future studies to confirm findings.

5.2 HAEMODYNAMIC CHANGES DURING SPINAL ANAESTHESIA IN ELDERLY

The role of cardiac output changes in the development of hypotension after spinal anaesthesia was outlined in a cohort of elderly patients in study I. Stroke volume and cardiac index, and consequently oxygen delivery index, decreased before the intrathecal injection and this decrease progressed after spinal anaesthesia in those who developed hypotension. In contrast, the non-hypotensive demonstrated an initial increase in cardiac index after spinal anaesthesia. The pre-anaesthetic reductions of cardiac and oxygen delivery index were associated with and showed high discriminative ability for development of post-spinal hypotension.

Reductions of stroke volume and oxygen delivery index were observed before and during spinal anaesthesia irrespective of treatment during a previous randomised controlled trial on GDHT in elderly hip fractured patients.⁶⁴ These findings were here reproduced prospectively in this non-interventional cohort of younger elderly undergoing elective surgery and were furthermore associated with the development of post-spinal hypotension. Pre-anaesthetic haemodynamic changes and responses are potentially useful predictors of hypotension. Heart rate- and blood pressure variability have in previous studies been associated with post-spinal hypotension.^{100,101} Higher baseline heart rate is a known risk factor.⁹³ This is in accordance with the observed association between high resting heart rate and heart rate variability with future functional decline in large cohorts of elderly.¹⁹⁶ The different haemodynamic changes in hypotensive and non-hypotensive patients before spinal anaesthesia might be attributed to decreased ability to regulate cardiac output in response to stress, position changes and fluid preloading. Nor position during or fluid given before intrathecal injection showed association with hypotension in this study, but given the small sample size such effects cannot be excluded.

In addition to impaired autonomous reflexes in elderly, pre-existing cardiac performance features have indeed been demonstrated relevant to haemodynamic changes during spinal anaesthesia in elderly. Lairez and colleagues conducted detailed echocardiographic measurements in patients over and under 70 years undergoing spinal anaesthesia.¹¹¹ In the elderly group, in which all hypotensive events occurred, E/A-ratio and LVEF was significantly lower at baseline indicating both decreased diastolic and systolic heart function. Spinal anaesthesia induced a larger decrease in cardiac and stroke volume index as well as systemic vascular resistance index. The prevalence of diastolic dysfunction increases with age and hypertension.^{15,17} We suggested that diastolic dysfunction was a potential mechanism for the changes observed in our study and that it should be further addressed by

echocardiography in future studies. However, the feasibility in obtaining the detailed measurements required is a major obstacle. Interestingly, a number of more recent studies have shown good predictability for post-spinal hypotension of dynamic inferior vena cava measurements by echocardiography.¹⁹⁷⁻¹⁹⁹

Decreases in cardiac output of 10-25% after spinal anaesthesia in elderly have been demonstrated in earlier studies using thoracic bioimpedance,^{103,106,200,201} transthoracic echocardiography^{110,111} and pulmonary artery thermodilution.¹⁰⁷ In elderly undergoing elective orthopaedic surgery, Meyhoff and colleagues demonstrated a biphasic change, similar to our non-hypotensive group, with an initial increase of 19% in cardiac output using LiDCO™plus.²⁰² In that study, participants who became hypotensive and required intervention were excluded from further analysis. The cardiac output changes presented were consequently those of the haemodynamically stable. An initial increase of cardiac output after spinal anaesthesia has also been shown in subsets of elderly patients.^{103,107} In obstetric patients receiving spinal anaesthesia for caesarean delivery, this initial cardiac output increase has been reported as large as 30-60% followed by return to baseline values.²⁰³

A plausible mechanism for the decrease in cardiac output induced by spinal anaesthesia seen in elderly, especially in those developing post-spinal hypotension, is an inability to compensate for the decreased venous return caused by sympathetic block and resulting vasodilation in the lower body. This latter process can be exacerbated by the higher resting sympathetic activity in elderly.^{13,204} Using radionuclide studies, blood volumes in splanchnic regions and legs have indeed been demonstrated to increase following spinal anaesthesia in elderly.¹⁰⁷ In our study, heart rate and stroke volume index were significantly lower at end of data collection in the hypotensive, illustrating this possible difference in compensatory cardiac output response to spinal anaesthesia. Unexpectedly, systemic vascular resistance index did not differ significantly in hypotensive and non-hypotensive. Decreases after spinal anaesthesia were similar to earlier studies when comparing with measurements just prior to injection.^{107,111,202} This further supports the hypothesis that inadequate cardiac output response might be a dominant mechanism of post-spinal hypotension in elderly.

The collecting of data at rest in the preoperative ward and just prior to spinal anaesthesia allowed for analysis of pre-anaesthetic haemodynamic changes. This approach has not been applied previously. By not excluding hypotensive patients who required vasopressors, haemodynamic responses over time in these could be revealed and compared to those maintaining blood pressure. However, the small sample size increases the risk of both type I and type II errors as well the impact of potential confounders. Another major concern is that

derived parameters such as oxygen delivery and systematic vascular resistance relied on continuous updates of variables. Hb and SaO₂ was entered as baseline and CVP was estimated to 7 mmHg and not measured. As stated, estimations of filling pressures by simultaneous echocardiographic measurements, although technically demanding, could have contributed further to characterise the haemodynamic changes.

5.3 OXYGEN CONSUMPTION CHANGES DURING GENERAL ANAESTHESIA AND SURGERY IN ELDERLY

The meta-analysis (study II) and the prospective cohort study in elderly (study III) demonstrated a similar decrease of oxygen consumption, 28 and 34 % respectively, after induction of general anaesthesia. Subsequent changes during surgery and in the postoperative period were largely similar. In the meta-analysis that included adult patients, not only elderly, advancing age was indicated to have an attenuating impact on the oxygen consumption decrease after induction of anaesthesia, but this was not statistically significant.

The meta-regression analyses could not demonstrate any impact by mode of anaesthesia, nor by use of neuromuscular blocking agents. Both inhalational and intravenous anaesthetic agents most commonly exhibit CNS depressing effects decreasing cerebral metabolic rate of oxygen (CMRO₂), with the exception of ketamine that leaves it unaltered or even increases it regionally.²⁰⁵ Only one of the 24 studies used ketamine for anaesthetic induction and maintenance, demonstrating a decrease in whole body oxygen consumption measured by pulmonary artery catheter.²⁰⁶ In study III, propofol was used for induction and sevoflurane for maintenance anaesthesia, both agents decreasing CMRO₂.^{207,208} In addition, patients in study III received bolus doses of atracurium for neuromuscular blockade and continuous epidural anaesthesia during surgery. Neuromuscular block also contributes to reduced oxygen consumption,¹¹⁷ but as it is clinically used in conjunction with sedation or general anaesthesia it is difficult to separate independent effects. In study III, the use of combined epidural and general anaesthesia can be of relevance for the larger intraoperative reduction of oxygen consumption. Older studies in patients with combined thoracic epidural and general anaesthesia, report reductions of oxygen consumption during general anaesthesia of 23-30%.²⁰⁹⁻²¹¹ Thoracic epidural anaesthesia in the postoperative period might also reduce postoperative increases in oxygen consumption, an effect enhanced by the reduced shivering response in elderly.²¹² In study III, postoperative oxygen consumption was not demonstrated to significantly differ from preoperative measurements. It is possible that this could be attributed to the thoracic epidural analgesia. Hypothermia is another well known depressor of whole-body oxygen consumption in anaesthetised subjects.²¹³ For this reason, studies in

patients under hypothermic cardiopulmonary by-pass or hypothermic for other reasons were excluded from the meta-analysis in study II. Data on body temperature was collected before each measurement in study III-IV to ensure that no patient was hypothermic. The study sample size was too small to reliably evaluate the impact all possible factors affecting oxygen consumption.

Study II only addressed oxygen consumption whereas study III also included simultaneous calculations of oxygen delivery and estimated oxygen extraction as secondary outcomes. A recent retrospective study in patients during CPB, using dependent Fick-derived calculations, could not demonstrate correlation between low levels of oxygen consumption and delivery that were under suggested critical values.²¹⁴ In study III, mean oxygen delivery was 277 (242, 313) ml min⁻¹ m⁻² after induction of anaesthesia, well under the critical levels previously stated by Lugo and Shibutani,^{48,49} yet mean estimated oxygen extraction was only 22 (19, 25) % and ScvO₂ 79 (76, 82)%. Oxygen consumption was obtained non-coupled by metabolic measurements using the same monitor for all time-points. The relative changes of oxygen consumption were analysed together with oxygen delivery demonstrating parallelity at all time-points when normalised to individual baseline measurements. Oxygen extraction was indicated to relatively increase more compared to oxygen consumption postoperatively, but this was not statistically significant. The parallelity demonstrates how these parameters change in a similar manner perioperatively. This should not be interpreted as indicative of supply-dependency as the study design was not designed to investigate such relationship. Nevertheless, the low levels and parallel changes of intraoperative oxygen consumption, delivery and extraction addresses important aspects of haemodynamic support in elderly. The findings indicate potentially relevant physiological changes and opportunities for individualised or age-adjusted targeting to be further studied. Ackland et al. associated return to individual preoperative oxygen delivery values with reduced morbidity regardless of intervention in elderly patients undergoing major abdominal or vascular surgery.⁷⁵ In the same study, inotropic support reduced parasympathetic activity and this was subsequently associated with complications. Similarly, the role of oxygen consumption and response to haemodynamic interventions could be addressed in intra- and postoperative settings and related to outcomes in elderly high-risk surgical patients.

The meta-analysis (study II) was unconventional in the sense that the outcome estimate was the change of a physiological parameter, the global oxygen consumption, rather than the effect of an intervention. Applying strict inclusion criteria, this approach enabled synthesis of comparable data points from detailed measurements reported in earlier publications.

Evidence quality of the effect estimate was evaluated with modern tools to evaluate risk of bias. It was only until recently that Cochrane recommendations for risk of bias assessment included a specific tool for non-randomised studies.²¹⁵ The NIH tool¹⁸⁶ used was appropriate for the before-after study designs but not validated or widely recommended. Another major methodological limitation in the meta-analysis was the high risk of bias and heterogeneity of the included studies. This decision to proceed to data synthesis was motivated by the detailed descriptions of the oxygen consumption measurements and anaesthetic interventions but this can be assumed to have affected the quality of the effect estimate. Subgroup analyses were not considered useful due to the multitude of potential moderators and high heterogeneity. Trial sequential analysis is a method to address random errors by using the features of interim analysis.²¹⁶ As this was not a conventional cumulative meta-analysis with a benefit/harm outcome and the expected effect had a clear direction (decrease), this method could not be expected to correctly address this issue and was therefore not applied.

The novel methodological approach of study III was the measurement of oxygen consumption in awake and anaesthetised states by indirect calorimetry, with simultaneously and independently obtained oxygen delivery and extraction by different routine monitoring technologies. The study design was not interventional nor standardised which impairs conclusions on causal relationships. Patients did not only undergo different surgical procedures but were also managed differently as demonstrated by the large variations in perioperative fluids given and the use of different fluid regimens. The sample size for measured oxygen consumption change after induction of anaesthesia was small when calculated from the meta-analysis. Consequently, the reported changes during surgery and postoperatively should be regarded as very indicative. Mixed effect models can be used amid the presence of missing data points, non-normality and timing differences in small-sized repeated measures data sets. Yet, it is a major limitation that the postoperative measurements were performed at such different time-points.

5.4 ESTIMATIONS OF OXYGEN CONSUMPTION DURING MAJOR SURGERY

Study IV evaluated estimated perioperative oxygen consumption from blood gas sampling (arterial and central venous) and minimal-invasive cardiac output measurements. In contrast to the few earlier similar studies, calibrated and validated cardiac output monitoring was used¹⁵⁵ and estimations were compared with independently obtained oxygen consumption measurements.¹⁵⁴ The estimation method did not show good agreement and consistently lower values compared to indirect calorimetry. Trending ability for relative changes over time was indicated when separating intra- and postoperative measurements and could be further studied.

As previously stated, oxygen consumption is rarely measured in current routine anaesthetic and postoperative practice. Preoperative metabolic measurements to assess maximum oxygen consumption (VO₂-max) as a part of cardiopulmonary exercise testing (CPET) are quite commonly performed and have demonstrated good predictability of postoperative complications.^{217,218} In contrast, large-scale intra- and postoperative measurements by calorimetric techniques are limited by technical requirements. Analysis of inspired and expired breathing gas in the anaesthetic circuit is theoretically appealing for intraoperative use but unreliable.¹³² In study III; intraoperative $\Delta\text{PCO}_2/\text{C(a-v)O}_2$ and ScvO₂ were unaltered over time, whereas measured oxygen consumption was indeed demonstrated to increase during this period. However, the estimated oxygen consumption (study IV) did not increase when comparing different absolute intraoperative values.

Study IV addressed important aspects of method comparison between Fick- and gas-derived oxygen consumption. The use of central venous oxygen content and minimal-invasive cardiac output instead of pulmonary artery measurements is presumably a limitation, but results compared quite well with previous studies.^{135,219} Several analytical challenges stressed the use of appropriate statistical methodology. We used intraclass correlation (ICC) to address agreement and correct for systematic differences which is not possible with conventional correlation analysis.¹⁹⁵ To avoid incorrect variance estimates arising from repeated measurements in the same subject, both ICC and Bland-Altman analysis were also separated for time-points. Adjustments can be made to correct for repeated measurements by different approaches.^{220,221} A statistically significant association between the methods was demonstrated, but with wide intervals of prediction and agreement. We applied mixed models to assess the relationship between the methods with regards to effects of different time-points and constituting variables of the estimation method. The only previous study addressing time-effects on the difference between the methods did not find such.²²² When analysing intra-and

postoperative measurements separately both measured and estimated oxygen consumption changed in parallel, indicating no overt change in method difference over time. This indicates that trending ability could be further studied with higher time-resolution. However, due the very limited number of postoperative observations, this should be interpreted with caution. As a pre-planned study based on data collected in study III, no power calculation was performed for this secondary outcome which limits many conclusions and the large variability introduces further uncertainty of the findings. Prediction of oxygen consumption based on this or similar estimation methods might be possible but need assessment in larger samples.

6 CONCLUSIONS

The results presented in this thesis are based on observational findings in small samples and should be regarded as hypothesis-generating.

I. Ability to maintain or increase cardiac output may be a dominant mechanism for haemodynamic stability in elderly during spinal anaesthesia. Pre-anaesthetic changes in cardiac output can potentially predict post-spinal hypotension.

II. In a systematic review and meta-analysis, oxygen consumption was demonstrated to decrease during general anaesthesia, but the effect estimate is uncertain and cannot be generalised to the current older surgical population.

III. Perioperative changes of oxygen consumption, similar to those demonstrated in the meta-analysis, were observed in elderly undergoing major abdominal surgery. Intraoperative oxygen consumption changes changed in parallel with decreased levels of oxygen delivery and extraction. The relevance of these changes in relation to outcomes and haemodynamic interventions needs future assessment.

IV. Estimations of oxygen consumption by minimal invasive cardiac output and arterial-central venous sampling systematically underestimated and showed poor absolute agreement compared to measurements by indirect calorimetry. Prediction models to estimate or trend oxygen consumption may be constructed, but need to be further studied in larger populations and with higher time-resolution.

7 FUTURE PERSPECTIVES

To improve outcomes for elderly high-risk surgical patients is, and will undoubtedly become, an increasingly important task for perioperative research and care initiatives. Mechanistic approaches that incorporates age-specific physiological features in the design of future trials can potentially offer better hypothesis-testing and more relevant interventions for this population. In this process, subgroup or meta-regression analyses of high-risk elderly in systematic reviews and meta-analyses of interventions might provide guidance. However, these approaches are problematic due to the heterogeneity issues previously described. A simpler first step could include age-adjustments of normal haemodynamic perioperative reference values. Large amounts of collectable output data from monitors with high-time resolution should be quite easily available. Pre-anaesthetic assessment of cardiac output or related changes by minimal-invasive monitoring as in study I or by ultrasound are cumbersome and relevant cut-offs need to be determined in larger studies. Recently, algorithms developed by machine-learning applied to large datasets of arterial waveforms have been demonstrated to predict²²³ and to reduce the time and depth of intraoperative hypotension.²²⁴ This gives a hint of the opportunities and future potential in perioperative haemodynamic monitoring. It also highlights the importance of data input from relevant populations, in this case elderly, to avoid unintentional bias. To dig deeper into the mechanisms behind the potential benefits of goal-directed haemodynamic support to find the optimal treatment algorithm is debated and there is a growing tendency towards individualisation.⁷⁶ Nevertheless, a certain degree of standardisation of protocols with appropriate age-adjusted values, timing of interventions and parameters to follow are probably still needed. To reappraise the role of perioperative oxygen consumption changes, and their association to outcomes and to other biomarkers or estimates, is one strategy in high-risk surgical elderly. Global oxygen consumption and delivery, when assessed together, should be measured by separate methods comparing individual baseline values with responses to standardised interventions. The results presented in this thesis do not provide solutions to these challenges but suggest hypotheses, methodological approaches and mechanisms that when further evaluated can help to do so.

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^v Non-magical people (Am. Eng), also known as muggles (Br. Eng). People who do not belong to the wizarding world. From J. K. Rowling., author of the *Harry Potter* series and *Fantastic Beasts and where to find them*.

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10 ERRATA TO PUBLISHED PAPERS

PAPER I

Page 1178:

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should read:

“¹Division of Anaesthesia and Intensive Care, Department of Clinical Science Intervention and Technology (CLINTEC), Karolinska Institutet and ²Department of Perioperative Medicine and Intensive Care, Karolinska University Hospital Huddinge, SE-141 86, Stockholm, Sweden “

Page 1178, 1179, 1184:

“..LiDCOplus™...” should read *“..LiDCO™plus...”*

Page 1179:

“...SaO₂>95%.” should read *“...SpO₂>95%.”*

PAPER II

Page 149:

Figure 2:

“Liboti (1971)” should read *“Libonati (1971)”*