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Katriina Lanning

PULMONARY ARTERY CATHETER COMPARED WITH LESS INVASIVE HEMODYNAMIC ASSESSMENT IN CARDIAC SURGICAL PATIENTS

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
MEDICAL RESEARCH CENTER OULU;
OULU UNIVERSITY HOSPITAL

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Abstract

Adequate function of the heart and circulatory system is necessary for oxygen supply and tissue perfusion. In patients undergoing cardiac surgery, these may be compromised even prior to the surgical procedure. Surgery, anesthesia, and the use of cardiopulmonary bypass (CPB) may further worsen cardiovascular performance and compromise oxygen supply in the end-organs such as the brain and kidneys. This can lead to end-organ dysfunction and death. Healthcare costs increase due to the prolonged intensive care and hospital stays.

In cardiac surgical patients, accurate hemodynamic monitoring and treatment is crucial, as these have been demonstrated to improve patient outcome. A pulmonary artery catheter (PAC) is utilized to monitor several hemodynamic variables valuable in evaluating cardiovascular function. Inserting a PAC is an invasive procedure and is associated with some potential risks. Therefore, less invasive devices and methods have been developed to replace the PAC.

In study I, we compared the noninvasive Starling SV and mini-invasive LiDCOrapid, which are continuous cardiac output monitors, to PAC in cardiac surgical patients with CPB. The trending ability of both devices was poor. LiDCOrapid showed sufficient accuracy, while the accuracy of the Starling SV was poor. Neither of the devices demonstrated sufficient measurement precision.

In study II, we compared central venous oxygen saturation ($ScvO_2$) values to mixed venous oxygen saturation (SvO_2) values drawn from a PAC. $ScvO_2$ values showed acceptable accuracy. The precision of $ScvO_2$ was inadequate, as was its trending ability.

Study III was performed to evaluate the association between transcranial near-infrared spectroscopy (NIRS) and cardiac index (CI) measured with PAC during cardiac surgery. The analysis of separate NIRS and CI pairs revealed a poor association. When the changes in NIRS from baseline or from the previous measurement were compared to those of CI, a significant association was discovered. This was particularly evident in patients undergoing off-pump coronary artery bypass (OPCAB).

In conclusion, CI values measured with Starling SV and LiDCOrapid, or $ScvO_2$ are not reliable enough to replace measurements obtained with a PAC in cardiac surgical patients. However, transcranial NIRS and CI demonstrate a significant association during cardiac surgery.

Keywords: cardiac surgery, central venous oxygen saturation, goal directed therapy, minimally invasive cardiac output monitor, mixed venous oxygen saturation, near-infrared spectroscopy, pulmonary artery catheter

Lanning, Katriina, Keuhkovaltimokatetrin vertailu vähemmän kajoaviin verenkierron riittävyyden arviointimenetelmiin sydänleikkauspotilailla.
Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala;
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Tiivistelmä

Sydänleikkauspotilaiden sydän- ja verenkiertoelimistön toimintakyky voi olla heikentynyt jo ennen leikkausta. Leikkaus, anestesia ja sydänkeuhkokoneen käyttö huonontavat tilannetta entisestään niin, että kudosten riittävä hapensaanti saattaa vaarantua. Tämä voi johtaa elinvaurioiden syntymiseen, kuolleisuuden nousuun, hoitoaikojen pitenemiseen ja terveydenhuollon kustannusten kasvuun.

Tarkka verenkierron riittävyyden arviointi on ensiarvoisen tärkeää sydänleikkauspotilaiden hoidossa ja sillä voidaan vaikuttaa potilaan ennusteeseen. Verenkierron riittävyyttä voidaan arvioida keuhkovaltimokatetrin avulla, mutta sen käyttöön liittyy mahdollisia haittoja. Tämän vuoksi on kehitetty vähemmän kajoavia laitteita ja menetelmiä korvaamaan keuhkovaltimokatetrista saatavaa tietoa.

Ensiksi vertasimme vähemmän kajoavan LiDCOrapid- ja täysin kajoamattoman Starling SV-monitorin antamia sydämen minuuttitilavuusarvoja (CI) keuhkovaltimokatetrista saataviin arvoihin sydänleikkauksissa, joissa käytettiin sydänkeuhkokonetta. Molempien vertailulaitteiden kyky seurata arvojen muutoksia oli huono. Yksittäisissä arvoissa LiDCOrapid-laitteen tarkkuus oli riittävä, kun taas Starling SV-monitorin tarkkuus oli huono. Kummankaan laitteen täsmällisyys ei ollut riittävä.

Toiseksi tutkimme keskuslaskimoveren happisaturaation ($ScvO_2$) luotettavuutta verrattuna keuhkovaltimokatetrista otettuun sekoittuneen laskimoveren happisaturaatioon (SvO_2). $ScvO_2$-arvot olivat riittävän tarkkoja, mutta niiden täsmällisyys ja kyky seurata SvO_2-arvojen muutoksia olivat riittämättömät.

Kolmanneksi vertasimme aivojen lähi-infrapunaspektroskopia-arvoja (NIRS) keuhkovaltimokatetrin avulla mitattuihin CI-arvoihin. Yksittäisten NIRS- ja CI-arvojen välinen yhteys oli heikko. Kun tarkasteltiin NIRS-ja CI-arvojen muutoksia joko lähtötilanteeseen tai edelliseen lukemaan verrattuna, muutosten välillä todettiin tilastollisesti merkitsevä yhteys etenkin ohitusleikkauksissa, jotka toteutettiin ilman sydänkeuhkokonetta.

Yhteenvetona todetaan, että LiDCOrapid ja Starling SV eivät ole tarpeeksi luotettavia korvaamaan keuhkovaltimokatetrin avulla mitattuja CI-arvoja sydänleikkauspotilailla. $ScvO_2$- ja SvO_2-arvot eivät ole keskenään vaihtokelpoisia sydänkirurgian aikana ja sen jälkeen. Sen sijaan aivojen NIRS-arvojen muutokset kuvastavat sydämen toimintakyvyn muutoksia sydänleikkauspotilailla.

Asiasanat: keskuslaskimoveren happisaturaatio, keuhkovaltimokatetri, lähi-infrapunaspektroskopia, sekoittuneen laskimoveren happisaturaatio, sydämen minuuttitilavuuden mittaaminen, sydänkirurgia, tavoiteohjattu hoito

It is worth remembering that it is often the small steps, not the giant leaps, that bring about the most lasting change.

Queen Elizabeth II

To my family

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Oulu January 2023 Katriina Lanning

Abbreviations

95% CI	95% confidence interval
AKI	Acute kidney injury
BSA	Body surface area
CABG	Coronary artery bypass grafting
CBF	Cerebral blood flow
CPB	Cardiopulmonary bypass
CI	Cardiac index
CO	Cardiac output
CO_2	Carbon dioxide
CS	Cardiogenic shock
CVP	Central venous pressure
DO_2	Oxygen delivery
ECMO	Extracorporeal membrane oxygenation
EF	Ejection fraction
e.g.	Exempli gratia
EGDT	Early goal directed therapy
$etCO_2$	End-tidal carbon dioxide
GDT	Goal directed therapy
HR	Heart rate
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
LCOS	Low cardiac output syndrome
LOA	Limits of agreement
LOS	Length of stay
LV	Left ventricle
MAP	Mean arterial pressure
MOF	Multiple organ failure
NIRS	Near-infrared spectroscopy
OPCAB	Off-pump coronary artery bypass
OR	Operating room
PAC	Pulmonary artery catheter
PAC-CCO	Continuous thermodilution with a PAC
PAH	Pulmonary artery hypertension
PAP	Pulmonary artery pressure
PAWP	Pulmonary artery wedge pressure

PE	Percentage error
PiCCO	Pulse index continuous cardiac output
PPV	Pulse pressure variation
PRAM	Pressure-recording analytical method
PVRI	Pulmonary vascular resistance index
PWTT	Pulse wave transit time
rSO_2	Regional tissue oxygenation
RV	Right ventricle
$ScvO_2$	Venous oxygen saturation
SV	Stroke volume
SvO_2	Mixed venous oxygen saturation
SVRI	Systemic vascular resistance index
SVV	Stroke volume variation
TA-TAVI	Transapical transcatheter aortic valve implantation
TEE	Transesophageal echocardiocraphy
TDCO	Thermodilution technique
VJI	Internal jugular vein
VO_2	Oxygen consumption

List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:

I Ylikauma, L., Lanning, K., Erkinaro, T., Ohtonen, P., Vakkala, M., Liisanantti, J., Juvonen, T., & Kaakinen, T. (2021). Realibility of bioreactance and pulse-power analysis in measuring cardiac index in patients undergoing cardiac surgery with cardiopulmonary bypass. *Journal of Cardiothoracic and Vascular Anesthesia, 36*(8 Pt A), 2446 −2453. https://doi.org/10.1053/jcva.2021.11.039

II Lanning, K., Erkinaro, T., Ohtonen, P., Vakkala, M., Liisanantti, J., & Kaakinen, T. (2021). Accuracy, precision, and trending ability of perioperative central venous oxygen saturation compared with mixed venous oxygen saturation in unselected cardiac surgical patients. *Journal of Cardiothoracic and Vascular Anesthesia, 36(7),* 1995 −2001.

III Lanning, K., Ylikauma, L., Erkinaro, T., Ohtonen, P., Vakkala, M., & Kaakinen, T. (2022). Changes in transcranial near-infrared spectroscopy (NIRS) values reflect changes in cardiac index during cardiac surgery. Acta Anaeshesiologica Scandinavica Acta Anaesthesiologica Scandinavica 2023, Feb 5. doi: 10.1111/aas.14210. Epub ahead of print.

Ylikauma, L and Lanning, K have equally contributed to study I

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1 Introduction

Although both mortality and morbidity related to cardiac surgery have decreased during recent decades (Aya et al., 2013; Kapoor et al., 2017; Thalji et al., 2018) there is still a need for improvement. Approximately 10% of cardiac surgical patients require prolonged postoperative care, mainly because of end-organ dysfunction, multiple organ failure (MOF), and hemodynamic instability (Higgins et al., 1996; Patel et al., 2020). Due to advanced supportive care and improved surgical techniques, cardiac surgery can be successfully performed even in high-risk patients (Thalji et al., 2018; Warner et al., 1997). Adequate postoperative cardiac output (CO) and a balance between oxygen delivery and consumption are important factors in determining survival after cardiac surgery(Patel et al., 2020).

Cardiopulmonary monitoring is essential for the successfull management of cardiac surgical patients. Conventional hemodynamic monitoring, such as mean arterial pressure (MAP), heart rate (HR), urine output, and performing laboratory tests alone, does not accurately reflect acute changes in organ perfusion, which may lead to a delayed recognition of the imbalance between oxygen supply and demand. In cardiac surgical patients, advanced hemodynamic monitoring is commonly utilized to guide decisions related to hemodynamic treatment during surgery as well as during postoperative care in the intensive care unit (ICU).

Several studies have shown that goal-directed hemodynamic therapy (GDT) may reduce postoperative complications in cardiac surgical patients and shorten both the ICU and in-hospital length of stay (LOS), thereby reducing health care costs (Aya et al., 2013; Osawa et al., 2016; Pölönen et al., 2000). The purpose of GDT is to improve tissue oxygenation by using fluids, vasopressors, and inotropes, thereby avoiding global tissue hypoxia, which is key in the development of MOF and death.

Low cardiac output syndrome (LCOS) is a major determinant of adverse outcome after cardiac surgery (Ding et al., 2015; Maganti et al., 2005). It is of paramount importance to accurately measure CO to detect LCOS. The pulmonary artery thermodilution technique (TDCO) has been the gold standard in measuring CO since the 1970s (Arya et al., 2022; Peeters et al., 2015; Swan et al., 1970). TDCO requires the insertion of a pulmonary catheter (PAC), which is also necessary for mixed venous saturation (SvO_2) sampling. Inserting a PAC is an invasive procedure and is associated with some potential risks for vascular injury, infection, and thrombosis (Evans et al., 2009). Therefore, the use of a PAC has markedly declined in many hospitals in recent decades (Balzer et al., 2015; Harvey et al., 2005; Rajaram et al., 2013; Sandham et al., 2003) and surrogate methods are often utilized in the hemodynamic assessment of cardiac surgical patients. Central venous oxygen saturation ($ScvO_2$) measurements, withdrawn from a central venous catheter, are being used as a substitute for SvO_2, but $ScvO_2$ is not identical to SvO_2 as it better reflects upper body rather than global oxygen balance.

Continuous mini- and non-invasive CO monitoring technologies have been developed and there are many different devices available. LiDCOrapid is a mini-invasive CO monitor, based on pulse power analysis through the pulse CO algorithm. Starling SV is a non-invasive CO monitor, which is based on the transthoracic bioreactance technique (Marik, 2013). Neither of these methods have been specifically validated in the context of cardiac surgery.

Near-infrared spectroscopy (NIRS) is a non-invasive technique that utilizes infrared light to continuously monitor regional tissue oxygenation (rSO_2). Cerebral rSO_2 values correlate well with SvO_2 values under different conditions (Baraka et al., 2006; Koike et al., 2004; Madsen et al., 2000; Paarmann et al., 2010; Paquet et al., 2008). There are only a few studies which examine the association between cerebral NIRS and cardiac function, and only one of them includes adult cardiac surgical patients (Paquet et al., 2008).

The aim of this thesis was to evaluate whether cardiac index (CI) measurements based on pulse power analysis, or transthoracic bioreactance, $ScvO_2$ values, or transcranial NIRS values provide adequate information when compared to measurements obtained with a PAC for the hemodynamic assessment of adult cardiac surgical patients.

2 Review of the literature

2.1 Outcome after cardiac surgery

Mortality and morbidity during and after cardiac surgery have decreased in recent decades (Aya et al., 2013; Kapoor et al., 2017; Thalji et al., 2018). Cardiac surgery can be safely performed in increasingly older patients with several comorbidities (Ferguson et al., 2002; Rhodes et al., 2011; Thalji et al., 2018). With regards major surgery, however, complication rates are still known to be greatest among cardiac surgical patients ("Global Patient Outcomes after Elective Surgery: Prospective Cohort Study in 27 Low-, Middle- and High-Income Countries," 2016). The incidence of major postoperative complications, which include stroke, renal failure, prolonged intubation, and sternal wound infection, occur in from 15% to 30% of cardiac surgical patients (Crawford et al., 2017). In the same study, operative mortality was 41% in patients with multiple complications vs 4.9% of those with an isolated complication and 0.7% of those without complications (Crawford et al., 2017). Complications lead to increased healthcare costs (Crawford et al., 2017; Higgins et al., 1996; Patel et al., 2020) due to prolonged ICU and in-hospital LOS, more frequent laboratory tests, and expensive medical and surgical therapies (Patel et al., 2020). It was estimated in 2012 that 313 million surgical procedures were performed worldwide that year. Depending on the type of surgery and the comorbidities present, 30-40% developed complications, 20% of which were classified as severe (Weiser et al., 2016). Although the etiology of postoperative complications is multifactorial, poor outcomes after major surgery are strongly associated with disorders in tissue oxygenation (O. Boyd et al., 1993; Jhanji et al., 2009; Kusano et al., 1997; Shoemaker W. C. et al., 1982). The major goal in optimizing tissue oxygenation is to maintain adequate blood flow through the organs, such as the brain, heart, kidneys and GI tract. The early diagnosis and treatment of impaired organ perfusion is crucial for maintaining their function and avoiding the development of MOF. A mismatch between oxygen supply and demand leads to tissue hypoxia and MOF. Global oxygen delivery (DO_2) is determined by CO and oxygen content of the arterial blood.

Postoperative heart failure and LCOS are the main causes of postoperative mortality and morbidity after cardiac surgery (O'Connor et al., 1998; Vánky et al., 2007). LCOS is a complication after cardiac surgery characterized by inadequate cardiac pump function resulting in reduced DO_2 and tissue hypoxia (Lomivorotov et al., 2017). LCOS ranges from myocardial stunning to severe cardiogenic shock with the need for mechanical ventricular assistance. The incidence of LCOS varies from 2 to 27% in the adult population (Algarni et al., 2011; Hogue et al., 2001; Maganti et al., 2010; Maganti et al., 2005; Osawa et al., 2016) and mortality up to 38% (Schoonen et al., 2022). Variety in definitions of LCOS partly explains the wide range in reported incidences of LCOS (Schoonen et al., 2022).

Adequate monitoring of the hemodynamic state is essential to guide the treatment and avoid any imbalance between DO_2 and oxygen consumption (VO_2). Mixed venous oxygen saturation reflects the balance between global DO_2 and global VO_2. The main clinical interventions to increase DO_2 are inotropic therapy to increase CO, intravenous fluid and blood therapy, and supplemental oxygen therapy. On the other hand, anesthesia, analgesia, and sedation are commonly used interventions to decrease VO_2.

2.2 Goal-directed therapy

GDT is a term used to describe the use of CO and other hemodynamic parameters to guide fluid and inotropic therapy. The goal of GDT is to achieve a balance between systemic oxygen delivery and demand, and thereby avoid complications. It has been suggested that the mortality rate in high-risk surgical patients may be reduced if the hemodynamic parameters noted in the survivors were used as goals in high-risk patients (Shoemaker et al., 1988).

In GDT, various monitoring techniques are used to guide hemodynamic treatment to avoid low CO and provide adequate DO_2 (Engelman et al., 2019). As opposed to an informal utilization of the hemodynamic measurements for clinical decisions, GDT uses a standardized algorithm to improve patient outcome (Engelman et al., 2019). The quantified goals include several parameters such as blood pressure, CO, SvO_2, $ScvO_2$, lactate and urine output (Engelman et al., 2019; Jones, 2010). In addition, cerebral NIRS, increased oxygen consumption and oxygen debt may augment therapeutic interventions (Engelman et al., 2019; Jones, 2010). GDT involves adjustments of cardiac function, i.e. preload, afterload and contractility, using fluids, vasopressors, and inotropes to balance oxygen delivery with oxygen demand (Rivers et al., 2001).

The concept of GDT has its origins in a study by Shoemaker et al (Shoemaker et al., 1988). They assessed 88 high-risk general surgical patients randomized into three groups: a CVP-control group, a PAC-control group, and a PAC-protocol group. In the PAC-protocol group the therapeutic goals were supranormal; CI > 4.5

L/min/m^2, oxygen delivery > 600 ml/min/m^2, and oxygen uptake > 170 ml/min/m^2. In the PAC-protocol group mortality was reduced to 4% compared to 33% in the PAC-control group and 23% in the CVP-control group. However, it was only after the Rivers study in 2001 (Rivers et al., 2001), that early GDT (EGDT) for the treatment of sepsis became popular. They randomized 130 sepsis patients in the early EGDT group and 133 patients in the standard therapy group upon arrival to an emergency department, before admission to the ICU. The hemodynamic goals in the EGDT group were as follows: CVP 8-12 mmHg, MAP 65-90 mmHg, and $ScvO_2$ ≥70%. In-hospital mortality was significantly lower (30.5% vs 46.5%) in the EGDT group than in the standard therapy group. The patients in the EGDT group received more red blood cell transfusions (68.4% vs 44.5%) as well as significantly more intravenous fluids (approximately 5 L vs 3.5 L) during the first six hours of the ICU care, yet there was no difference in the total fluid amount administered during the first 72 hours. They showed that the low $ScvO_2$ was associated with high in-hospital mortality and concluded that aggressive therapy to increase $ScvO_2$ can reduce mortality (Rivers et al., 2001).

A meta-analysis of 95 randomized controlled trials including 11,659 adult surgical patients demonstrates that GDT reduces mortality, morbidity and in-hospital LOS (Chong et al., 2018). Concerning overall mortality, the number needed to treat was 59, being 34 in high-risk patients. However, the quality of evidence was considered low or very low. Interestingly, there was no mortality benefit for fluid-only GDT (Chong et al., 2018). This may be since it has been shown that only about 50% of patients respond positively to a volume challenge (Boyd et al., 2011). Consequently, it is essential to assess the intravascular volume status (preload) and the ability to improve CO after fluid administration when treating a hemodynamically unstable patient.

The optimization of CO in patients undergoing major surgery has been shown to reduce postoperative complications as well as both the ICU and hospital LOS (Gan et al., 2002; Hamilton et al., 2011; Pölönen et al., 2000). However, co-morbidities are the most important determinant of perioperative complications (Maheshwari & Sessler, 2020). As complications are more likely to occur in higher-risk patients, they may possibly benefit more from GDT (Maheshwari & Sessler, 2020). In the review article by Engelman et al, GDT was recommended to decrease postoperative complications (class 1, level B recommendation). Reduced complication rates were seen especially in cardiac surgical patients (Engelman et al., 2019). A systematic review and meta-analysis by Hamilton et al showed that preemptive GDT in the perioperative period reduces both morbidity and mortality in moderate and high-risk surgical patients (Hamilton et al., 2011).

2.2.1 Goal-directed therapy in cardiac surgery

Limited cardiovascular reserve and extracorporeal circulation are the main risks of inadequate perioperative oxygen delivery in cardiac surgical patients (Routsi et al., 1993; Smulter et al., 2018). The risk of adverse events increases in patients with co-morbidities, such as recent myocardial infarction, poor left ventricular EF, pulmonary disease, or renal dysfunction (Ghotkar et al., 2006; Messaoudi et al., 2009). An inadequate hemodynamic response to surgical stress, limited cardiac function (Ryan et al., 1997) and increased oxygen extraction (Pölönen et al., 1997) immediately after cardiac surgery have been shown to be independent predictors of prolonged ICU LOS. Hemodynamic instability, organ dysfunction, and MOF are the main reasons leading to prolonged postoperative in-hospital LOS after cardiac surgery (Crawford et al., 2017; Higgins et al., 1996).

GDT has been shown to improve outcome in cardiac surgical patients (Pölönen et al., 2000). In the study by Pölönen et al, patients who achieved the targets of $SvO_2 > 70\%$ and lactate ≤ 2.0 mmol/L, had one day shorter in-hospital LOS and experienced less prolonged ICU stays, and less organ dysfunction (1% vs 6%). There was no difference in mortality between the GDT and standard hemodynamic treatment groups (Pölönen et al., 2000).

Fluid administration is generally the first step in the management of severely ill patients with inadequate tissue perfusion. Patel et al prospectively studied 478 post cardiac surgical patients randomized into a standard hospital care and a GDT group. In the GDT group, the aims of an $ScvO_2 > 70\%$ and serum lactate ≤ 2.0 were achieved by fluids, inotropes, and red blood cell transfusions (Patel et al., 2020). There was a higher incidence of AKI (23.1% vs 13.2%) in the control group, and the time in mechanical ventilation was longer (11.12 h vs 9.45 h). There were no significant differences in the ICU LOS, mortality, or central nervous complications between the groups. In a prospective single-center study by Meersch et al on 276 cardiac surgical patients with a high-risk for AKI, the primary endpoint was the incidence of AKI within 72 hours after cardiac surgery on CPB (Meersch et al., 2017). There was a significant reduction in the incidence of AKI in the GDT group (55.1%) compared to that of the control group (71.7%) In the GDT group, they applied the Kidney Disease: Improving Global Outcomes (KDIGO) recommendations on volume management, adequate blood pressure, and avoidance of nephrotoxic drugs to avoid AKI (Meersch et al., 2017).

In a study by Kapoor et al, 163 off-pump coronary artery bypass (OPCAB) patients were randomized into a GDT group and a control group. The final analysis included 66 GDT patients and 76 control patients. The ICU and in-hospital LOSs were significantly higher in the control group, 4.2 ± 0.82 vs 2.53 ± 0.56 days and 7.42 ± 1.48 vs 5.61 ± 1.11 days, respectively. The duration of the need for inotropes was significantly lower in the GDT group, 2.89 ± 0.68 h vs 3.24 ± 0.73 h. (Kapoor et al., 2017).

In the study by Goepfert et al, 40 CABG patients with GDT were compared to a historical control group (Goepfert et al., 2007). In the GDT group, the optimization of end-diastolic volume index was performed with the mini-invasive PiCCO catheter. The need for vasopressor use (187 min vs 1458 min) and the duration of mechanical ventilation (12.6 h vs 15.4 h) were significantly lower in the GDT group. They concluded that the treatment of patients undergoing cardiac surgery is improved when preload and CO are optimized (Goepfert et al., 2007).

In a systematic review with 699 cardiac surgical patients from 5 studies, Aya et al did not find any improvement in mortality with GDT compared to standard treatment group (Aya et al., 2013). There was, however, a significant reduction in the hospital length of stay (−2.21; 95% CI −3.84 to −0.57).

Table 1. Prospective controlled GDT studies on cardiac surgery (CS) patients.

Authors/year	Patients	Study design	Hemodynamic targets	Interventions	Primary endpoint	Results
Pölönen et al 2000	403 CS	Randomized controlled	SvO_2> 70%, lactate ≤ 2 mmol/L (PAC) GEDVI>640ml/m^2,	Fluids, dobutamine	ICU and in-hospital LOS	Reduced in-hospital LOS and morbidity in the GDT group.
Goephert et al 2007	80 CABG	Prospective, GDT group and historical group	CI>2.5L/min/m^2, (PiCCO), MAP>70	Fluids, vasopressors	Vasopressor support, ICU LOS	Shorter duration of vasopressors, reduced ICU LOS
Meersch et al 2017	276 (CPB) high-risk for AKI	Randomized, controlled	KDIGO criteria (PiCCO)	Hemodynamic optimization, avoiding hyperglycemia and nephrotoxic drugs.	Incidence of AKI during 72 h after surgery	Less moderate/severe AKI in the GDT group
Kapoor et al 2017	163, ICU, after OPCAB	Randomized, controlled multicenter	CI, SVRI,SVV, continuous $ScvO_2$, EVLW, global EDV, (FloTrack, E-V 1000)	Fluids, inotropes	Inotropes, ICU and hospital LOS	Reduced ICU and hospital LOS, shorter duration of inotropes
Patel et al 2020	47 CS	Prospective, controlled	$ScvO_2$>70%, lactate ≤ 2 mmol/L	Fluids, inotropes, red blood cells	AKI, time on ventilator	Less AKI and shorter time on ventilator on GDT group

CABG, coranary artery bypass grafting; OPCAB, off-pump coronary artery bypass; ICU, intensive care unit; CPB, cardiopulmonary bypass; SvO2, mixed venous oxygen saturation; GEDVI, global end-diastolic volume index; EDV, end-diastolic volume; SVV, stroke volume variation; CI, cardia index; SVRI, ystemic vascular resistance index; $ScvO_2$, venous oxygen saturation; AKI:acute kidney injury; GDT, goal directed therapy; LOS, length of stay.

2.3 Pulmonary artery catheter

The first method for estimating CO was based on the Fick principle described by Adolph Fick in the 1870`s (Fick, 1870; Peeters et al., 2015), which states that the total uptake or release of oxygen by the lungs is the product of blood flow through the lungs and the arteriovenous difference in oxygen content (Fick, 1870). The Fick method is a cumbersome technique and considered not suitable for bedside monitoring. The pulmonary artery catheter (PAC), also called the Swan–Ganz catheter, was introduced by Jeremy Swan and William Ganz in 1970 (Swan et al., 1970). Since then, PAC has been used in clinical practice to monitor the hemodynamic status in order to guide the treatment of cardiac surgical and critically ill patients. However, the use of PAC has declined over the past decades (Harvey et al., 2005; Rajaram et al., 2013; Sandham et al., 2003) while less invasive methods for measuring CO have been developed. Regardless, PAC remains as the gold standard for measuring CO.

2.3.1 Pulmonary artery catheter - hemodynamic values and waveforms

The main advantage of PAC is its utility in monitoring several hemodynamic variables that are valuable in the treatment of critically ill patients. PAC enables CO monitoring using TDCO, in which a predetermined, usually 10 ml, volume of saline of known temperature that is colder than blood is injected into the right atrial lumen, creating a thermal deficit in blood. The blood temperature is measured with a thermistor located at the catheter tip in the pulmonary artery. CO is then derived using the thermodilution curve computed from the change in blood temperature, and the temperature and the volume of the saline bolus. CO represents the volume of blood ejected from the left ventricle during one minute. Cardiac index (CI) is a measurement of the CO based on the patient´s size and it is calculated by dividing CO with the patient´s body surface area (BSA). In practice, CI is used more often than CO in the assessment of cardiac function. Pulmonary artery pressure (PAP) indicates the afterload of the right ventricle, i.e. the amount of pressure that the right ventricle must work against to eject blood during systole. Pulmonary artery wedge pressure (PAWP), which can be measured by occluding the pulmonary artery with a balloon in the tip of the catheter, represents the filling pressures in the left side of the heart (Forrester et al., 1972). Central venous pressure (CVP) reflects the right heart filling pressure (Marik et al., 2008).

PAC allows an estimation of vasomotor tone via the pulmonary (PVR) and systemic (SVR) vascular resistances, and resistance indexes (PVRI, SVRI) which are calculated from pulmonary, and systemic resistance and BSA (Barash et al., 1980; Kwan et al., 2019). Furthermore, PAC is needed for SvO_2 sampling to assess the systemic balance between oxygen consumption and delivery.

CO and the other information obtained with PAC can differentiate the etiology of systemic shock into cardiogenic (low CO with high filling pressures), hypovolemic (low CO with low filling pressures), and distributive (high CO with low systemic vascular resistance) origin. The etiology of the RV dysfunction can be divided into ventricular failure (high CVP and low PAP) or increased afterload (high PAP) (de Backer et al., 2013). The morphology of the pressure waveforms may enable the diagnosis of pericardial constriction or mitral regurgitation (Leurent et al., 2020). A PAC allows the administration of drugs and fluids into the central vein and some PAC types can also be used for pacing. Some versions of the catheters enable continuous CO (PAC-CCO) and SvO_2 monitoring while other specific versions allow the measurement of the right ventricular volume and ejection fraction (EF) (de Backer & Vincent, 2018).

There are several possible sources of error while using PAC, including timing of the measurements during respiration, the temperature and volume of the injectate, the rate of injection, and the presence of shunts and other cardiac abnormalities (Nishikawa & Dohi, 1993). McMillan and Morris stated that accuracy of the CO measurements cannot be enhanced by initiating injections at specific moments of the ventilatory cycle (McMillan & Morris, 1988). However, CVP, PAP and PCWP values should be read at the end of expiration (Bootsma et al., 2022). Neither CVP nor PCWP appear to be a useful predictor of preload when optimizing cardiac performance (Kumar et al., 2004; Osman et al., 2007). The pulmonary artery temperature typically decreases after CPB, which may lead to an underestimation of TDCO (Bazaral et al., 1992) and an error rate of 13%, even after three measurements, has been reported (Stetz et al., 1982). If the volume of the injectate is less than expected, the calculated CO will be falsely high (Nadeau & Noble, 1986). However, misinterpretation of the obtained data is probably the most common reason leading to complications (Jain et al., 2003). One must bear in mind that the monitoring systems are only measurement tools. When coupled with treatment protocols, the use of hemodynamic monitors may improve the patient outcome (Ramsingh et al., 2012).

2.3.2 Proper insertion and use of PAC

The PAC (Figure 1) is introduced during a sterile procedure via a central venous access through the right atrium and ventricle and floated into the pulmonary artery. It is recommended that ultrasound guidance be used for the venous puncture (Saugel et al., 2017). The right internal jugular vein (VJI) provides the most direct route into the right ventricle, and is therefore, the most used vein to insert a PAC (Whitener et al., 2014). Other possible accesses are the femoral and subclavian veins. During PAC insertion, the dynamic changes in the vascular pressure waveform measured from the catheter tip indicate the tip location (Figure 2).

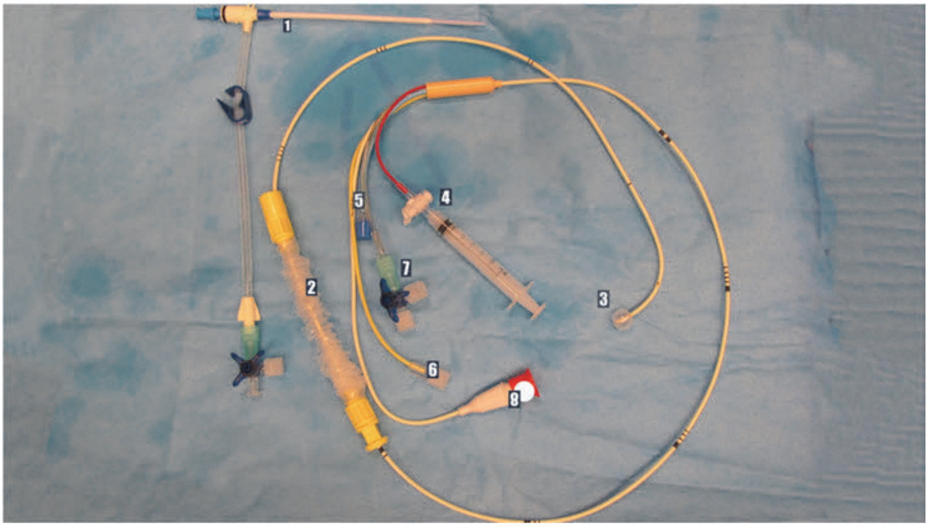

Fig. 1. Anatomy of the PAC. 1) Introducer sheath, 2) sliding sleeve with a locking mechanism, 3) balloon, 4) balloon inflation port, 5) proximal, blue, right atrial lumen, 6) distal, yellow, pulmonary artery lumen, 7) proximal infusion port and 8) thermistor port. Photo: Katriina Lanning.

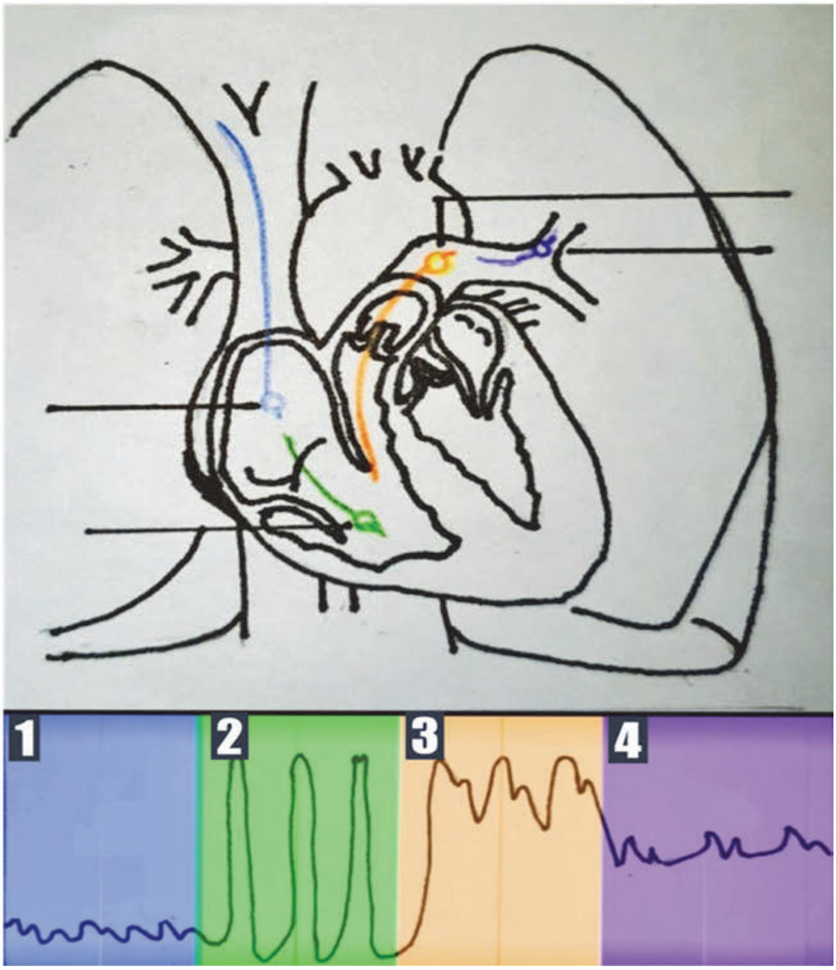

Fig. 2. The pressure waveforms during PAC insertion. 1) Central venous pressure, 2) right ventricular pressure, 3) pulmonary arterial pressure, 4) pulmonary capillary wedge pressure. Picture by Pipsa Naamanka. Modified with permission (Bootsma et al., 2022). This work is licensed under a Creative Commons Attribution 4.0 International License.

2.3.3 PAC- associated outcome

After more than fifty years of experience, there are still conflicting results concerning the usefulness of PAC in cardiac surgical and other critically ill patients. In the US, there were reductions in PAC use from 1993 to 2004 of 63% among surgical ICU patients and 65% among other ICU patients (Wiener & Welch, 2007).

In 2013, a Cochrane database systematic review article on the use of PAC in intensive care patients was published (Rajaram et al., 2013). The review included 13 studies with 5686 adult ICU patients and analyzed the effect of PAC on mortality, on ICU and in-hospital LOS, and costs. The conclusion was that PAC does not affect the mortality rate, nor does it influence the ICU or in-hospital LOS. Four of these studies, all in the US, reported higher average hospital expenses in the PAC group but overall, the use of PAC did not have an impact on the treatment costs of adult ICU patients.

In 2020, a retrospective multicenter study on 1414 patients in cardiogenic shock (CS) discovered that the use of PAC-derived hemodynamic data before the initiation of mechanical circulatory support, such as venoarterial extracorporeal membrane oxygenation (ECMO), was associated with lower mortality (Garan et al., 2020). A large retrospective cohort study by Hernandez et al included more than nine million patients either with existing heart failure (HF) or who developed CS during the hospitalization (Hernandez et al., 2019). They demonstrated that the use of a PAC is associated with improved outcomes in patients with CS. It was suggested that one reason for the positive results might be a more pertinent patient selection than earlier, or more appropriate use of the data to guide the therapies (Hernandez et al., 2019).

The use of PAC in cardiac surgical patients has also been studied. Some studies have even reported that using a PAC may worsen the outcome after cardiac surgery (Connors et al., 1996; Ramsey et al., 2000; Schwann et al., 2011). In 1996, a large, non-randomized multicenter study by Connors et al revealed an increased 30-day mortality associated with the use of PAC. Based on these studies, the use of PAC declined worldwide. In a retrospective study with 116,333 cardiac surgical patients, 40,036 of which had a PAC in place, Brovman et al discovered a decrease in blood transfusion rate by 75% in the PAC group. There were no significant differences in intraoperative mortality (Brovman et al., 2016). They concluded that the use of PAC remains the mainstay of cardiac anesthesia practice (Brovman et al., 2016). On the other hand, a review article by Joseph et al revealed an increased mortality rate in high-risk cardiac surgical patients who had a PAC, (12.2% vs 9.6%). In addition, an in-hospital LOS of >30 days was more common in the PAC group (Joseph et al., 2018). There was no difference in overall mortality, however, or in the number of complications between the groups. Still, they concluded that PAC should not be routinely used in low-risk patients undergoing cardiac surgery (Joseph et al., 2018). Ramsey et al published a retrospective study including 13,907 CABG patients, 58% of whom received PAC. After adjustment for confounding factors, they found a relative risk of in-hospital mortality of 2.1 (95% CI from 1.4 to 3.1) in the PAC group compared with patients without PAC. However, in patients with PAC, the severity of illness was greater by 7% (Ramsey et al., 2000). In a prospective observational multicenter study including 5065 patients, the use of PAC during CABG was associated with increased mortality (3.5% vs 1.7%) and morbidity (Schwann et al., 2011).

Taken together, even though the use of PAC has declined over the decades, there has been a trend in recent years towards a revival in its use. It seems that the PAC still has a place in the monitoring of severely ill patients. Therefore, adequate training for doctors and nurses should be provided to maintain the expertise necessary to benefit from the PAC use (de Backer et al., 2018).

2.3.4 PAC-related complications

The insertion of the PAC is a highly invasive procedure with several possible complications. Complications can occur during the central vein cannulation, while advancing the PAC, when the catheter is in residence, or during the removal of the catheter. The most common complications during the insertion are arrhythmias, which usually resolve spontaneously once the catheter lodges in the pulmonary artery (Senoner et al., 2022). However, a complete atrioventricular block can be a rare complication in patients with left bundle branch block (Senoner et al., 2022) and asystole has also been reported in case reports (Barbara & White, 2015; Chaudhuri et al., 2012).

The most feared complication related to the use of PAC is a pulmonary artery rupture. Fortunately, it is a very rare complication with an incidence of 0.031%, but the mortality rate is as high as 70% (Kearney & Shabot, 1995). The most common cause of the rupture is overinflating the balloon in the tip of the catheter, especially in the presence of pulmonary artery hypertension. Hemoptysis is a typical sign of the pulmonary artery rupture. A thoracotomy is often needed to repair the artery (Evans et al., 2009).

Other reported complications include pneumothorax and hemothorax, pulmonary artery thrombosis and pulmonary infarction, infection, and valvular damage. In addition, extravasation from the introducer sheath has been reported, leading to a lack of therapeutic drug effect, or even to a compartment syndrome (Evans et al., 2009). Complications arising from venous access, such as positive blood cultures during catheter use, were found equally as frequently with the central venous catheter and PAC (The National Heart, 2006). Subclavian access is associated with fewer infections in comparison with VJI or femoral accesses, but possible bleeding complications may have more serious consequences. However, arterial punctures seem to be more common with the VJI compared to the subclavian route, while a review article found no difference in the incidence of hemo- or pneumothorax among the groups (Ruesch et al., 2002). When ultra-sound guidance was routinely used for central venous access, the incidence of mechanical complications was 7.7%, of which 0.4% were major complications(Adrian et al., 2022). The variables found to be independently associated with major mechanical complication were: patient BMI <20 kg/m^2, male operator gender, limited operator experience, and more than one skin puncture (Adrian et al., 2022). Thrombotic complications have become rare after the development of heparin-coated catheters in the early 1980`s (Senoner et al., 2022) but, on the other hand, cases of heparin induced thrombocytopenia have been reported (Evans et al., 2009).

2.4 Minimally invasive cardiac output monitors

2.4.1 Overview of available technologies

The term minimally invasive CO monitor includes both noninvasive and mini-invasive devices. Many types of devices have been developed during the last decades, but PAC remains the gold standard for CO measurement and is used as a reference method for other devices (Peeters et al., 2015).

There are many different minimally invasive devices on the market utilizing divergent technologies. The pulse contour analysis monitoring technique assumes that stroke volume (SV), and therefore CO, can be continuously measured by analyzing the arterial pressure waveform obtained from an arterial line. The arterial pressure waveform is influenced by the interaction between SV, arterial compliance, aortic impedance, and peripheral arterial resistance (Alhashemi et al., 2010). All monitors using pulse contour analysis provide an automated quantification of stroke volume variation (SVV), and some of them also provide pulse pressure variation (PPV), both of which can be used to estimate fluid responsiveness (Alhashemi et al., 2010). Arrhythmias may decrease the accuracy of measurements and the use of an IABP prevents the accurate performance of these devices (Sundar & Panzica, 2010). The most frequently used pulse contour devices are the FloTrac/Vigileo (Edward Lifesciences, USA) device, the LiDCO (LiDCO Ltd., UK) monitoring system that is available as either an uncalibrated (LiDCOrapid) or a calibrated (LiDCOplus) device and the calibrated PiCCOplus (Pulse index Continuous Cardiac Output) system (Pulsion Ltd, Munich, Germany). The FloTrac/Vigileo system contains a FloTrac transducer which is connected to a standard arterial catheter and to the monitor. The PiCCOplus system utilizes a combination of trans-cardiopulmonary thermodilution and pulse contour analysis (Litton & Morgan, 2012). Consequently, the PiCCOplus requires both arterial and central venous cannulation which limits its use in clinical practice.

The continuous, totally non-invasive bioreactance method evaluates the pulsatile flow-induced frequency changes and phase shifts of the transthoracic voltage after delivering an oscillating current into the thorax (Sivakumar & Lazaridis, 2020). The NICOM device (Cheetah Medical, Portland, OR) is the first-generation device providing CO readings averaged over 30 seconds. The concern about its ability to track rapid changes in CO led to the development of the second-generation device Starling SV (Cheetah Medical, Newton, Massachusetts, USA), in which the averaging time of CO is reduced to 8 seconds (Sivakumar & Lazaridis, 2020).

The pressure-recording analytical method (PRAM) (Vygon, Vytech, Padua, Italy) is a technology that has some differences compared to other methods based on pulse contour analysis. The PRAM considers both the pulsatile and the continuous contribution of the physical forces when calculating the area under the arterial pressure curve (Romagnoli et al., 2017). The system samples the signal at a frequency of 1000 Hz instead of 100 Hz in other methods (Marik, 2013). Barile et al studied 59 unstable cardiac surgical patients postoperatively and found a good agreement of CI between PRAM and a PAC, but not, however in patients with atrial fibrillation (Barile et al., 2013).

The esCCO (Nihon Kohden, Tokyo, Japan) is an uncalibrated device using the Pulse Wave Transit Time (PWTT) technology to measure CO. This noninvasive device utilizes the information obtained with pulse oximetry and the ECG (Kobe et al., 2019).

Transesophageal echocardiography (TEE) is a clinical tool commonly used by cardiac anesthesiologists. Among other information, TEE allows the measurement of CO by non-Doppler or Doppler-based methods, the latter being commonly used in clinical practice. Doppler-based TEE has been shown to be a reliable tool for evaluating significant changes in CO (Parra et al., 2006). However, Graeser et al found wide LOA of −1.8 to 2.5 L/min and a PE of 55% between the Doppler-derived 3D TEE and TDCO (Graeser et al., 2018). Smaller devices utilizing an esophageal Doppler probe have also been developed, such as the ODM II (Abbott

Laboratories, North Chicago, IL). A meta-analysis of Doppler-derived CO monitors showed high validity for monitoring changes in CO in critically ill patients (Dark & Singer, 2004). In the studies included in this meta-analysis, however, most of the patients were hemodynamically stable. Furthermore, the accuracy of both TEE and esophageal Doppler are highly dependent upon the skills and experience of the operator (Alhashemi et al., 2010).

The NICO (Novametrix Medical Systems, Wallingford, CT) system uses a partial (CO_2) rebreathing technique based on the Fick principle to measure CO in intubated, mechanically ventilated patients. There are studies suggesting a poor agreement with TDCO (Nilsson et al., 2001; van Heerden et al., 2000). The NICO does not permit the monitoring of volume status or fluid responsiveness.

2.4.2 Comparison and validation of CO monitors

A CO monitor should be accurate and precise, and it should be able to track short-term changes in CO values reliably, (Joosten et al., 2017). The Bland-Altman analysis is the standard statistical method to evaluate the accuracy and precision of CO monitors, assessing how well the study method agrees with the reference method (Bland & Altman, 1986; Cecconi, Rhodes, et al., 2009). According to Bland and Altman, the bias against mean CO represents accuracy while the limits of agreement (LOA) describe precision (Bland & Altman, 1986). A bias of 0.5 L/min and LOA of ±1.0 L/min has been suggested to be acceptable when measuring CO in patients undergoing surgery with major hemodynamic disturbances (Montenij et al., 2016). The percentage error (PE) is also a measure of precision and is considered clinically acceptable if below 30% (Critchley & Critchley, 1999). The 4-quadrant plot with error grids is the preferred method to evaluate the trending ability of a CO monitor (Montenij et al., 2016). It plots the change of CO (ΔCO) measured with the study device against that of the reference method and uses the direction of change to determine the clinical concordance (Critchley et al., 2010).

2.4.3 The bioreactance method in cardiac surgery

The human thorax and thoracic content can be considered as an electric circuit with a resistor and a capacitor, which together create the thoracic impedance when an electric current is passed through the thorax (Kobe et al., 2019). A pulsatile flow is necessary to produce a phase shift in the transthoracic voltage. Most of the pulsatile flow passing through the thorax is from the aorta and should hence be closely related to CO (Jakovljevic et al., 2014). To produce the bioreactance signal, two dual-sensor pads are placed on the right side and two pads on the left side of a patient´s thorax. A low-amplitude high-frequency current is passed between the two outer sensors of each side, the inner sensors being the receiving electrodes (Mehta et al., 2021). The bioreactance monitor contains a highly sensitive phase detector that catches both the phase shift and the frequency modulations between the input and output voltage (Sivakumar & Lazaridis, 2020) which results in the bioreactance signal that is used to calculate the SV (Marik, 2013) (Figure 3).

There are only a few studies comparing the bioreactance devices with TDCO in cardiac surgical patients. Ylikauma et al compared the Starling SV to a PAC in 20 OPCAB patients (Ylikauma, Ohtonen, et al., 2021). They took 579 simultaneous CI measurements during surgery and postoperatively in the ICU up to the first postoperative morning. The Starling SV showed an acceptable mean bias of 0.13 L/min/m^2 (95% CI 0.07 to 0.18), but imprecision due to a wide LOA (–1.23 to 1.51 L min/m^2), and a high PE (60.7%). The trending ability, as assessed using the 4Q method, was poor (Ylikauma, Ohtonen, et al., 2021).

Cheung et al examined 50 OPCAB patients (Cheung et al., 2015). CO was measured using both NICOM and a PAC ten times during the operation, the first being right after the induction of anesthesia and the last one 5 min after the sternal closure. None of the measurements were performed during the side-clamping of the aorta (i.e., proximal anastomoses) or during the distal anastomoses when the heart is tilted. They used the Bland-Altman method to assess agreement and their conclusion was that the NICOM underestimates the high CO values of over 6 L/min and overestimates the values below 4 L/min. The correlation of CO between the two measurement methods, determined by linear regression, was found to be good (r=0.77). However, they did not evaluate the trending ability of the NICOM device with the 4-quadrant plot, as recommended in the literature (Critchley et al., 2010). They also reported that the PAC was inserted after the induction of anesthesia. Since the insertion of a PAC takes at least 15 min, the first CO measurements cannot be taken right after induction, as they stated. In addition, the study was limited only to the operating room and did not include postoperative measurements (Cheung et al., 2015).

Squara et al compared the NICOM system to continuous PAC-CCO in 110 cardiac surgery patients postoperatively (Squara et al., 2007). In total, they analyzed 65,888 pairs of CO measurements resulting in a bias of 0.161 L/min, LOA of ±1.04 L/min and a relative error of 9%. They also concluded that the NICOM can track changes in CO but again, the four-quadrant method was not used.

Furthermore, this study was performed with a PAC-CCO, which is not considered as a valid reference technique for measuring CO (Montenij et al., 2016). PAC-CCO enables continuous CO measurements by using a thermal filament which heats up the blood at random.

NICOM has also been compared with TDCO in 21 postoperative cardiac surgical patients during the first two hours in the ICU (Lamia et al., 2018). The ejection fraction (EF) of all the patients was >45%. The mean bias was –0.71 L/min but the LOA was wide at ±2.70 L/min, and the PE was 47%.

The bioreactance method also has various limitations. It is affected by the patient´s body size and temperature, presence of arrhythmias, pleural and pericardial effusions, and any possible movements on the part of the patient (Han et al., 2015; Kobe et al., 2019). The accuracy of CO is not good under varying hemodynamic conditions (Kobe et al., 2019).

To summarize, based on previous research the bioreactance method still has limitations concerning the agreement of the measured CO with TDCO, even in patients that are hemodynamically stable. In particular, the ability of this technology to assess trending values has not been adequately assessed.

Fig. 3. The bioreactance system Starling SV and its connection to the body. A high-frequency current is passed through the outer electrodes. The resulting voltages are recorded between the inner electrodes. The relative phase shift and rate of change between the signals are determined and used in the calculations. Photo by Katriina Lanning.

2.4.4 The pulse power analysis in cardiac surgery

The LiDCO system is a minimally invasive CO monitor requiring only an arterial line (Figure 4). CO measurement using the LiDCO system is based on the pulse power analysis, the theory behind which is that the fluctuations of blood pressure are directly related to SV and CO. The technique is based on the principle that the SV can be estimated by analyzing the arterial pressure waveform, which is affected by the interaction between the SV and vascular compliance, peripheral arterial resistance, and aortic impedance (Alhashemi et al., 2010). The originally introduced LiDCOplus needs to be calibrated using the transpulmonary lithium indicator dilution technique (Cecconi, Dawson, et al., 2009). The newer device, the LiDCOrapid is an uncalibrated version of the LiDCOplus. The LiDCOrapid continuously analyzes the entire pulse wave (i.e. systole and diastole) using an autocorrelation algorithm named the PulseCO system. The LiDCOrapid system provides both PPV and SVV and thereby helps to guide fluid treatment (Lee et al., 2011).

The reliability of the LiDCO system during cardiac surgery has been studied with conflicting results. Phan et al compared LiDCOrapid and TDCO in 15 elective cardiac surgical patients (Phan et al., 2011). They took 22 measurements of the change in CO after a fluid bolus of at least 250 ml. An increase in CO after the fluid bolus was reported in 41% of the LiDCOrapid and 82% of TDCO measurements. Their conclusion was that the LiDCOrapid should not be used interchangeably with a PAC to track the changes in CO. In another study on 24 cardiac surgical patients, the Bland-Altman analysis showed a bias of −0.17 and the LOA of −1.55 to 1.20 L/min for LiDCOplus compared with a PAC (de Wilde et al., 2007). The study by Mora et al compared LiDCOplus to TDCO in 30 patients with a left ventricular ejection fraction (EF) lower than 40%. They performed a total of 220 paired measurements during the first four hours after cardiac surgery and found an adequate accuracy and an overall PE of 27%, but the LOA were wide (−1.41−1.96 L/min) (Mora et al., 2011). Lamia et al compared LiDCOplus with PAC in 21 cardiac surgical patients during the first two postoperative hours and found an acceptable bias of –0.10 L/min with a wide LOA of ± 2.01 L/min and a PE of 35% (Lamia et al., 2018).

Severe vasoplegia with low systemic vascular resistance (SVR) and low CO are common complications of cardiac surgery, particularly in patients undergoing CPB (Barnes et al., 2020; Fischer & Levin, 2010; Lomivorotov et al., 2017). These complications may affect the reliability of all CO monitoring methods, but the

LiDCO system in particular has shown unreliability in measuring CO during decreased SVR (Costa et al., 2014; Yamashita et al., 2007). Yamashita et al studied 20 OPCAB patients and concluded that in the presence of decreased SVR, the LiDCOplus might underestimate CO compared to TDCO and is, therefore, not considered suitable for cardiac surgery (Yamashita et al., 2007).

The accuracy of the LiDCO algorithm may be compromised under many other circumstances, including aortic regurgitation, the use of an IABP, severe peripheral vasoconstriction, arteriovenous shunts, and arrhythmias. An over- or under-damped arterial waveform is also a potential source of error (Lee et al., 2011).

Accordingly, in previous literature, the pulse power analysis has consistently shown acceptable accuracy, but imprecision compared to TDCO. Since the technology is vulnerable to the types of hemodynamic interference (such as rapid changes in CO, need for vasoactive therapy, the function of the ventricles) commonly encountered during cardiac surgery, the trending ability of the LiDCO system should be further evaluated in cardiac surgical patients.

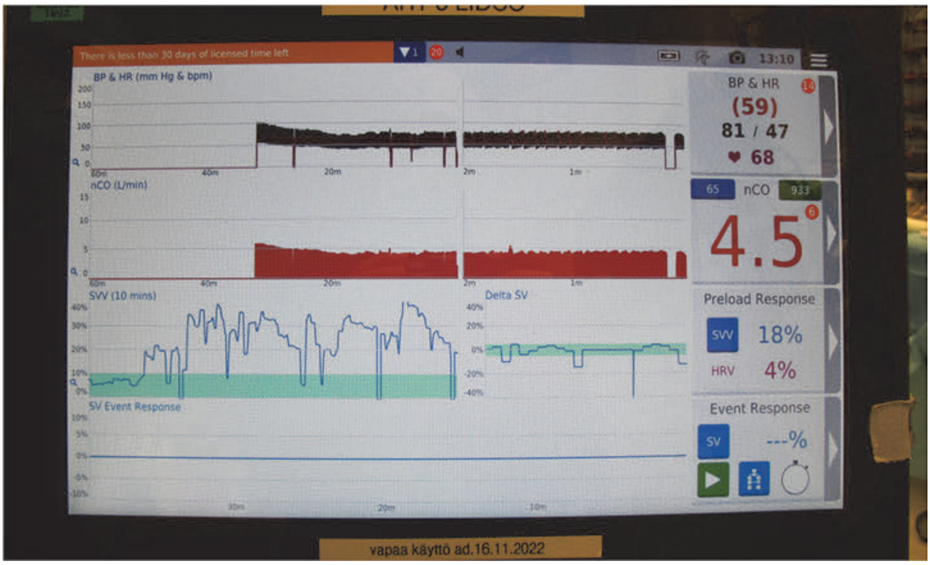

Fig. 4. LiDCOrapid monitor. Photo by Katriina Lanning.

2.5 Mixed venous oxygen saturation and central venous oxygen saturation

The main function of the cardiovascular system is to provide adequate oxygenation to the organs. Major surgery is associated with an increased risk of organ dysfunction, as well as with increased mortality and morbidity (Khuri et al., 2005). Patients with limited cardiovascular or respiratory reserves as well as emergency patients are at a higher risk for these adverse events (Khuri et al., 2005).

SvO_2 and $ScvO_2$ are used in clinical practice to determine the degree of systemic oxygenation, indicating the balance between the oxygen supply and demand. Both are commonly used as a target for GDT in high-risk surgery. SvO_2 represents the oxygen content of the blood returning to the heart after perfusing the entire body, while $ScvO_2$ rather reflects the upper body oxygen balance. When there is an imbalance between oxygen consumption and delivery, SvO_2 decreases and reflects an inadequacy in the systemic oxygenation. The oxygen consumption of organs is mainly independent of oxygen delivery (Hartog & Bloos, 2014). If the cardiovascular system cannot compensate for the increased oxygen demand and no more oxygen can be extracted, tissue hypoxia and lactate acidosis occur (Hartog & Bloos, 2014). The oxygen consumption in different organs varies from less than 10% in the kidneys to up 60% in myocardium (Hartog & Bloos, 2014). SvO_2 and $ScvO_2$ are directly related to CO, hemoglobin and arterial oxygen saturation. Interventions to increase venous blood oxygenation include fluid and blood transfusions, vasoactive agents, and means to decrease oxygen consumption, such as general anesthesia, mechanical ventilation, muscle relaxation and temperature maintenance. However, the capacity of these interventions to increase SvO_2 and $ScvO_2$ is limited.

Normal values for SvO_2 vary from 65% to 75% (Kandel, 1983). In healthy individuals, the blood in the superior vena cava has a lower oxygen content than in the inferior vena cava, since the kidneys receive a high portion of CO but utilize little oxygen (Barratt-Boyes & Wood, 1957; Reinhart & Bloos, 2005). Therefore, the oxygen saturation in the superior vena cava is also lower than in the inferior vena cava, resulting in a higher SvO_2 than $ScvO_2$. During shock and other critical illness, the oxygen extraction rate is higher than normal and the blood flow to the heart and brain is maintained while the blood flow to the kidneys and splanchnic region is reduced. Consequently, SvO_2 may be lower than $ScvO_2$ (Lee et al., 1972; Pikwer et al., 2008) in critically ill patients. Furthermore, the difference between SvO_2 and $ScvO_2$ values may vary interindividually (Sander et al., 2007). Therefore, a moderately altered $ScvO_2$ can be associated with markedly decreased SvO_2 values

(Sander et al., 2007). In septic shock, $ScvO_2$ values are imprecise in estimating SvO_2 values (Varpula et al., 2006). Of note, SvO_2 values are not reliable if there is a left-to-right shunt in the heart (Kandel, 1983).

SvO_2 samples are drawn from the PAC´s pulmonary line. As the use of PACs has declined in recent decades (Balzer et al., 2015; Harvey et al., 2005; Rajaram et al., 2013; Sandham et al., 2003), $ScvO_2$ obtained from the distal line of a central venous catheter is often used as a substitute for SvO_2. In a multi-center trial in high-risk surgery patients, perioperative low $ScvO_2$ values were associated with an increased risk of postoperative complications ("Multicentre Study on Peri- and Postoperative Central Venous Oxygen Saturation in High-Risk Surgical Patients," 2006). It has been shown in cardiac surgical patients that also supranormal (> 77-80%) $ScvO_2$ values are associated with increased morbidity and mortality, especially when combined with high lactate levels (Balzer et al., 2015; Perz et al., 2011). These high values may indicate that the tissue is not capable of extracting more oxygen (Bloos & Reinhart, 2005). In a prospective study with 20 cardiogenic or septic shock patients, Ho et al found that $ScvO_2$ overestimated SvO_2 by a mean bias of 6.9% and wide LOA (–5.0% to 18.8%). The difference between $ScvO_2$ and SvO_2 was more significant when SvO_2 was <70%. Their conclusion was that $ScvO_2$ and SvO_2 are not interchangeable in this patient group (Ho et al., 2010).

There are also studies suggesting that $ScvO_2$ and SvO_2 could be interchangeable. In a prospective study in 70 neurosurgical patients undergoing surgery in the sitting position, the exact numerical values of $ScvO_2$ and SvO_2 were not equivalent under varying hemodynamic conditions, yet the trends of $ScvO_2$ and SvO_2 were comparable. However, trending was analysed using correlation coefficients, which are not the recommended statistical tests in method comparison studies (Bland & Altman, 1999). In a study on 42 ICU patients, a good correlation between the $ScvO_2$ and SvO_2 was found using linear regression analysis (Tahvanainen et al., 1982). Reinhart et al compared 32 critically ill ICU patients, 29 of which both had a central venous catheter and a PAC with fiberoptic continuous SvO_2 and $ScvO_2$ measurements. They concluded that $ScvO_2$ values could replace fiberoptically measured SvO_2 values, especially if $ScvO_2$ is also continuously monitored. However, the presence of very low $ScvO_2$ values is probably indicative of even lower SvO_2 values (Reinhart et al., 2004).

2.5.1 SvO_2 and $ScvO_2$ in cardiac surgery

Since LCOS is a major determinant of adverse outcome after cardiac surgery (Ding et al., 2015; Maganti et al., 2005), adequate hemodynamic monitoring and subsequent therapy are essential to avoid organ failure and death (O'Connor et al., 1998; Vánky et al., 2007). SvO_2 is an important diagnostic and therapeutic tool in the successful management of cardiac surgical patients (Holm et al., 2011; Pölönen et al., 2000; Vincent et al., 2008). SvO_2 monitoring with PAC is considered a prognostic predictor in cardiac surgery patients (Holm et al., 2011; Kaakinen et al., 2022; Pölönen et al., 2000).

SvO_2 levels less than 60% at ICU admission after CABG were associated with a higher incidence of postoperative complications, such as AKI and perioperative myocardial infarction (Holm et al., 2011). In addition, the time on ventilator, ICU LOS, and 30-day mortality (5.4% vs 1.0%) were increased, and there was even a difference in the 5-year survival rate (81.4% vs 90.5%). In another study on 403 elective cardiac surgical patients, the median in-hospital LOS was shorter (6 vs 7 days) among patients reaching the targets of $SvO_2 > 70\%$ and lactate < 2 mmol/L within 8 hours after the surgery (Pölönen et al., 2000). There was no difference between the groups in the mean ICU LOS, but prolonged ICU stays were less common in patients who achieved these targets (Pölönen et al., 2000). In a retrospective study on aortic valve surgery patients, SvO_2 levels less than 58% at ICU admission were associated with increased postoperative mortality (Holm et al., 2010). In a retrospective study with 7064 cardiac surgical patients, SvO_2 values <60% at ICU admission and 4 hours later were associated with increased 30-day and 1-year mortality (Kaakinen et al., 2022).

In the cardiac surgical setting, there are only a few studies comparing $ScvO_2$ to SvO_2, especially during the course of both OR and the ICU stay. Lequeux et al assessed 15 cardiac surgical patients undergoing CBP (Lequeux et al., 2010). They used continuous fiberoptic catheters and collected 9267 pairs of measurements in the OR and during 24 hours postoperatively. The mean bias was high at 4.4% and the LOA were wide (–13.6 to 22.5%). Furthermore, the interindividual variability between $ScvO_2$ and SvO_2 values was large (Lequeux et al., 2010). In a prospective controlled study on 60 CABG patients, 300 $ScvO_2$ and SvO_2 sample pairs were compared under different hemodynamic conditions (Sander 2007). Blood samples were taken after the induction of anesthesia, 15 min after CBP, and 1, 6 and 18 h after ICU admission. They found that moderately decreased $ScvO_2$ levels (60−70%) can be associated with markedly altered SvO_2 values (Sander et al., 2007). In a prospective observational study, Lorentzen et al concluded that $ScvO_2$ and SvO_2 are not interchangeable. The overall bias between the measurements was acceptable at 1.9%, but in the subgroup of aortic valve replacement patients the bias was 6.4%. When peripheral arterial saturation was low (<92%) the bias was 10.7%, compared with 0.8% when saturation was at least 99%. Additionally, low hemoglobin and low CO increased the gap between SvO_2 and $ScvO_2$ (Lorentzen et al., 2008).

In conclusion, low postoperative SvO_2 is a recognized predictor of poor prognosis in cardiac surgical patients. Although $ScvO_2$ also reflects the hemodynamic changes during the perioperative period, its value as a marker of systemic oxygenation is still controversial.

2.6 Transcranial near-infrared spectroscopy

2.6.1 NIRS technology

NIRS is a light-based technology to measure rSO_2. The technique is based on a modification of the Beer-Lambert law for the measurement of the concentration of a substance according to its light absorption (Murkin & Arango, 2009). NIRS utilizes infrared light at an optical window of 690−900 nm, depending on the monitoring device, and passes through the skin and the bone to the underlying tissue. A change of optical properties of hemoglobin when it binds to oxygen and the change of absorption pattern for specific light wavelengths are the principles behind NIRS. It can be used at many measuring sites, such as the brain, muscles, paravertebral region and kidneys (Vretzakis et al., 2014). NIRS measurements do not require pulsatile flow such as pulse oximetry does, so it can also be used also during CPB.

Hemoglobin is a protein present in red blood cells. In oxygenated hemoglobin (i.e., oxyhemoglobin) the hemoglobin molecules are bound and saturated with oxygen molecules. Deoxygenated hemoglobin (i.e., deoxyhemoglobin) is the type of hemoglobin that is not bound to oxygen (Gell, 2018). Oxyhemoglobin formation occurs mainly in the pulmonary capillaries. When oxyhemoglobin reaches organs and tissues, it releases oxygen to the cells. In the near-infrared range of light, oxy- and deoxy-hemoglobin have different peak absorption wavelengths, and NIRS exploits this difference to estimate the oxygen balance of a tissue (Scheeren et al., 2012).

2.6.2 Overview of cerebral oximetry

Cerebral rSO_2 monitoring is performed by placing two NIRS pads on the patient´s forehead, one on the left and the other on the right side. NIRS monitors rSO_2 in the frontal and superficial cortical areas (Erdoes et al., 2018). The pads contain one near-infrared light source with two detectors, although the number of these can vary depending on the device. The light source is a LED (e.g. INVOS) or a laser (e.g. Fore-sight). The two detectors in the pads are placed at a short distance from each other. The detector closer to the light source records the measurements from the superficial layers of the forehead while the measurements from the more distal one originate from the brain. The value measured by the closer sensor is subtracted from the value recorded by the other sensor allowing for an estimation of cerebral rSO_2. In the cerebral cortex the venous blood is responsible for about 70%, the arterial blood for 25%, and the capillary blood for 5% of the vascular bed, and therefore cerebral rSO_2 mainly refers to venous blood. An increase in the venous blood volume of the brain, for instance due to venous congestion, leads to a decrease in rSO_2 (Paquet et al., 2008). Existing devices use similar technology but differentiate in the number of absolute values of wavelengths, in the number of light sources and detectors and in the computational algorithm

Table 2. Examples of commercial NIRS systems.

Device	Source of light	Wavelengths (nm)	Number of light sources/detectors
INVOS 5100C	LED	730, 810	1/2
FORE-SIGHT ELITE	Laser	690, 730, 770, 810, 870	1/2
NIRO 300	LED	735, 810, 85	1/3
SenSmart X-100	LED	730, 760, 805, 830	2/2
EQUANOX 7600	LED	730, 810, 880	2/2

NIRS, near-infrared spectroscopy; LED, light emitting diode

There is a wide variability in baseline cerebral rSO_2 values. The mean cerebral rSO_2 prior to the induction of general anesthesia was 62.01% ± 10.38% among breast cancer or inguinal hernia patients (Valencia et al., 2015). Values of 55−60% or even lower are common in cardiac surgical patients (Subramanian et al., 2016). There is no consensus on which rSO_2 values represent a clinically important threat to cerebral oxygenation. However, widely used desaturation thresholds are a >20% reduction from the baseline value, or an absolute value of < 50% (Murkin & Arango, 2009). These values have mostly been derived from older data on patients undergoing carotid endarterectomy with actual cerebral ischemia. Importantly, due to the wide intra- and interindividual variability, NIRS should rather be considered as a trending monitor than an absolute oxygen saturation measurement (Bickler et al., 2013; Henson et al., 1998).

Transcranial NIRS has some limitations in the assessment of cerebral oxygenation. It only reflects oxygen saturation in a small superficial region of the frontal lobes. The amount of water, skin pigment, cytochromes and bilirubinemia may affect NIRS values (Davie & Grocott, 2012; Murkin & Arango, 2009). An epi- or a subdural hematoma and brain edema also limit the value of rSO_2 assessment. A strong external source of light in the operating room can disturb signal detection. Elderly patients may have cerebral cortex atrophy, which can reduce the reliability of transcranial NIRS values. Norepinephrine and other vasoconstrictors can induce skin vessel vasoconstriction, which may influence the measurement of rSO_2 (Murkin, 2013). Grocott and Davie demonstrated that scalp contamination can be responsible for even a 17% saturation change in the NIRS signal, although the newer generation devices can avoid this contamination much better (Grocott & Davie, 2013). Caccioppola et al examined 20 healthy volunteers and 20 brain-dead patients with ultrasound tagged NIRS monitors to measure the cerebral flow index (CFI) which is a parameter related to the changes in CBF (Caccioppola et al., 2018). The median CFI value of the brain-dead patients was 41(36−47) while that of the healthy volunteers was 33 (27−36), indicating significant extracranial contamination of NIRS values.

2.6.3 Cerebral oximetry in cardiac surgery

The weight of the adult brain is about 2% of the entire body weight but accounts for approximately 20% of the total body oxygen consumption, and for 15−20% of CO (Kirkness, 2005). Neurological postoperative complications, such as delirium and stroke, are common among cardiac surgical patients (Hogue et al., 2006; Selnes et al., 1999), who are at risk for neurological complications related to cerebral hypoxia. However, hyperoxia has also been shown to increase the incidence of postoperative delirium (Lopez et al., 2017). To reduce the risk of neurological complications in cardiac surgery, the cerebral rSO_2 has been of the highest interest. NIRS is used to detect ischemic events and guide interventions to improve cerebral oxygen balance and, therefore, avoid complications. There are many studies on neurological outcome and NIRS in the setting of cardiac surgery, but with conflicting results (Holmgaard et al., 2019; Momeni et al., 2019; Tian et al., 2022). In a meta-analysis of randomized controlled studies, Hogue et al state that there is insufficient evidence at present to support or refute whether interventions for cerebral oxygen desaturations during surgery improve neurological outcomes (Hogue et al., 2021). Yet, as over 50% of strokes occur postoperatively after an initial uneventful recovery, postoperative ICU care should perhaps also aim at optimizing the cerebral oxygen balance (Hogue et al., 1999).

A study by Heringlake et al demonstrated that the baseline cerebral rSO_2 values were independently associated with mortality and morbidity in cardiac surgical patients (Heringlake et al., 2011). Subramanian et al (Subramanian et al., 2016) studied 235 CABG or valvular surgery patients and reported a mean baseline rSO_2 of 61% (99%CI 57−65%). After separation from the CPB the mean rSO_2 was 56% (99%CI 53-60%) and upon arrival to the ICU it was 61% (95% CI 59−63%) (Subramanian et al., 2016).

Blood flow is autoregulated not only in the brain, but also in the kidneys to satisfy the metabolic needs of the organ. Cerebral autoregulation is an individual trait, which leads to challenges when targetting adequate MAP during and after cardiac surgery. CBF autoregulation can be monitored by NIRS and MAP. Cerebral autoregulation monitoring may provide information with regards to individual MAP targets and the optimization of cerebral blood flow (Brady et al., 2010; Nakano et al., 2021). In patients with low cerebral rSO_2, the oxygen perfusion of other organs may also be low (Balci et al., 2018). In a retrospective study of 45 CABG patients by Balci et al, postoperative AKI developed in 12 patients, and their cerebral rSO_2 levels were significantly lower than in patients without AKI (Balci et al., 2018). Cioccari et al have shown that after cardiac surgery on CPB, the rSO_2 values of most patients are below the baseline values for up to seven postoperative days, which is not seen in non-cardiac surgical patients (Cioccari et al., 2021). Regrettably, they did not include OPCAB patients for comparison.

Particularly during aortic surgery, aortic and venous cannula malposition may induce a sudden drop in rSO_2. The adequacy of selective antegrade cerebral perfusion can be confirmed with NIRS. NIRS can also act as a first alert of a failure in oxygen delivery into the CPB circuit or warn about the failure to start normal ventilation after CPB (Zheng et al., 2013). During peripheral VA-ECMO the differential hypoxia syndrome (i.e., the so-called Harlequin syndrome) may be detected by cerebral NIRS monitoring (Pozzebon et al., 2018). It has also been shown that cerebral desaturation is an independent predictor of hospital mortality during ECMO support (Pozzebon et al., 2018).

The means to raise rSO_2 are limited. Commonly used interventions to optimize rSO_2 include increasing all the following: the inhaled oxygen concentration (FiO_2), the partial carbon dioxide pressure of arterial blood ($PaCO_2$), MAP, CO, and hemoglobin (Denault et al., 2007). Increasing FiO_2 and hemoglobin increases the oxygen content of arterial blood. One should bear in mind, however, that inappropriate blood transfusions are associated with increased morbidity in cardiac surgical patients, e.g. infections, atrial fibrillation and stroke, and prolonged in-hospital LOS (Dorneles et al., 2011; Scott et al., 2008). Cerebral blood flow (CBF) can be improved by increasing CO, MAP and $PaCO_2$. However, if the CBF exceeds what is necessary for optimal cerebral metabolism during CPB, it can increase the delivery of CPB related air bubbles and particulates into the cerebral circulation (Denault et al., 2007).

In conclusion, the trends of cerebral rSO_2 permit the early detection of cerebral hypoxia and can aid in guiding therapy to restore oxygen balance. Transcranial NIRS provides continuous insight into the cerebral rSO_2, and it therefore serves as a first-alert indicator of intraoperative events that may affect patient outcome (Vretzakis et al., 2014). The brain can be considered as an indexing organ which reflects the adequacy of oxygenation in other vital organs.Cerebral rSO_2 monitoring in CABG patients helps to avoid profound cerebral desaturation and is associated with a significantly lower incidence of major dysfunction (Murkin et al., 2007). It has also been suggested, however, that once the brain desaturation occurs it is likely that other tissues have been desaturated long before, as cerebral oxygenation is maintained at the expense of other organs during CPB (Boston et al., 2001).

2.6.4 Comparison of rSO_2 and SvO_2

SvO_2 as drawn from the pulmonary artery line of PAC reflects the systemic oxygen balance and its use for GDT has been shown to improve outcome after cardiac surgery (Pölönen et al., 2000). Since inserting PAC is an invasive procedure, it is not commonly used in a routine non-cardiac anesthesia setting. Transcranial NIRS offers an option for the non-invasive and continuous determination of the cerebral oxygen balance, and the data available suggest that cerebral rSO_2 also reflects the balance of systemic oxygen supply and delivery (Heringlake et al., 2011).

Several groups of investigators have studied the relationship between cerebral NIRS and SvO_2 in cardiac patients with conflicting results (Dullenkopf et al., 2007; Guan et al., 2018; Schön et al., 2011). Dullenkopf et al studied 35 cardiac surgical patients postoperatively in the ICU. Their main finding was that the NIRS cannot replace SvO_2 (r=0.33) or the other monitored parameters of systemic oxygenation, but it had an acceptable sensitivity to detect changes in SvO_2 (Dullenkopf et al., 2007). As all patients were hemodynamically stable, these results cannot be applied to unstable patients.

In another study by Schön et al, 26 cardiac surgical patients were assessed postoperatively after extubation (Schön et al., 2011). They used Pearson's correlation coefficient and the Bland-Altman analysis for their comparison of rSO_2 and SvO_2 values. The patients were assessed twice, with and without supplemental oxygen via a face mask. During the supplemental oxygen administration, SvO_2 and rSO_2 showed a correlation coefficient of r=0.85, a bias of –2.5%, the LOA of –14.2 to 9.2%, and a PE of 17.2%. Without oxygen, the corresponding values were r=0.77, a bias of –2.0%, the LOA –15.0 to 10.9% and PE of 20.3%, respectively. The difference between SvO_2 and rSO_2 was smaller in the low range of SvO_2. Their conclusion was that in their hemodynamically stable awake patients, rSO_2 measurements were sufficiently representative of the SvO_2 levels (Schön et al., 2011).

Guan et al studied 56 elective OPCAB patients. They recorded rSO_2 and SvO_2 at five time points during surgery. MAP, CVP, PAP, CO, partial pressure of oxygen /FiO_2, $PaCO_2$, and hemoglobin concentration were also recorded at these time points. There was a positive correlation between rSO_2 and SvO_2 at each time point (r=0.70−0.92). They also discovered that a change in FiO_2 simultaneously influenced rSO_2 and SvO_2 values, and the variation trend of rSO_2 and SvO_2 was consistent (Guan et al., 2018).

Paarman et al studied twenty patients undergoing transapical transcatheter aortic valve implantation (TA-TAVI). They analyzed six pairs of SvO_2 and rSO_2 values in different hemodynamic states during the operation and found a good correlation. The correlation coefficients varied from 0.5 to 0.84 depending on the time point. They also used the Bland–Altman analysis for method comparison and the PE varied from 12.3% to 23.1%. A drop in rSO_2 reflected a drop in SvO_2 (Paarmann et al., 2012). The same group has also released a case report on a TA-TAVI patient with cardiopulmonary resuscitation (Paarmann et al., 2010). During the initial cardiovascular collapse, continuous SvO_2 and rSO_2 decreased concomitantly from around 70% to a minimum of around 30% while during resuscitation they both increased back to levels about 50% (Paarmann et al., 2010).

Marimón et al assessed twenty postoperative pediatric cardiac surgical patients and found a moderate but statistically significant correlation between the absolute values of rSO_2 and $ScvO_2$. Of note, the blood samples were obtained from the superior vena cava instead of the pulmonary artery (Marimón et al., 2012).

In Table 3, the reliability of the cerebral rSO_2 as a substitute parameter of systemic oxygen balance is shown, but these findings are somewhat controversial due to the low number of the patients in the published data.

Table 3. Correlation between rSO_2 and SvO_2.

Author/year	Patients/number of sample pairs	Setting	Study design	Results	Conclusion
Dullenkopf/ 2007	35/172	ICU	Prospective	fair-to-moderate correlation, r=0.33	rSO_2 cannot replace SvO_2
Schön/ 2011	26/52	ICU	Prospective	sufficient correlation, r=0.77−0.85	rSO_2 represent SvO_2 in stable patients
Paarman/ 2012	20/120	TA-TAVI	Prospective	moderate-to-close correlation, r=0.5−0.83	rSO_2 correlates with SvO_2
Marimón/ 2012	20/ continuously 630 hours	Pediatric/ICU	Prospective	moderate correlation, r=0.58	$ScvO_2$ or NIRS can be chosen
Guan/ 2018	56/280	OPCAB	Prospective	moderate to strong correlation r=0.70−0.92	rSO_2 adequately reflects SvO_2,

rSO_2, regional tissue oxygenation; CI, cardiac index; ICU, intensive care unit; TA-TAVI, transapical transcatheter valve implantation; OPCAB, off-pump coronary artery grafting; r, correlation coefficient.

2.6.5 rSO_2 and cardiac function

In addition to the arterial oxygen content, cerebral oxygenation is also dependent on the cardiopulmonary function of the patient. Accordingly, reduced cardiac performance is associated with lower rSO_2 values (Vretzakis et al., 2014). In the study by Madsen et al in normotensive patients with acute heart failure and neurological symptoms, baseline rSO_2 was low while successful treatment increased not only the rSO_2 values but also the well-being of the patient (Madsen et al., 2000). They evaluated three study groups: patients with acute heart failure and cerebral symptoms, patients with predominantly a rheumatic or a skin disease, and healthy volunteers, for whom respective baseline rSO_2 values were 34% (19−58), 65% (55−78), and 75% (59−91). When the acute heart failure patients were treated with oxygen, furosemide and nitroglycerine and were seated, their rSO_2 values increased to 50% (19−58), and their cerebral symptoms were relieved. One patient with a rSO_2 of 19% died (Madsen et al., 2000).

In a retrospective study of Paquet et al, the rSO_2 values were associated with cardiac function as assessed by transesophageal echocardiography (Paquet et al., 2008). They also discovered that rSO_2 was superior to hemodynamic parameters in predicting left ventricular dysfunction. However, no significant correlation between the baseline rSO_2 and CI values was found (Paquet et al., 2008).

Al-Subu et al examined the correlation between rSO_2 and CI in pediatric cardiac surgical patients. They retrospectively evaluated 10 patients with a median age of 14 years admitted to a pediatric cardiac ICU after heart transplantation surgery. They recorded rSO_2 and CI once an hour and found only a weak correlation (r=0.14). Their conclusion was that cerebral rSO_2 may not be an accurate indicator of CI in pediatric cardiac surgical patients (Al-Subu et al., 2018). However, only the absolute values, and not the changes in CI and NIRS, were studied. Another study in 29 pediatric heart-transplant patients undergoing myocardial biopsy reported a modestly significant correlation coefficient of 0.45 between cerebral NIRS and CI. Of note, these patients were hemodynamically stable (Bhutta et al., 2007).

During exercise, the oxygen demand of muscle cells increases up to 15 times greater than during rest. To meet this sudden demand, the blood flow to the muscles must increase. If CO cannot be adequately increased, it may subsequently lead to hypoperfusion of other organs. Koike et al studied cerebral oxygenation during exercise-testing using a cycle ergometer in 33 patients with valvular heart disease and in 33 healthy volunteers (Koike et al., 2004). rSO_2 decreased during exercise in patients with valvular disease whose CO failed to increase. They concluded that rSO_2 during exercise is dependent on the function of cardiovascular and pulmonary systems (Koike et al., 2004).

Taken together, there is insufficient evidence in the current literature to draw definitive conclusions as to any possible association between rSO_2 and CI (Table 4).

Table 4. Correlation between rSO_2 and CI.

Author/year	Patients/number of sample pairs	Setting	Study design	Results
Bhutta/2007	29 children/ 58	Cath lab	Prospective	Significant correlation, r=0.45
Paquet/2008	99 adult/ 99	Cardiac surgery/ OR	Retrospective	Weak correlation, r=0.12
Al-Subu/2018	10 children/ 410	Heart transplant/ICU	Retrospective	Weak correlation, r=0.104

rSO_2, regional tissue oxygenation; CI, cardiac index

3 Aims of the study

The general aim of this study was to evaluate whether CI measurements based on pulse power analysis or transthoracic bioreactance, $ScvO_2$ values, or transcranial NIRS values provide adequate information when compared to measurements obtained with PAC for the hemodynamic assessment of adult cardiac surgical patients. The more specific aims of the present study are as follows:

1. To compare the accuracy, precision, and trending ability of noninvasive bioreactance-based Starling SV and mini-invasive pulse power device LiDCOrapid to the bolus TDCO technique with PAC when measuring CI in the cardiac surgical setting with CPB.
2. To determine whether $ScvO_2$ measurements could be used interchangeably with SvO_2 measurements in adult cardiac surgical patients.
3. To determine whether changes in transcranial NIRS values reflect changes in CI in adult cardiac surgical patients.

4 Patients and methods

4.1 Patients

In study I, we included 20 patients undergoing elective or urgent cardiac surgery with CPB between March and June 2019 at the Oulu University Hospital. The population of study II consisted of 85 consecutive adult cardiac surgical patients at the Oulu University Hospital who had surgery between March and August 2020. Study III was a post-hoc analysis comprising 124 cardiac surgical patients from three prospective method comparison studies at Oulu University Hospital between March 2018 and August 2020. None of the studies included emergency cases. In studies I and III, the only exclusion criteria was the refusal by the patient to participate in the study. In study II, an atrial septal defect with left-to-right shunting was an additional reason for exclusion in addition to patient refusal.

Table 5. Demographic data of studies I-III.

Demographic	Study I	Study II	Study III
Age/years	66 (58−68)	65 (59−71)	66 (59−70)
Gender male	15 (75)	70 (82.4)	102 (82.3)
BMI kg/m^2	27 (24−29)	27 (24−30)	27 (24−30)
EF>50%	18 (90)	64 (75.3)	97 (78.2)
EF 31-50%	1 (5)	20 (23.5)	23 (18.5)
EF 21-30%	1 (5)	1 (1.2)	4 (3.2)
EuroSCORE II, %	1.4 (0.89−2.50)	1.6 (1.1−2.6)	1.6 (1.0−2.6)
Elective surgery	14 (70)	46 (54.1)	69 (55.6)
Urgent surgery	6 (30)	39 (45.9)	55 (44.4)
ICU length of stay	2 (1−2)	1 (1−2)	1 (1−2)

The values given are medians with 25th and 75th percentiles, or number of patients (n) with percentages (%). BMI, body mass index; EF, ejection fraction; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II

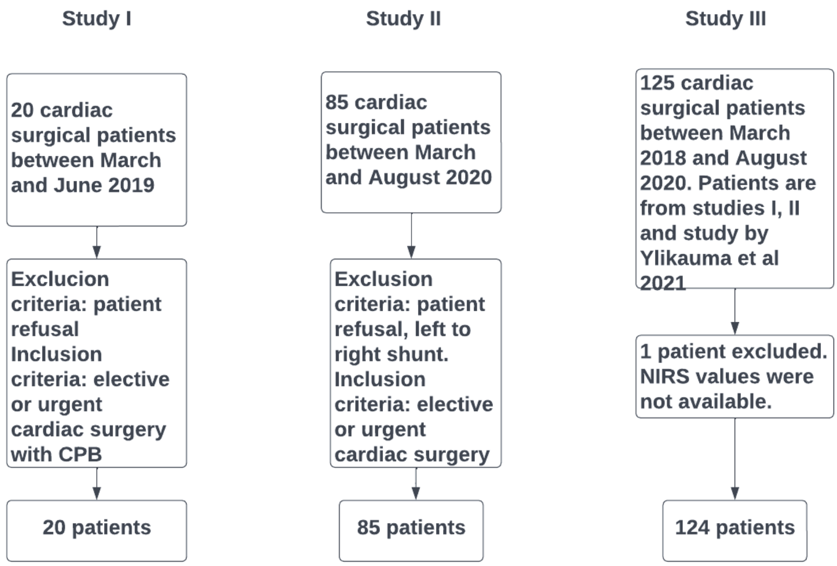

Fig. 5. Flowchart of the studies I-III.

4.2 Methods

4.2.1 Anesthesia

All patients were premedicated with oral diazepam and intramuscular morphine one hour before entering the OR. Anesthesia was induced with intravenous infusions of propofol and remifentanil, and a single dose of rocuronium was administered to facilitate tracheal intubation. Sevoflurane and remifentanil infusion were used to maintain general anesthesia and analgesia. In most cases, these were combined with a low dose propofol infusion. The patients were transferred to the ICU after the surgery under propofol and remifentanil infusions. Later in the ICU, remifentanil infusion was replaced with intravenous oxycodone as boluses or an infusion. The patients were extubated after emerging from sedation according to local fast-track principles.

4.2.2 Monitoring

After arrival to the OR, an arterial line was placed into the radial or brachial artery (BD Arterial Cannula 20G, Becton Dickinson and Company, Franklin Lakes, New Jersey, USA). A PAC (Criticath SP5507U TD Catheter, Merit Medical, South Jordan, Utah, USA) was inserted before the induction of anesthesia via an 8.5F sheath placed in the right internal jugular vein. Two NIRS sensors were placed on the patient´s forehead; the INVOS^{TM} (Somanetics/Covidien, Inc., Boulder, CO) monitor was used. Additionally in study I, LiDCOrapid (LiDCOrapid V2.03−318, LiDCO, London, UK) was connected to the arterial line and the patient monitor (Carescape B850 Monitor, GE Healthcare, Chicago, Illinois, USA) and four dual-electrode sensors of Starling SV (CMM-ST5, 2017-12-01, version 5.2, Cheetah Medical, Newton, Massachusetts, USA) were placed on the patients back. All patients underwent TEE after the induction of anesthesia.

4.2.3 Data collection

In study I, simultaneous CI measurements with PAC, LiDCOrapid and Starling SV were taken at least every 30 minutes prior to and after CPB. In the ICU, these measurements were performed at least once per hour before extubation, and at least every 3 hours after extubation until the first postoperative morning. At least three TDCO injections were performed for each CI measurement, using 10 ml 0.9% saline bolus injections at room temperature. TDCO measurements were not synchronized with the respiratory cycle. After careful inspection, all unreliable thermodilution curves were rejected. The Starling SV was automatically calibrated at the beginning of the monitoring session, and an additional manual calibration was performed every time the position of the patient or the heart was significantly altered, or if the signal became unreliable. The LiDCOrapid was calibrated with the reference method TDCO at the start of the monitoring session and upon arrival to the ICU. The data were divided into four phases. The first phase was before CPB, and the second phase after CPB. The third and the fourth phases were in the ICU, before and after extubation. The TDCO and LiDCO rapid data were collected from the electronic patient record systems and the Starling SV data from its own database.

In study II, the blood samples for SvO_2 and $ScvO_2$ measurements were obtained from the distal pulmonary artery line and the proximal central venous line of the PAC, respectively. We drew three sample pairs in the OR and four pairs in the ICU, resulting in a total of 590 sample pairs. In the OR the sample pairs were drawn before and after the induction of anesthesia and 15 minutes after protamine administration. In the ICU, the samples were taken immediately after admission, four hours postoperatively, at midnight, and on the first postoperative morning. The samples were analyzed for blood gases and venous saturations with a GEMPremier 4000 (Instrumentation Laboratory, Bedford, MA) blood gas analyzer.

In study III, the electronic anesthesia record was used to collect post-hoc data. NIRS values, arterial oxygen saturation, $etCO_2$, and MAP were collected simultaneously with each CI measurement. Several measurements were taken in each patient during surgery. No data was collected from the postoperative ICU period.

4.2.4 Statistical analysis

The summary statistics are given as medians with 25^{th} and 75^{th} percentiles, or numbers of patients (n) with percentages (%) unless stated otherwise.

In study I, we calculated the sample size for an equivalence study and considered the data structure with multiple independent measurements within the subject (Julious, 2004). We used data from our previous study, in which the mean CI was 2.4 with TDCO and 2.2 with Starling SV (Ylikauma, Ohtonen, et al., 2021). Type I error was set at 0.05 and power at 0.90. The standard deviation of differences was 0.7 and the noninferiority margin 0.36, resulting in a sample size of 414 measurements. We used the Bland-Altman method to calculate the mean bias between the CI measurements to evaluate the accuracy of the devices, combined with the LOA with 95% CI to assess precision (Montenij et al., 2016). The data structure with multiple independent measurements within the subject was considered when calculating the LOA, using the method in which the true value varies (Bland & Altman, 1999; Montenij et al., 2016). The PE with 95% CI was calculated to further describe the precision. Based on previous literature, the predefined targets for acceptable bias, LOA and PE were set at 0.25 L/min/m^2, 0.5 L/min/m^2, and 30%, respectively (Critchley & Critchley, 1999; Montenij et al., 2016). To assess trending ability, both Starling SV and LiDCOrapid were plotted against TDCO in the 4Q plot consisting of two consecutive CI measurements. The exclusion zone was set according to previous literature (Critchley et al., 2010; Montenij et al., 2016). Based on the clinical concordance categories of the 4Q plot, error grids were constructed to create four zones to determine the level of agreement between the changes in CI measured with TDCO and each of the study devices. In zone 1, the CIs have changed in the same direction to the same extent, or in other words, both have changed less than 5%, 5% to 15%, or more than 15%, leading to uniform treatment decisions. In zone 2, they have changed in the same direction but not to the same extent, possibly inducing insufficient or exaggerated treatment. In zone 3, only one measured CI value has changed, implying that unnecessary treatment may be initiated or necessary treatment withheld. In zone 4, the changes have been opposite, leading to incorrect treatment decisions.

To assess a proper sample size for study II, we collected preliminary data from 35 patients, gaining 245 samples. From this data, we performed the sample size calculation for an equivalence study, in which the mean SvO_2 and $ScvO_2$ were 74.4 % and 72.9% respectively. The results were as follows: standard deviation of differences 7.5, noninferiority margin 5, alpha 0.05, and beta 0.10 (power 0.9) giving a sample size of at least 541 measurements. We used the Bland-Altman method to calculate the mean bias between the SvO_2 and $ScvO_2$ measurements and the LOA with 95% CI. The PE with 95% CI was also calculated. The trending ability was assessed with 4Q plots of two consecutive venous saturation measurements, with the exclusion zone set at 3%. To evaluate clinical concordance, error grids were created as described above.

A power analysis of the post-hoc data was not performed in study III. CI values were compared with the means of right- and left-sided rSO_2 readings. A hierarchical linear regression model with the patient as a random effect was used to assess the association of the changes in CI from baseline and the previous value with those of rSO_2. We calculated a crude model with the mean rSO_2 as the only variable, and an adjusted model, where MAP, $etCO_2$ and arterial oxygen saturation were used as adjusting factors. We used multiple methods of analysis to understand their impact on the regression coefficients. Due to the exploratory nature of the study, with its focus on regression coefficients, no adjustment for multiplicity was conducted. We present the regression coefficients with 95% CI and two-tailed p-values as a result from the regression model.

The sample calculation for studies I and II were performed using MedCalc for Windows (version 20, MedCalc Software, Ostend, Belgium). All other analyses in studies I-III were performed with the statistical programs SAS (version 9.4 SAS Institute Inc., Cary, NC, USA) and SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp).

4.2.5 Ethical considerations

Studies I and II were single-center prospective observational studies, whereas study III was a post-hoc analysis of prospectively collected data from studies I, II, and a third method comparison study of our group (Ylikauma, Ohtonen, et al., 2021). All the studies were approved by the Ethics Committee of the Northern Ostrobothnia Hospital District (I: 56/2018; II, III: 17/2020, III: 66/ 2017). After written and oral informed consent was obtained from the patients for studies I and II, they were included in the study. The patients were not exposed to superfluous invasive procedures due to the study protocols, as an arterial cannula and a PAC are routinely used to monitor all cardiac surgical patients in our hospital. In addition, cerebral NIRS is always used during cardiac surgery. In study I, Starling SV and LiDCOrapid were used as additional monitors. LiDCOrapid was connected to the arterial line and no additional lines were required. There were no side effects concerning the Starling SV pads. More blood was drawn from the patients in study II due to the additional blood samples required, but the overall volume needed was considered clinically insignificant. Importantly, hemodynamic management was not specified in the protocols of studies I-II but was always based on the clinical judgement of experienced cardiac anesthesiologists and ICU specialists. Moreover, clinical decisions were based on TDCO and SvO_2 and not on CI values measured with the study I devices nor on $ScvO_2$ values.

5 Results

5.1 Study I

Study I included twenty patients who underwent elective (14) or urgent (6) cardiac surgery with CPB between March and June 2019. Of the patients, 4 (20%) underwent CABG, 5 (25%) single aortic valve surgery and 5 (25%) single mitral valve surgery. In addition, 4 (20%) patients underwent a combined procedure, and one patient underwent descending aortic surgery. Of the patients, 15 (75%) were male, and the median age of the patients was 66 years (58-68). The EF was normal in 18 (90%) patients, while it was 21−30 % in one patient (5%). None of the patients died during the hospital stay. There were no PAC-associated complications.

498 measurements pairs with TDCO and Starling SV and 444 pairs with TDCO and LiDCOrapid were collected. The median number of measurements pairs per patient was 25. In the 4Q plot, there were 470 and 396 delta CI measurement pairs when comparing TDCO with Starling SV and LiDCOrapid, respectively. Considering all measurement points, Starling SV (Figure 5a) and LiDCOrapid (Figure 6a) were associated with biases of 0.43 L/min/m^2 (95% CI 0.37−0.50) and 0.22 L/min/m^2 (95% CI 0.16–0.27), respectively, while the respective LOAs were –1.07 to 1.94 L/min/m^2 and –0.93 to 1.43 L/min/m^2. The PEs of Starling SV and LiDCOrapid were 66.3% and 53.2%, respectively. Figures 5b and 6b show the 4Q plots plotting the changes in CI measured by Starling SV or LiDCOrapid and TDCO plotted against each other. The error grids based on the 4Q plots demonstrate that the level of agreement in trending was 26% in zone 1 for Starling SV and 39% in zone 1 for LiDCOrapid. Considering all measurement points, the regression coefficients were 0.14 L/min/m^2 and 0.00 L/min/m^2 for Starling SV and LiDCOrapid respectively.

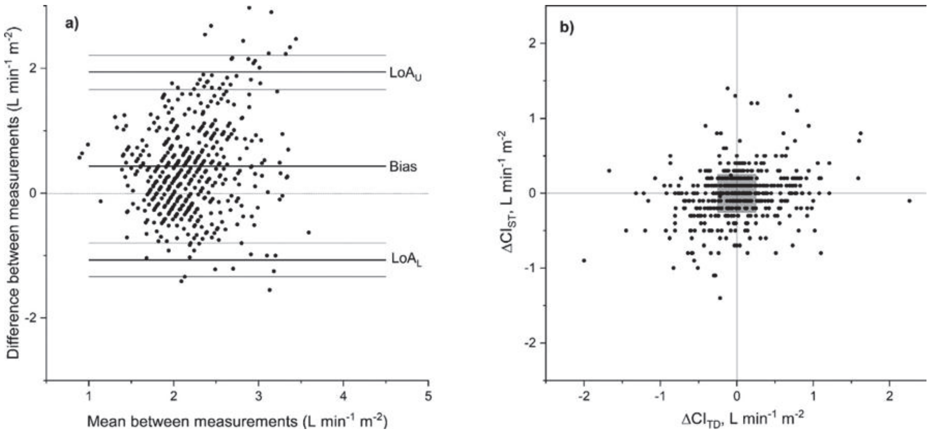

Fig. 6. (a) The Bland-Altman plot for CI measured with TDCO and Starling SV at all measurement points. The lines for bias, LOA, and 95% CIs of LOA are shown. (b) The 4Q plot showing the trending ability of Starling SV by plotting the change of consecutive CI measured with Starling SV and TDCO. (Ylikauma, Lanning, et al., 2021)

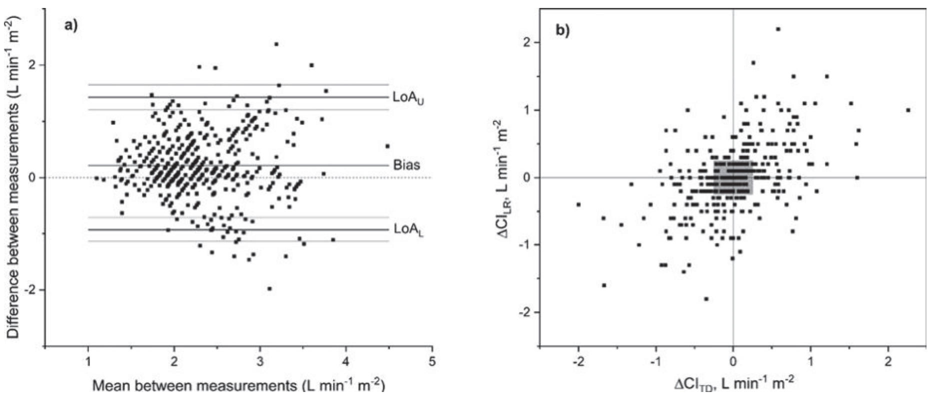

Fig. 7. (a) The Bland-Altman plot for CI measured with TDCO and LiDCOrapid at all measurement points. The lines for bias, LOA, and 95% CIs of LOA are shown. (b) The 4Q plot showing the trending ability of LiDCOrapid by plotting the change of consecutive CI measured with LiDCOrapid and TDCO. (Ylikauma, Lanning, et al., 2021)

5.2 Study II

Study II assessed 85 cardiac surgical patients, 43 (50.6%) of whom underwent coronary artery bypass grafting, 28 (32.9%) on CPB and 15 (17.6%) as an OPCAB. The other procedures were 15 (17.6%) aortic valvular, 9 (10.6%) mitral valvular, 4

(4.7%) ascending aortic, and 12 (14.1%) combined procedures. Additionally, one patient underwent aortic arch surgery, and one patient underwent pericardiectomy. The median age of the patients was 65 (59-71) years, and only 15 (17.6%) of these were female. EF was normal in 64 (75.3%) patients, while it was <30% in one patient only. There were no complications associated with the insertion, use, or removal of PAC. One patient died during the hospital stay due to a cardiac arrest during the fourth postoperative day.

In the Bland-Altman analysis of all 588 sample pairs (Figure 7), the mean bias between SvO_2 and $ScvO_2$ was –1.9 (95% CI, –2.3 to –1.5) and the LOA were –11.5 to 7.6. The PE was 13.2%. Based on the 4Q plot (Figure 7), only 50% of the measurement pairs were in zone 1, while 10.9% were in zone 2, 36.2% in zone 3, and 2.9% in zone 4.

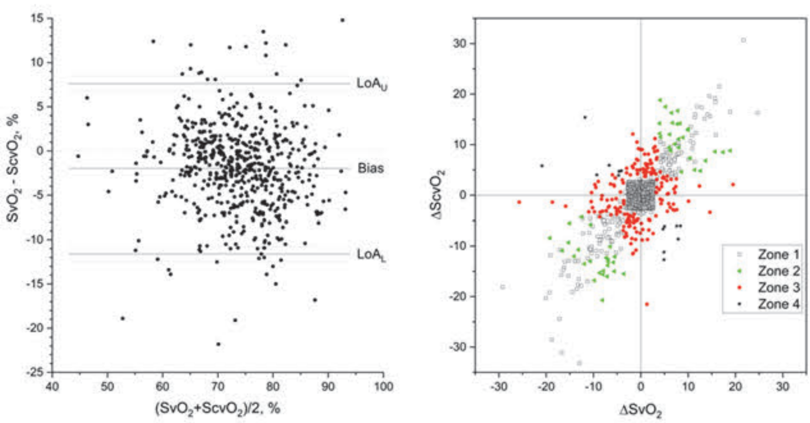

Fig. 8. The Bland-Altman blot (left) and 4Q plot (right) determined from SvO_2 and $ScvO_2$ values, all measurement points. The lines for bias, LOA, and 95% CIs of LOA are shown. The 4Q method plots the change in $ScvO_2$ against the change in SvO_2 showing the trending ability of $ScvO_2$ at all measurement points and different zones. (Lanning et al., 2021)

5.3 Study III

We collected data from 125 cardiac surgical patients, but one patient was excluded from the analysis because the NIRS values had not been recorded onto the electronic anesthesia chart. The median age of the patients was 66 (59−70) years and only 22 (17.6%) of them were female. Of the patients, 35/124 (28.2%) underwent OPCAB surgery. Of the others, 32 (25.8%) underwent either coronary artery bypass grafting on CPB, 20 (16.1%) underwent aortic valvular surgery, 14 (11.3%) mitral valvular surgery, 4 (3.2%) ascending aortic correction, and 16 (12.9%) combined procedures. In addition, one patient underwent aortic arch surgery, one patient descending aortic surgery, and one patient underwent pericardiectomy. Overall, 89 (71.6%) patients underwent cardiac surgery on CPB. The preoperative ejection fraction was normal in 97 patients (78.2 %) while it was <30% in four patients (3.2%). 69 (55.6%) procedures were elective and the rest were urgent operations. One patient died in the ICU during the fourth postoperative day. No PAC-associated complications were reported.

505 data pairs from OPCAB patients and 796 pairs from CPB patients were collected. The results of the multivariate regression model are shown in Table 5. The analysis of separate NIRS and CI pairs revealed a poor association in both OPCAB and CPB patients, which was not statistically significant when adjusted with the chosen confounders. However, when NIRS and CI values were compared to baseline or to the previous measurement, a statistically significant association between the changes in NIRS and CI existed and persisted in the adjusted models. Compared to baseline and to the previous measurement, respectively, the regression coefficients with 95% CIs were 0.048 (0.041−0.056) and 0.064 (0.055−0.073) in OPCAB patients, and 0.022 (0.016−0.029) and 0.026 (0.020−0.033) in those who underwent CPB. Accordingly, in the adjusted analysis of OPCAB patients, a 10-percentage point change from the previous NIRS value was associated with a 0.64 (0.55−0.73) L/min/m^2 change in CI values.

Table 6. Regression coefficients with 95% confidence intervals between CI and the means of right- and left-sided NIRS values.

CI/NIRS	OPCAB	P-value	CPB	P-value
ΔCI/ΔNIRS to baseline values	0.049 (0.041−0.056)	<0.0001	0.017 (0.012−0.023)	<0.001
-Adjusted analysis	0.048 (0.041−0.056)	<0.0001	0.022 (0.016−0.029)	<0.001
ΔCI/ΔNIRS, from previous values	0.064 (0.055−0.074)	<0.0001	0.024 (0.018−0.03)	<0.001
-Adjusted analysis	0.064 (0.055−0.073)	<0.0001	0.026 (0.02−0.033)	<0.001
CI/NIRS, absolute values	0.047 (0.04−0.054)	<0.0001	0.017 (0.012−0.022)	<0.001
-Adjusted analysis	0.004 (-0.001−0.01)	0.10	0.004 (0.001−0.009)	0.12

CI: cardiac index, NIRS: near-infrared spectroscopy, OPCAB: off-pump coronary artery bypass, CABG: coronary artery bypass grafting.

6 Discussion

6.1 Main findings of the thesis

The present thesis evaluates whether less invasive methods provide adequate information when compared to measurements obtained with PAC in the hemodynamic assessment of adult cardiac surgical patients. The less invasive methods assessed were CI values based on pulse power analysis or transthoracic bioreactance (I), $ScvO_2$ values (II), and cerebral NIRS values (III).

When assessing CI in patients undergoing cardiac surgery with CBP, the non-invasive, bioreactance-based Starling SV monitor showed inaccuracy with a high mean bias compared with TDCO, whereas the accuracy of the mini-invasive pulse-contour monitor LiDCOrapid was sufficient. With increasing CI, the bias increased with both devices. As the LOAs were wide and the PEs were high, neither of the devices was sufficiently precise. Additionally, the trending ability was poor with both devices. Accordingly, study I indicates that LiDCOrapid and Starling SV monitors are not interchangeable with TDCO in cardiac surgical patients (I).

When $ScvO_2$ was compared with SvO_2 in cardiac surgical setting, the bias was low, suggesting acceptable accuracy. However, the wide LOA indicates that $ScvO_2$ was not precise enough. Furthermore, the trending ability was inadequate. Therefore, we suggest that $ScvO_2$ is not interchangeable with SvO_2 in patients undergoing cardiac surgery (II).

In study III, the analysis of separate NIRS and CI pairs revealed a poor association. However, when the changes in NIRS from baseline or from the previous measurement were compared to those of CI, we observed a clinically and statistically significant association between the measurements both in OPCAB patients and in patients operated on CPB. The association was strongest in OPCAB patients, among whom a 10-percentage point change in NIRS values was associated with a 0.6 L/min/m^2 change in CI values. Accordingly, we were able to demonstrate that the changes in cerebral rSO_2 reflect changes in CI during cardiac surgery (III).

6.2 Monitoring CO in cardiac surgery (I)

The accuracy of the monitor refers to its ability to measure CO near to the true value. However, in clinical practice the measurement of true CO value is difficult because the reference technique can only provide an approximation of the true CO (de Waal et al., 2009). The Bland-Altman analysis determines the mean difference (bias) between two different measurement techniques (experimental and reference) as a measure of accuracy. Precision refers to the spread of the repeated values and 95% LOA are used to represent precision. The wider the LOA, the more imprecise the monitor. The Bland-Altman method addresses how well the experimental model agrees with the reference method, but it fails to show whether the experimental model reliably detects changes in CO (trending) (Critchley et al., 2010). The 4Q method is used to evaluate trending ability, plotting the change in experimental CO against the change in the reference CO. (Bland & Altman, 1999; Montenij et al, 2016). A poor trending ability may lead to a wrong treatment decision. Clinically acceptable boundaries for bias and LOA should be defined in advance depending on the patient group being monitored (Montenij et al., 2016).

An ideal CO monitor (which does not exist yet) would be reliable, non-invasive, continuous, operator-independent, cost-effective and would have a fast response time (de Waal et al., 2009). PAC was the first bedside monitor enabling the measurement of CO, and TDCO using a PAC is still considered to be the gold standard for measuring CO. However, there are several complications associated with the use of PAC, of which the pulmonary artery rupture is the most feared, and often fatal. In addition, there are several potential sources of error when TDCO is used, including the temperature and volume of the injectate, the timing of the injection during respiration, the rate of injection, and intracardiac abnormalities (Nishikawa & Dohi, 1993). Furthermore, TDCO measurements can only be performed intermittently. Therefore, several continuous minimally invasive devices have been developed to replace TDCO. As the reference device must be reliable when new CO monitors are studied, we chose the gold standard, TDCO as our reference method (Montenij et al., 2016).

We compared the non-invasive Starling SV and the mini-invasive LiDCOrapid to TDCO in patients undergoing cardiac surgery with CPB. This study showed that these less invasive monitors are not interchangeable with TDCO when assessing CI in this setting. Compared with the predefined targets of an acceptable mean bias of 0.25 L/min/m_2 for accuracy and LOA of 0.5 L/min/m^2 for precision (Montenij et al., 2016), the Starling SV showed inaccuracy, whereas the accuracy of LiDCOrapid was sufficient. The data were divided into four essential phases. The first phase was prior to initiation of CPB and the second phase after CPB. The third and fourth phases were in the ICU, before and after extubation. We discovered a proportional bias in phases 1–3 with Starling SV and in phase 3 with LiDCOrapid, suggesting decreasing accuracy as CI increases. The LOAs were wide, and the PEs were high with both devices, indicating imprecision during cardiac surgery on CBP, where notable hemodynamic changes can occur. Considering the trending ability, the error grids based on the 4Q plots demonstrated that only 26% of Starling SV measurements and 39% of LiDCOrapid measurements would have yielded a similar treatment decision compared to TDCO.

Our study is one of the first studies assessing the reliability of bioreactance devices in cardiac surgical patients. Ylikauma et al compared the Starling SV to TDCO in patients undergoing OPCAB surgery (Ylikauma, Ohtonen, et al., 2021). In OPCAB patients, the Starling SV was associated with a bias of 0.13 L min/ m^2 (95% CI, 0.07 to 0.18) compared to our CPB study with a bias of 0.43 L /min/m^2 (95% CI 0.37 to 0.50). We speculate that the mild hypothermia in patients undergoing surgery with CPB may - at least in part - explain the better accuracy in OPCAB patients, as changes in body temperature are known to affect bioreactance measurements (Han et al., 2015). In both OPCAB (Ylikauma, Ohtonen, et al., 2021) and CPB (I) patients, the LOAs were wide (− 1.23 to 1.51 L/min/m^2 and –1.07 to 1.94 L/min/ m^2, respectively) and the PEs were high (60.7% and 66.3%, respectively), indicating poor precision. In addition, the trending ability was poor in both studies. In another study NICOM, - an earlier version of bioreactance, was compared to PAC-CCO after cardiac surgery (Squara et al., 2007). The authors concluded that under a wide range of hemodynamic situations, the NICOM most often showed acceptable accuracy, precision and responsiveness. However, although the bias was low and the LOA were acceptable, the results are not comparable to ours because trending ability was assessed using correlation coefficients and not the modern statistical methods recommended for CO device comparison studies (Montenij et al., 2016). In addition, PAC-CCO is not considered a valid reference technique for measuring CO (Montenij et al., 2016).

There are several studies comparing LiDCO devices to TDCO in patients undergoing cardiac surgery with CPB, however, the sample sizes of these studies are often small (de Wilde et al., 2007; Mora et al., 2011; Phan et al., 2011) and the studies are most often limited to the immediate postoperative period (Hadian et al., 2010; Lamia et al., 2018; Mora et al., 2011). The studies by Phan (Phan et al., 2011) and de Wilde (de Wilde et al., 2007) compared LiDCO devices to TDCO during cardiac surgery with CPB and reached a similar conclusion to ours, with acceptable biases of 0.11 and −0.17 L/min, and wide LOAs of −1.42 to 1.63 L/min and −1.55 to 1.2 L/min, respectively. In addition, studies comparing LiDCOplus to TDCO in postcardiac-surgery patients also resulted in acceptable biases but wide LOAs (Hadian et al., 2010; Lamia et al., 2018). However, the respective PEs of 35% and

29% were lower than in our study, suggesting slightly better precision than that of LiDCOrapid (Hadian et al., 2010; Lamia et al., 2018). Mora et al compared LiDCOplus to TDCO in 30 patients who had impaired left ventricular function after cardiac surgery (Mora et al., 2011). Altogether, 220 paired measurements were performed during the first four postoperative hours, resulting in adequate accuracy and a PE of 27%, but again, wide LOA of −1.41 to 1.96 L/min (Mora et al., 2011). Although the results from the Bland-Altman analyses of previous studies are in accordance with ours, it is important to note that none of these studies adequately assessed the trending ability of LiDCO devices in cardiac surgery.

Minimally invasive CO monitors have many potential benefits, including that they are easy to use, and they allow the continuous measurement of CO. However, it appears that further development of technologies is necessary to improve accuracy and, in particular, precision and trending ability of these devices. Our study demonstrates that - at present - the non-invasive Starling SV and the mini-invasive LiDCOrapid are not interchangeable with TDCO, neither during nor after cardiac surgery with CPB.

6.3 Venous saturations in cardiac surgery (II)

Circulatory failure has been shown to be associated with significant mortality (Nguyen et al., 2006). Acute circulatory failure can lead to a shock state in which the circulation is unable to satisfy the oxygen demands of the tissues. A decrease in systemic oxygen supply leads to increased oxygen extraction and subsequently to decreased SvO_2 and $ScvO_2$. When the limits of the compensatory mechanisms are reached, the anaerobic metabolism initiates resulting in lactate production. In the final stage of shock there is an impairment of oxygen utilization, which then results in increased lactate levels and elevated venous saturations (Nguyen et al., 2016).

SvO_2 drawn from a PAC´s pulmonary line reflects the oxygen saturation of the venous mixture of the upper and lower body, including the coronary veins. $ScvO_2$ drawn from the central venous catheter reflects mainly the oxygen saturation of the upper body. In healthy individuals, the blood in the superior vena cava has a lower oxygen content than in the inferior vena cava (Barratt-Boyes & Wood, 1957; Reinhart & Bloos, 2005) resulting in higher values for SvO_2 than for $ScvO_2$. During shock and other critical illness, the oxygen extraction rate is higher than it is under normal conditions, and as the myocardial and cerebral blood flows are maintained while the renal and splanchnic blood flows are reduced, this may lead to a lower SvO_2 than $ScvO_2$ (Lee et al., 1972; Pikwer et al., 2008). This implies that the association between SvO_2 and $ScvO_2$ might not be constant during and after cardiac surgery, where major fluctuations in hemodynamic values often occur.

There are only a few previous studies comparing the agreement between $ScvO_2$ to SvO_2 in the cardiac surgical setting. The studies are often limited to either the intraoperative (Suehiro et al., 2014) or immediate postoperative period (Lorentzen et al., 2008; Romagnoli et al., 2014; Yazigi et al., 2008). We have found only two studies which extend over the course of both intraoperative care in the OR and postoperative treatment in the ICU (Lequeux et al., 2010; Sander et al., 2007), and neither of these present a statistical assessment on the trending ability of $ScvO_2$ compared to SvO_2. In the study by Lequeux et al, SvO_2 and $ScvO_2$ were continuously measured using fiberoptic catheters during surgery and up to 24 hours postoperatively. The authors found a high mean bias of 4.4% and wide LOA of −13.6% to 22.5% (Lequeux et al., 2010). However, fiberoptic venous saturations are not interchangeable with values determined from venous blood samples (Baulig et al., 2008; Bendjelid et al., 2004).

In our study, we compared SvO_2 and $ScvO_2$ samples drawn from the distal pulmonary and the proximal central venous lines of a PAC, respectively. We used the Bland-Altman analysis and the 4Q method to assess the accuracy, precision, and trending ability of $ScvO_2$ compared to SvO_2 in cardiac surgical patients. In the 4Q plot, we discovered that only 50.0% of the data points were in zone 1, indicating that only half of the $ScvO_2$ measurements would have yielded a similar treatment decision as compared to SvO_2. Furthermore, 36.2% of the data points were in zone 3, implying that compared to SvO_2, more than one-third of $ScvO_2$ measurements might have resulted in initiating unnecessary or withholding necessary treatment. $ScvO_2$ values showed acceptable accuracy as the mean bias was −1.9% (95% CI, −2.3 to −1.5%), which was clearly less than the previously suggested maximal acceptable difference of 3% between fiberoptic SvO_2 and that determined from pulmonary arterial blood samples (Bendjelid et al., 2004). However, $ScvO_2$ values were not sufficiently precise, which was seen as wide LOA of –11.5 (95% CI, – 12.5 to –10.7%) to 7.6 (95% CI 6.8 to 8.5). In addition, the trending ability of $ScvO_2$ was inadequate, as only half of the $ScvO_2$ measurements would have yielded a similar treatment decision as compared to SvO_2.

Our conclusions are in line with earlier studies in cardiac surgical patients (Cavaliere et al., 2014; Lorentzen et al., 2008; Romagnoli et al., 2014; Sander et al., 2007; Yazigi et al., 2008). However, most of the previous studies included only elective patients, while 45.9% of the procedures in our study were urgent.

6.4 Transcranial NIRS in cardiac surgery (III)

Because NIRS measures tissue oxygenation, it serves as an indirect measure of tissue perfusion of the organ monitored. In an unselected cardiac surgical population with 124 patients and 1301 pairs of NIRS and CI measurements, we demonstrated that the changes in cerebral rSO_2 reflect changes in CI, especially during OPCAB procedures. However, there was a poor association between the separate NIRS and CI pairs. Accordingly, our results comply with previous findings suggesting that NIRS should rather be considered a trending monitor than an absolute oxygen saturation measurement (Bickler et al., 2013; Henson et al., 1998), and demonstrate the potential of transcranial NIRS as a reliable, non-invasive, and continuous monitoring technique to evaluate the trends in cardiac performance during OPCAB surgery.

A standard reference level for baseline cerebral rSO_2 does not exist but baseline values of 55–60% or even lower are common in cardiac surgical patients (Subramanian et al., 2016). Heringlake et al demonstrated that low baseline cerebral rSO_2 values were independently associated with mortality and morbidity (Heringlake et al., 2011). Low preoperative baseline values (<50%) were predictive for death in children undergoing repair for congenital heart defects. The mean baseline rSO_2 value in these children was 64% (Fenton 2005). In the review article on cerebral NIRS and circulatory shock, baseline rSO_2 levels seem to predict mortality and help to identify patients with the most severe forms of shock (Varis et al., 2020). In a prospective controlled study, rSO_2 values in 39 healthy individuals were higher than those of 8 patients with acute heart failure with cerebral symptoms (65% vs. 34%) (Madsen et al., 2000). In the present study, the baseline for the means of left- and right-sided rSO_2 readings was 68% while it was less than 50% in only 2 patients, which is well in line with the normal preoperative EF of most of our patients, as well as with the low mortality (0.8%) among our study population.

Only a few previous studies have been published on the association between cerebral NIRS and cardiac function, and only one of them includes adult cardiac surgical patients (Paquet et al., 2008). In a retrospective analysis of 99 cardiac surgical patients, Paquet et al did not find a significant correlation between the baseline values for rSO_2 and CI pairs, which is in agreement with our results and demonstrates that there is only a poor association between separate rSO_2 and CI pairs. The trending ability was not evaluated in their study (Paquet et al., 2008) as they only compared the baseline values of rSO_2 and CI. Al-Subu et al retrospectively studied 10 children with a median age of 14 years admitted to a pediatric ICU after heart transplantation surgery (Al-Subu et al., 2018). rSO_2 and CI were recorded hourly from 8 to 92 hours post-transplantation, resulting in 410 sample pairs. There was a poor correlation between cerebral NIRS and CI, but again, they only analyzed absolute values and not the changes in CI and rSO_2 (Al-Subu et al., 2018). However, another study in 29 pediatric heart transplant patients undergoing myocardial biopsy reported a modestly significant correlation coefficient of 0.45 between 58 absolute cerebral and CI pairs (Bhutta et al., 2007). Hence, the previous studies are scarce and evaluate a limited number of sample pairs with partly conflicting results and omit to analyze the trends of CI and rSO_2. It is therefore obvious that further designated prospective studies with cardiac surgical and other patient groups are required to verify our findings on the relationship between cerebral NIRS and cardiac function.

6.5 The strengths of the study

Our studies have several strengths. In our hospital, a PAC is used in every cardiac surgical patient. Consequently, the doctors and nurses are well trained in its use. This further justifies our use of PAC as a reference method in study I, as it is the gold standard for CO measurement. In addition, both the OR and the ICU have advanced electronic patient records, which automatically include all hemodynamic data and enable the collection of multiple parameters precisely at the same time point. This was essential for the data collection of our post-hoc study III. Study II further supports the previous studies suggesting that SvO_2 and $ScvO_2$ are not interchangeable in adult cardiac surgical patients. Our study involved many improvements compared to previous studies, in which the number of sample pairs were often insufficient, as a power analysis was only conducted in some studies. Instead, we performed a sample size calculation for an equivalence study using preliminary data from 35 patients. In addition, we used the 4Q method with error grids, while none of the previous studies included an adequate assessment of trending ability. Furthermore, our biostatistician was closely involved throughout the prospective studies, enabling appropriate sample size calculations. As opposed to most previous research on minimally invasive CO monitors and $ScvO_2$, we included both elective and urgent cases, and collected the data both intraoperatively in the OR and postoperatively in the ICU. Most importantly, we used the recommended modern statistical methods to determine the accuracy, precision and especially, the trending ability of Starling SV, LiDCOrapid and $ScvO_2$. We therefore believe that our approach includes many important improvements over previous work in this field and adds to the current evidence. Furthermore, our biostatistician was closely involved throughout the prospective studies, enabling appropriate sample size calculations.

6.6 Weaknesses of the study

In study I, we only assessed 20 patients. However, we took 579 measurements altogether, while the calculated sample size necessary was 414 measurements. The number or timing of the measurements was not determined in advance, although most of them were taken every 30 minutes in the OR and once every hour on the ICU. In the OR, the attending cardiac anesthesiologist usually performs the TDCO measurements, but on the ICU, well-trained nurses perform the CO measuring. Another limitation of the study is that our reference method is intermittent while the study devices are continuous. However, none of the continuous monitors are reliable enough to be used as a reference method (Montenij et al., 2016). The median Euroscore II of the patients was 1.40%, so the results might not be consistent in more high-risk patients. As we studied patients undergoing cardiac surgery with CPB, our results may not be directly applicable to other patient groups, although corresponding results were seen in patients undergoing OPCAB surgery (Ylikauma, Ohtonen, et al., 2021).

In study II, we did not insert a separate central venous catheter for $ScvO_2$ sampling, but the samples were taken from the proximal blue line of PAC. It is therefore likely that a significant number of blood samples were in fact taken from the right atrium (Pikwer et al., 2008). However, as it has previously been suggested that right atrial saturation may be a better estimate of SvO_2 than is $ScvO_2$ (Chawla et al., 2004), the chosen approach does not distort our conclusions. The median Euroscore of the patients was 1.6%, and only 25% of them had an EF < 50%. This may limit the generalization of the results to higher-risk patients.

Study III was a post-hoc analysis containing patients from three prospective studies, of which none was originally designed to assess the relationship between CI and rSO_2 values. Therefore, hemoglobin concentration could not be used as one of the confounders as the blood samples were not synchronized with CI measurements. In clinical practice, we draw blood samples for blood gas analysis at the beginning of surgery, at least twice during CPB, after the protamine administration, and as needed. In OPCAB patients, blood samples are only drawn routinely at the beginning of surgery and after protamine administration. This limits the possibility of simultaneous CI and hemoglobin measurements if not accounted for in the study protocols. 82.4% of our patients were male. Bickler et al found that gender significantly affected the magnitude of the cerebral oximeter bias with the INVOS monitor (Bickler 2013). Furthermore, lifting the heart may induce tricuspid regurgitation in OPCAB patients, which may affect the accuracy of TDCO. We did not perform a power analysis for our post-hoc data, but the confidence intervals of the regression coefficients were quite small, which most likely indicates a sufficiently sized data sample.

6.7 Clinical implications and future research

Adequate hemodynamic monitoring leading to correct therapeutic interventions is important when managing cardiac surgical and critically ill patients. The goal of hemodynamic optimization is to avoid organ hypoperfusion leading to organ failure. Organ perfusion is determined by CO and perfusion pressure. Therefore, the accuracy of CO measurements is of vital importance. A pulmonary artery catheter with TDCO is still considered the most reliable method to measure CO. In addition, PAC provides other important information, such as SvO_2 and pulmonary artery pressures, that cannot be obtained from other devices.

Due to the invasiveness of PAC, minimally invasive CO monitoring devices have been developed. In addition, $ScvO_2$ is being used as a substitute for SvO_2 to describe overall oxygen balance. Our results suggest that neither the non-invasive bioreactance based Starling SV nor the mini-invasive LiDCOrapid based on pulse power analysis can replace TDCO in cardiac surgical patients with CPB. In addition, our results demonstrate that $ScvO_2$ cannot be used as a substitute for SvO_2 when assessing the adequacy of the whole-body oxygen balance in the cardiac surgical setting. Since these less invasive parameters of hemodynamic performance were not interchangeable with those obtained with PAC, our results support the continued use of PACs, at least in high-risk cardiac surgical patients. Patients with impaired EF probably receive the most benefit from accurate CO measurements in the guiding of therapeutic decision-making (Mora et al., 2011). In high-risk cardiac surgery, even small hemodynamic changes may be relevant and thus require immediate interventions. However, the minimally invasive CO monitors and $ScvO_2$ should perhaps be compared to TDCO and SvO_2 in a larger patient group with strictly standardized, goal-directed perioperative care to gain more information on the possible benefit of PAC.

Transcranial NIRS is a non-invasive and continuous monitoring technique to evaluate the adequacy of cerebral oxygenation. We showed that the changes in cerebral rSO_2 reflect the changes in CI in cardiac surgical patients, especially during OPCAB surgery. This suggests that NIRS devices might be used as real-time trending monitors for not only cerebral and systemic oxygenation, but also for cardiac function during cardiac surgery. Cerebral NIRS has the potential to serve as a first-alert indicator of adverse events even in lower-risk patients, but this should be further investigated. In addition, designated prospective studies in cardiac surgical patients, also using hemoglobin and arterial blood gas analyses as an adjusting factor are required in the future to explore the applicability of transcranial NIRS in evaluating cardiac function. The association between NIRS, CI and patient outcome in cardiac surgical patients should be investigated postoperatively in the ICU.

7 Conclusions

Based on this study, the following conclusions can be made:

1. Compared with TDCO, the Starling SV demonstrated inaccuracy with a high mean bias, whereas the mean bias of the LiDCOrapid was lower, suggesting sufficient accuracy. The wide LOA and the high PE of both devices indicate imprecision. The trending ability of both study devices was poor.
2. $ScvO_2$ values showed acceptable accuracy as the mean bias was low. However, precision was inadequate; while the PE was acceptable, the LOA were wide. The trending ability was inadequate. Consequently, $ScvO_2$ measurements cannot be used interchangeably with SvO_2 measurements in adult cardiac surgical patients.
3. The analysis of separate NIRS and CI pairs revealed a poor association. When the changes in NIRS from baseline or from the previous measurement were compared to those of CI, a clinically and statistically significant association was observed especially during OPCAB surgery. Accordingly, NIRS values reflect changes in CI in adult cardiac surgical patients

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