



**UNIVERSITY OF
PLYMOUTH**

**A VALIDATION AND FEASIBILITY STUDY OF THE NON-
INVASIVE MEASUREMENT OF OXYGEN DELIVERY AND
CONSUMPTION AFTER ELECTIVE MAJOR ABDOMINAL
SURGERY**

by

ADAM KIMBLE

A thesis submitted to the University of Plymouth
in partial fulfilment for the degree of

DOCTOR OF MEDICINE

Peninsula Medical School

March 2019

Copyright Statement

This copy of the thesis has been supplied on condition that anyone who consults it is understood to recognise that its copyright rests with its author and that no quotation from the thesis and no information derived from it may be published without the author's prior consent

AUTHOR'S DECLARATION

A validation and feasibility study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery submitted by Adam Kimble of the Plymouth University Peninsula Schools of Medicine and Dentistry as a thesis for the degree of Doctor of Medicine, July 2017

At no time during the registration for the degree of *Doctor of Medicine* has the author been registered for any other University award without prior agreement of the Doctoral College Quality Sub-Committee.

Work submitted for this research degree at the University of Plymouth has not formed part of any other degree either at the University of Plymouth or at another establishment.

This study was financed with the aid of grants from the National Institute of Academic Anaesthesia, Bowel Cancer West and the Plymouth Hospitals Charitable Trust.

Published abstracts arising from this thesis:

Kimble A, Minto G, Struthers R, Sneyd JR. A validation study of the non-invasive measurement of oxygen consumption and delivery after elective major abdominal surgery. *Eur J Anaesthesiol.* 2015; **32**(Suppl 53):285

Presentations arising from this thesis:

Kimble A, Minto G, Struthers R, Sneyd JR. A feasibility study of the non-invasive measurement of oxygen consumption and delivery after elective major abdominal surgery

EBPOM: London Peri-Operative Medicine Congress: EBPOM 2016

3rd Prize The David Bennett Prize

London, 7 July 2016

Kimble A, Minto G, Struthers R, Sneyd JR. A validation study of the non-invasive measurement of oxygen consumption and delivery after elective major abdominal surgery

Euroanaesthesia 2015, The European Anaesthesiology Congress Presentation

Berlin, 1 June 2015

Kimble A, Minto G, Struthers R, Hosie KB, Sneyd JR. A validation study of the non-invasive measurement of oxygen consumption and delivery after major abdominal surgery

Plymouth Hospitals NHS Trust Research Conference

1st Prize

Plymouth, 26 September 2014

Word count of main body of thesis: 21,198

Signed.....Date.....

A validation and feasibility study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery
Mr Adam Kimble

ABSTRACT

Major surgery triggers a physiological stress response that results in an increase in post-operative metabolic demand and oxygen consumption ($\dot{V}O_2$), which must be met by an increased oxygen delivery (DO_2). Historical studies described the increase in $\dot{V}O_2$ in patients after major surgery and presented evidence that the inability to meet this increase oxygen demand and the temporal pattern of this oxygen deficit appears to differ according to whether patients survive, or develop complications or not. The survival and complication profile of patients in modern practice is different from that previously described, And the methods employed in these historical studies were invasive and inconsistent with contemporary practice. $\dot{V}O_2$ can be measured non-invasively with indirect calorimetry, and DO_2 calculated from non-invasive cardiac output monitors, and haemoglobin and oxygen saturation measurement devices. This thesis describes two prospective observational studies which 1) validate and 2) assess the feasibility of non-invasive measurements of $\dot{V}O_2$ and DO_2 and explore their temporal patterns after contemporary abdominal surgery.

These techniques demonstrate moderate to good trending ability when measuring changes in $\dot{V}O_2$ and DO_2 . The non-invasive measurement of $\dot{V}O_2$ and DO_2 is feasible in patients after major abdominal surgery. There appear to be distinct patterns of $\dot{V}O_2$ and DO_2 after contemporary abdominal surgery in those who develop complications or not. Contemporary patterns of net cumulative oxygen debt appear to differ from those previously described.

ACKNOWLEDGEMENTS

Helen (Kimble) for all of her tolerance and unquestionable support

Grace, Reuben & Jude (Kimble) for the missed weekends and evenings with Daddy

My supervisory team for their support and patience

Mr K B Hosie for mentoring and helping me to “make it happen”

Gary Minto for his enthusiasm and getting me excited about peri-operative medicine

Richard Struthers for his academic support and guidance

Prof J R Sneyd for his intellectual input and critical review of the thesis

Dr Adam Streeter (University of Plymouth) for assisting with the statistical analysis of the feasibility study

The National Institute for Academic Anaesthesia, Bowel Cancer West and The Plymouth Hospitals Charitable Trust for funding part of these studies.

Austin Bradley of GEMNutrition for servicing the GEM and always being at the end of the phone when needed

The Patients

TABLE OF CONTENTS

INTRODUCTION	10
1.1 AIMS OF THIS THESIS.....	11
1.2 BACKGROUND	13
1.3 RISK ASSESSMENT OF SURGICAL PATIENTS.....	17
1.3.1 FUNCTIONAL ASSESSMENT	21
1.3.2 CARDIOPULMONARY EXERCISE TESTING (CPET).....	24
From Swart & Carlisle (2012) [48] CCU, Critical Care Unit	
1.4 STRESS RESPONSE TO SURGERY	27
1.5 ENHANCED RECOVERY AFTER SURGERY.....	30
1.6 GOAL DIRECTED THERAPY (GDT).....	34
1.7 THE NEED FOR FURTHER RESEARCH.....	38
METHODS.....	41
2.1 OXYGEN CONSUMPTION	42
2.1.1 Non-invasive measurement.....	42
2.1.2 Invasive measurement	45
2.2 OXYGEN DELIVERY	48
2.2.1 Non-invasive measurement.....	48
2.2.2 Invasive measurement	50
2.3 VALIDATION STUDY.....	52
2.3.1 STUDY DESIGN	52
2.3.2 HPB SURGERY CLINIC.....	52
2.3.3 PRE-OPERATIVE ASSESSMENT.....	53
2.3.4 ELIGIBILITY CRITERIA.....	54
2.3.5 CONSENT	55
2.3.6 PERIOPERATIVE MANAGEMENT	55
2.3.7 STUDY OBSERVATIONS.....	59
2.3.8 STATISTICAL ANALYSIS.....	63
2.4 CO ₂ ST – A feasibility study.....	68
2.4.1 STUDY DESIGN	68
2.4.2 COLORECTAL SURGICAL CLINIC.....	68
2.4.3 PRE-OPERATIVE ASSESSMENT.....	69
2.4.4 ELIGIBILITY CRITERIA	70
2.4.5 CONSENT	71
2.4.6 PERIOPERATIVE MANAGEMENT	71
2.4.7 STUDY OBSERVATIONS.....	72
2.4.8 POST-OPERATIVE MORBIDITY SURVEY	76
2.4.9 STATISTICAL ANALYSIS.....	77

A VALIDATION STUDY OF THE NON-INVASIVE MEASUREMENT OF OXYGEN DELIVERY AND CONSUMPTION AFTER ELECTIVE MAJOR ABDOMINAL SURGERY	80
3.1 INTRODUCTION.....	81
3.2 METHODS	84
Measurement of $\dot{V}O_2$.....	85
Non-invasive measurement.....	85
Invasive measurement	86
Measurement of DO_2	86
Non-invasive measurement.....	87
Invasive measurement	87
Statistical analysis.....	87
3.3 RESULTS.....	89
3.4 DISCUSSION	117
Conclusion.....	125
CO₂ST: THE COST IN OXYGEN OF SURGICAL TRAUMA – A FEASIBILITY STUDY OF THE NON-INVASIVE MEASUREMENT OF OXYGEN DELIVERY AND CONSUMPTION AFTER MAJOR ABDOMINAL SURGERY	126
4.1 INTRODUCTION.....	127
4.2 METHODS	130
$\dot{V}O_2$ measurement	131
DO_2 measurement	132
Post-Operative Morbidity Survey.....	132
Statistical analysis.....	133
4.3 RESULTS.....	135
4.3.1 Study Population.....	135
4.3.2 Patient Characteristics	137
4.3.3 Post-operative $\dot{V}O_2$ and DO_2.....	140
4.3.4 Post-operative oxygen balance.....	144
4.3.5 Missing data.....	147
4.4 DISCUSSION	148
Conclusion.....	152
DISCUSSION.....	153
5.1 STUDY FINDINGS.....	154
5.2 STUDY IMPLICATIONS	155
5.2.1 Measuring $\dot{V}O_2$ Post-operatively	155
5.2.1 Measuring DO_2 Post-operatively.....	158
5.3 STUDY LIMITATIONS	159
5.3.1 Limitations of equipment used.....	160
5.3.2 Post-operative complications	162
5.4 CONCLUSIONS AND FUTURE WORK.....	164

REFERENCES	166
APPENDIX 1 Validation study patient information sheet.....	177
APPENDIX 2 Validation study consent form.....	185
APPENDIX 3 CO₂ST patient information sheet	187
APPENDIX 4 CO₂ST consent form.....	194
APPENDIX 5 Adverse event report Validation Study	196
APPENDIX 6 GEM manufacturer’s annual service and calibration, and monthly alcohol burn data	209

LIST OF FIGURES

Figure 1	The effect of postoperative complications on longterm survival	14
Figure 2	Surgical stress responses & peri-operative events	16
Figure 3	Temporal patterns of post-operative oxygen deficit/excess	23
Figure 4	Age, fitness and mortality rates from hepatobiliary surgery in 398 patients	26
Figure 5	The systemic responses to surgery	29
Figure 6	Enhanced Recovery After Surgery	33
Figure 7	The optimal fluid administration curve	36
Figure 8	The GEM indirect calorimeter gas collection hood	43
Figure 9	The esCCO cardiac output monitor	49
Figure 10	The Pronto-7 pulse co-oximeter	50
Figure 11	Local hemi-hepatectomy ERAS pathway	57
Figure 12	Flowchart for the acquisition of clinical data collection for validation study	62
Figure 13	Example 4-quadrant plot	65
Figure 14	Example polar plot	67
Figure 15	Flowchart for the acquisition of clinical data collection for feasibility study	75
Figure 16	Calculation of net cumulative O ₂ debt/excess	79
Figure 17	Validation Study population	90
Figure 18	Scatter plot and Bland-Altman Plot for VO ₂ measurements	94
Figure 19	Scatter plot and Bland-Altman Plot for DO ₂ measurements	95
Figure 20	Scatter plot and Bland-Altman Plot for CO measurements	96
Figure 21	Scatter plot and Bland-Altman Plot for arterial versus Pronto-7 [Hb]	97
Figure 22	Scatter plot and Bland-Altman Plot for venous versus Pronto-7 [Hb]	98
Figure 23	Scatter plot and Bland-Altman Plot for arterial versus central venous [Hb]	99

Figure 24	Scatter plot and Bland-Altman Plot for S_aO_2 versus Pronto-7 SpO_2	100
Figure 25	Four-quadrant concordance plot and polar plot for changes in VO_2 measured invasively compared to the GEM cart	102
Figure 26	Four-quadrant concordance plot and polar plot for changes in DO_2 measured invasively and non-invasively	103
Figure 27	Four-quadrant concordance plot and polar plot for changes in CO measured with LiDCOrapid and the esCCO monitors	104
Figure 28	Four-quadrant concordance plot and polar plot for changes in Hb measured arterially compared to the Pronto-7 monitor	105
Figure 29	Four-quadrant concordance plot and polar plot for changes in Hb measured central venously compared to the Pronto-7 monitor	106
Figure 30	Four-quadrant concordance plot and polar plot for changes in Hb measured arterially compared to central venously	107
Figure 31	Four-quadrant concordance plot and polar plot for changes in Oxygen saturations measured arterially compared to the Pronto-7 monitor	108
Figure 32	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	110
Figure 33	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	111
Figure 34	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	112
Figure 35	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	113
Figure 36	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	114
Figure 37	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	115
Figure 38	Individual patient patterns of post-operati VO_2 and DO_2 measured invasively and non-invasively	116

Figure 39	An integrative concept for the use of cardiac output (and VO₂ and DO₂) monitoring devices	124
Figure 40	CO₂ST Study population	136
Figure 41	Serial measurements of mean VO₂	142
Figure 42	Serial measurements of mean DO₂	143
Figure 43	Net cumulative oxygen balance for survivors, survivors with complications and non-survivor	146
Figure 44	Comparison of net cumulative O₂ balance graphs, current study compared with Shoemaker et al. (1992)	157

LIST OF TABLES

Table 1	Clinical criteria for high-risk patients	18
Table 2	Postoperative cardiac events	27
Table 3	ERAS Society guidelines by specialty and year of publication	32
Table 4	Eligibility criteria for validation study	54
Table 5	Eligibility criteria for CO₂ST Study	70
Table 6	The Post-Operative Morbidity Survey (POMS)	77
Table 7	Patient characteristics	91
Table 8	Statistical data for Bland-Altman, four-quadrant plots and polar plots	92
Table 9	Reasons for missed readings in validation study	109
Table 10	Demographic data of survivors, survivors with complications and non-survivor	138
Table 11	Pre-operative values of survivors, survivors with complications and non-survivor	139
Table 12	VO₂ and DO₂ patterns by group and results of mixed model analysis	141
Table 13	Post-operative tissue oxygen deficit	144
Table 14	Net cumulative oxygen balance patterns by group and results o mixed model analysis	145
Table 15	Reasons for missed readings in feasibility study	147

Chapter 1

INTRODUCTION

1.1 AIMS OF THIS THESIS

The aim of this thesis was to perform original research to investigate the question “what is the oxygen consumption ($\dot{V}O_2$) after contemporary major abdominal surgery?” using non-invasive technology and consider if there were differences in $\dot{V}O_2$ between patients who developed complications and those who did not.

Two research studies were undertaken:

- 1) **A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.**

NRES Committee South West - Cornwall & Plymouth: 13/SW/0177

NIHR CRN 15072

A prospective observational cohort study was conducted on patients undergoing elective major liver resections at the Peninsula Hepato-pancreato-biliary Surgical Unit, Derriford Hospital, Plymouth, UK.

Principal Research Questions:

- a) To determine the validity of non-invasive measurement of $\dot{V}O_2$ using indirect calorimetry in a cohort of patients after major abdominal surgery
- b) To determine the validity of non-invasive measurement of DO_2 in the same cohort using non-invasive measures of cardiac output, oxygen saturation and haemoglobin (pulse wave transit time and co-oximetry techniques)

Secondary Research Questions:

- a) To explore the temporal pattern of postoperative $\dot{V}O_2$ and DO_2 by these techniques

2) **CO₂ST: The Cost in Oxygen of Surgical Trauma – a feasibility study of the non-invasive measurement of oxygen delivery and consumption after major abdominal surgery**

NRES Committee South West - Cornwall & Plymouth: 14/SW/1109

ClinicalTrials.gov: NCT02238561

A prospective observational cohort study was conducted on patients undergoing elective major colorectal resections at Derriford Hospital, Plymouth, UK.

Principal Research Questions:

- a) To determine the feasibility of non-invasive measurement of $\dot{V}O_2$ using indirect calorimetry in a cohort of patients undergoing elective major abdominal surgery
- b) To determine the feasibility of non-invasive measurement of DO_2 in the same cohort using non-invasive measures of cardiac output (CO), oxygen saturation and haemoglobin concentration (pulse wave transit time and co-oximetry techniques)

Secondary Research Questions:

- a) To explore the temporal pattern of post-operative $\dot{V}O_2$ and DO_2 measured by these techniques, and their relationship with post-operative complications as measured by the Post-operative Morbidity Survey (POMS)
- b) Data obtained might allow a formal power calculation for a future study examining the relationship between post-operative $\dot{V}O_2$ and adverse outcomes

1.2 BACKGROUND

Major abdominal surgery can be associated with significant morbidity and mortality. It is estimated that worldwide, 234 million people per year have surgery requiring an inpatient stay [3]. In the UK, in a study of 4.1 million selected non-cardiac surgical procedures, the overall mortality was 1.9%. However, concealed within this figure was a subgroup of high-risk patients who accounted for 12.5% of inpatient surgical procedures but for >80% of postoperative deaths [4, 5]. These patients are older, with complex needs, significant comorbidities, and limited physiological reserve [2, 6]. They are undergoing major surgery, often performed as an emergency, associated with a significant physiological stress response in the peri-operative period [7]. Moreover, Khuri *et al.* [2] reported a series of 105,951 patients whose demographic, intraoperative and outcome data were routinely collected in the National Surgical Quality Improvement Program (NSQIP) database. They found that the most important determinant of decreased postoperative survival was the development of at least one of 22 defined complications in the immediate postoperative period. Furthermore, the occurrence of a 30-day postoperative complication reduced median long-term patient survival by 69% (*Figure 1*) and was more important than pre-operative patient risk and intraoperative factors in determining survival after major surgery[2]. In addition, Rhodes *et al.* [8] found that long-term survival after major surgery is related to a number of factors, including patient age and avoidance of postoperative complications.

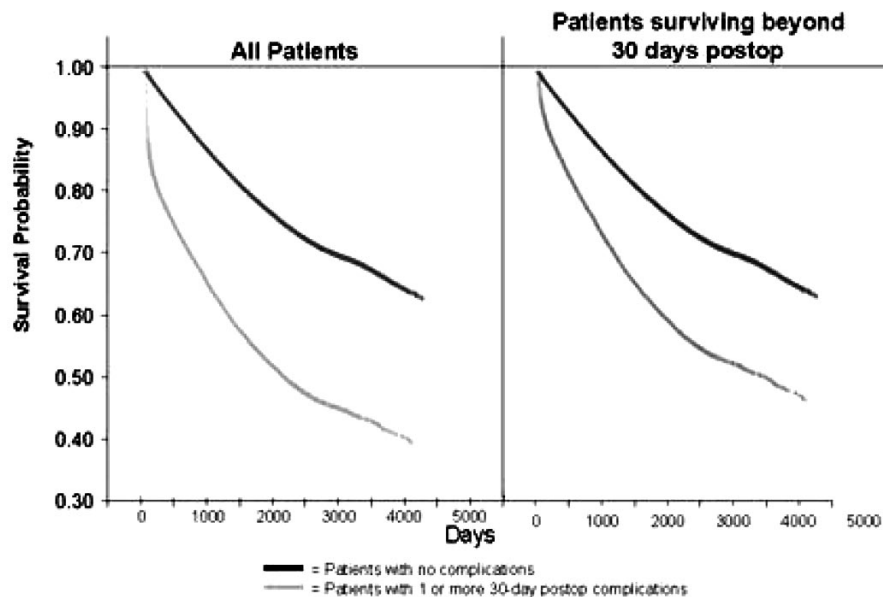


Figure 1 The Effect of Postoperative Complications on Long-term Survival

Cox survival curves of patients who sustained a 30-day postoperative complication compared with those who did not. Reproduced from Khuri *et al.* (2005) [2]

Major postoperative complications have both short- and long-term consequences. A recent prospective observational study from Australasia in patients aged ≥ 70 years old undergoing elective non-cardiac surgery showed that those suffering at least one major complication had a 30-day mortality rate of 14% and significantly increased median total postoperative length of stay (LOS) compared to those with uncomplicated recoveries (13 vs. 5 days, $p < 0.001$) [9]. The question then arises as to how we predict which patients are going to develop complications or not?

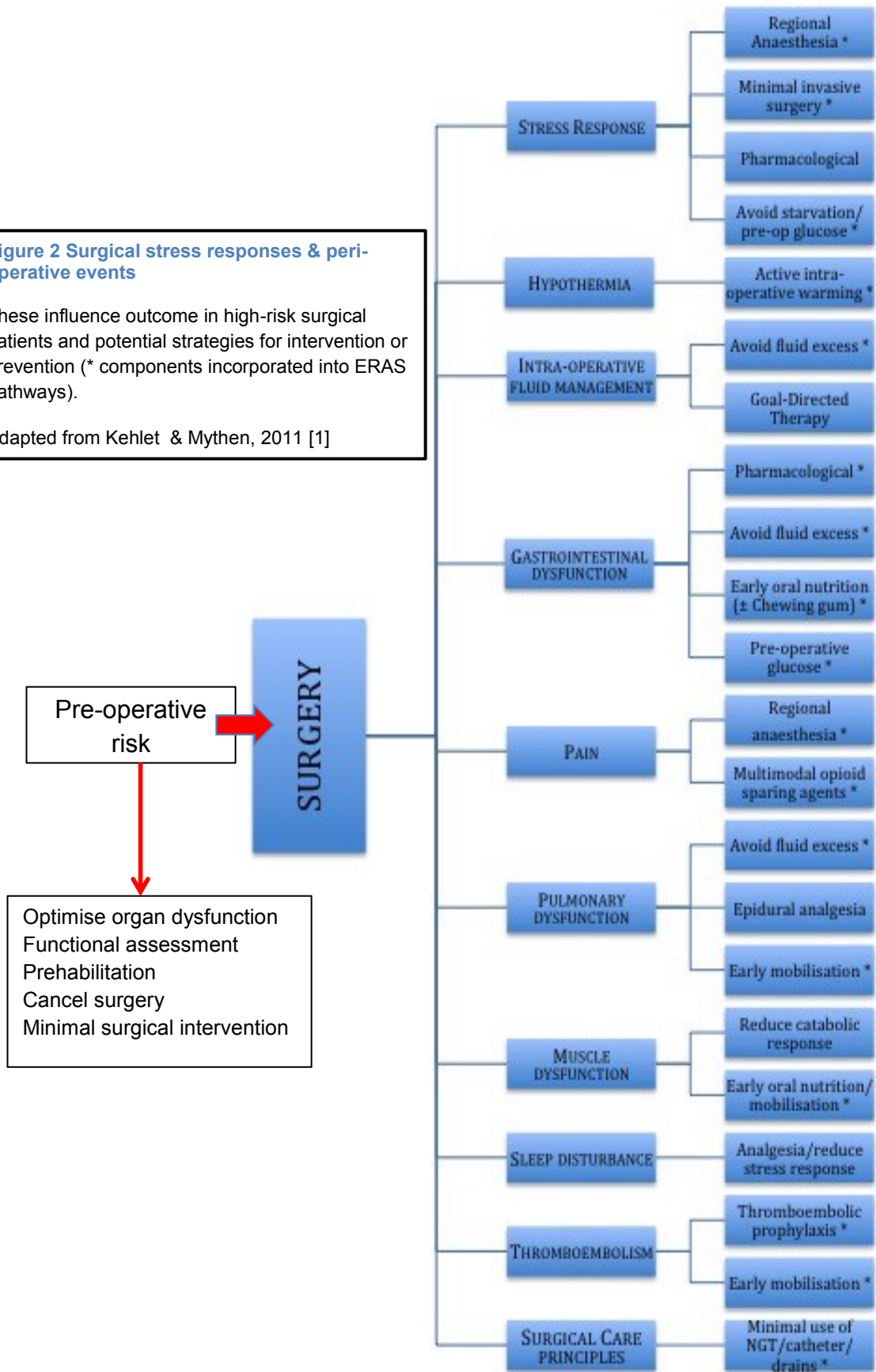
Three prominent reports from the Royal College of Surgeons of England, the UK National Confidential Enquiry into Patient Outcome & Death (NCEPOD), and The European Surgical Outcomes Study (EuSOS) highlighted deficiencies in the identification of the high-risk surgical patient and the subsequent planning

of their peri-operative care. They suggested that accurate risk assessment would be achieved by objectively measuring functional status and cardiopulmonary performance, with proper allocation of critical care resources [10-12]. Kehlet and Mythen advocate that pre-operative risk stratification allows optimisation of organ dysfunction, advice regarding cessation of alcohol and smoking, and also allows assessment and optimisation of cardiopulmonary functional impairment [1]. Accurate estimation of risk also helps inform the patient of risk/benefit and allows planning of appropriate peri-operative care. It would seem that a multi-factorial approach to the management of high-risk patients, as advocated in Enhanced Recovery After Surgery (ERAS) protocols, focussing on minimising surgical stress and inflammatory responses whilst optimising peri-operative care would be the ideal (*Figure 2*).

Figure 2 Surgical stress responses & peri-operative events

These influence outcome in high-risk surgical patients and potential strategies for intervention or prevention (* components incorporated into ERAS pathways).

Adapted from Kehlet & Mythen, 2011 [1]



1.3 RISK ASSESSMENT OF SURGICAL PATIENTS

Who then, is the high-risk surgical patient? Estimation of the likelihood of adverse outcome (mortality and morbidity) after surgery is a central objective of pre-operative assessment [5]. A variety of methods have been used to identify patients at increased risk of adverse outcome following major surgery and to quantify the level of this risk. Risk assessment requires a balance between ease of use in the clinical setting and precision in distinguishing between the different levels of risk.

Recent UK data indicates that only a minority of high-risk patients are admitted directly to critical care after surgery, and that many postoperative deaths occur following delayed admission to critical care with initial treatment on a standard surgical ward [4, 13]. These results highlight the fact that accurate identification of at-risk patients is essential to plan appropriate decision-making about offering surgery, aspects of peri-operative care and effective utilisation of expensive critical care resources, particularly as the development of early postoperative complications is associated with both worse short-term [9] and long-term outcomes (*Figure 1*) [2, 8].

Shoemaker *et al.* [14] produced a list of patient characteristics and clinical criteria that could be used to define those undergoing “high-risk” surgery. Boyd *et al.* subsequently adapted these, and they are presented in *Table 1* [15, 16]. Whilst these clearly identify patients at much higher risk than those in the general population of patients undergoing surgery, this approach is open to subjective interpretation and provides only a dichotomous classification of the

presence or absence of risk, rather than a graded or continuous measure of risk, and many would argue that they are somewhat out-dated.

Previous severe cardiorespiratory illness - Acute myocardial infarction, chronic obstructive pulmonary disease, or stroke
Late-stage vascular disease involving aorta
Age > 70 years with limited physiological reserve in one or more vital organs
Extensive surgery for carcinoma (e.g. oesophagectomy, gastrectomy, cystectomy)
Acute abdominal catastrophe with haemodynamic instability (e.g. peritonitis, perforated viscus, pancreatitis)
Acute massive blood loss > 8 units
Septicaemia
Positive blood culture or septic focus
Respiratory failure: PaO ₂ <8.0 kPa on FiO ₂ >0.4 or mechanical ventilation > 48 hours
Acute renal failure: urea > 20 mmol/l or creatinine > 260 mmol/l

Table 1 Clinical criteria for high-risk surgical patients

Adapted from Shoemaker *et al.* (1988) [14]

Within the pre-operative assessment clinic several approaches to identifying the high-risk surgical patient are available. Many of those currently routinely available in such clinics within the UK have limitations to their use: Self-reported metabolic equivalent of task (METs), have been shown to correlate poorly with other more objective assessments of functional capacity [17]. In addition, a study comparing three measures of functional capacity: Duke Activity Status

Index (DASI) questionnaire, incremental shuttle walk test, and CPET did find a significant correlation existed between the various tests [18]. However, DASI and shuttle walks had a poor negative predictive value, with many patients with poor questionnaire scores or shuttle walks achieving a satisfactory CPET result, which questions their ability to accurately determine risk in a heterogeneous surgical population.

Echocardiography is commonly performed pre-operatively to assess cardiac function in those perceived to be at high-risk. However, this has limited use since it only assesses one element of the oxygen delivery process i.e. cardiac function. Indeed, in a retrospective study of 264,824 patients undergoing elective non-cardiac surgery in Canada, 15.1% of patients had a pre-operative echocardiogram, which was not associated with an improvement in mortality or length of stay when compared with matched controls [19].

Numerous risk scores and risk prediction models are available such as the American Society of Anesthesiologists physical status classification (ASA score), Lee's Revised Cardiac Risk Index (RCRI), the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM), and its specialty-specific score, ColoRectal POSSUM (CR-POSSUM), and more recently the Surgical Outcome Risk Tool (SORT) score that was developed in conjunction with NCEPOD. These all vary in their ease of calculation, but also in their clinical utility and ability to accurately predict mortality and morbidity:

- i. ASA is simple to calculate and has been shown to have a significant association with both mortality and post-operative complication, although there can be significant interoperator variability, and correct prediction of complications can be as low as 16% [20-22].
- ii. Lee's RCRI, and the subsequent revisions, were developed to predict post-operative cardiac complications, rather than all-cause post-operative mortality and morbidity, in patients undergoing non-cardiac surgery [23]. Studies have shown that the index is predictive of cardiovascular mortality [24], however, the NSQIP data demonstrate that there is a mortality differential that exists between those with and without post-operative complications regardless of type of complication [2]. In addition, data from 101 patients undergoing high-risk general surgical procedures demonstrate that on day 5 post-operatively, only 4% developed cardiovascular complications compared to 19.8% with pulmonary complications, 28.7% with infectious complications, 21.8% with renal complications and 65.3% with gastrointestinal complications [25].
- iii. POSSUM takes into account patient physiological and operative factors [26], but is criticised for over-predicting the risk of death by up to six-fold, especially for those patients with a predicted risk of mortality <10% [27]. CR-POSSUM, is simpler to calculate, but can only be calculated post-operatively as it requires the degree of peritoneal soiling, complexity of surgery and histological staging [28].

Risk prediction scores have an inherent limitation – they can only stratify individual patients into groups based on population risk, and cannot accurately

allocate risk to the individual. More novel and individualised approaches such as plasma biomarkers are gaining in popularity, but their place in peri-operative risk stratification remains unclear, and more research is required [29, 30].

Due to the limitations described above, and the importance placed on pre-operative risk stratification, most would advocate a formal assessment of a patient's capacity to deliver oxygen to metabolically active tissues to identify those at "high risk" of morbidity and mortality following surgery, so called functional assessment. However, these methods can be resource intensive in terms of capital outlay and clinician utilisation.

1.3.1 FUNCTIONAL ASSESSMENT

Prevailing theory is that the premise of assessing functional capacity of patients is that major surgery generates a systemic inflammatory response that results in an increase in post-operative metabolic demand, which in turn leads to an increase in $\dot{V}O_2$ with a consequent increased demand in DO_2 [15, 31]. Whilst the model is not universally accepted [32], patients with poor cardio-respiratory reserve, or pre-existing cardiac or respiratory disease, may struggle to meet this metabolic demand and are at increased risk of major cardio-respiratory morbidity, or death after surgery [15, 16, 31, 33-36].

When Bland *et al.* [37] compared the haemodynamic and oxygen transport variables of survivors and non-survivors who were critically-ill following general surgical operations, they found that the non-survivors generally had:

(a) reduced myocardial performance, with a lower cardiac index (CI) and left ventricular stroke work in the presence of high ventricular filling pressures, (b) reduced pulmonary function, (c) pulmonary vasoconstriction, and (d) decreased DO_2 despite maintenance of normal arterial blood gases and comparable haemoglobin values [37]. This suggested that the development of an oxygen deficit/debt (manifested as tissue hypoxia) was an important determinant in poor surgical outcomes [15, 37, 38], and not reflected in traditional measures of heart rate, blood pressure and blood gas measurement. Shoemaker estimated patients' postoperative oxygen consumption requirement (using their measured preoperative baseline $\dot{V}O_2$ corrected for temperature) and suggested that oxygen deficit was present when this figure exceeded measured $\dot{V}O_2$. The temporal pattern of post-operative oxygen deficit appears to differ according to whether patients survive, develop complications or not (*Figure 3*).

DO_2 is dependent on the amount of oxygen in the blood and the cardiac output. Shoemaker *et al.* "optimised" patients considered at high risk (*Table 1.*) with intravenous fluids, inotropes and O_2 therapy to so-called "supra-normal values" for CO and tissue DO_2 , demonstrating a reduction in mortality from 28% to 4% ($p < 0.02$) [14]. They aimed to test the hypothesis that increased CI and DO_2 were circulatory compensations for increased postoperative metabolism which prevented the development of a tissue oxygen debt, and the survivors could either attenuate the physiological increase in oxygen demand and/or they could increase their DO_2 [15]. However, the supra-normal values were derived from the median values of survivors of high-risk surgical operations who were previously observed to have significantly higher mean CI and DO_2 , and these impressive results favouring targeted DO_2 were achieved on a cohort of only

4.8% of patients, as only 146/2086 were considered high-risk and a further 45 patients were excluded as invasive monitoring was not used.

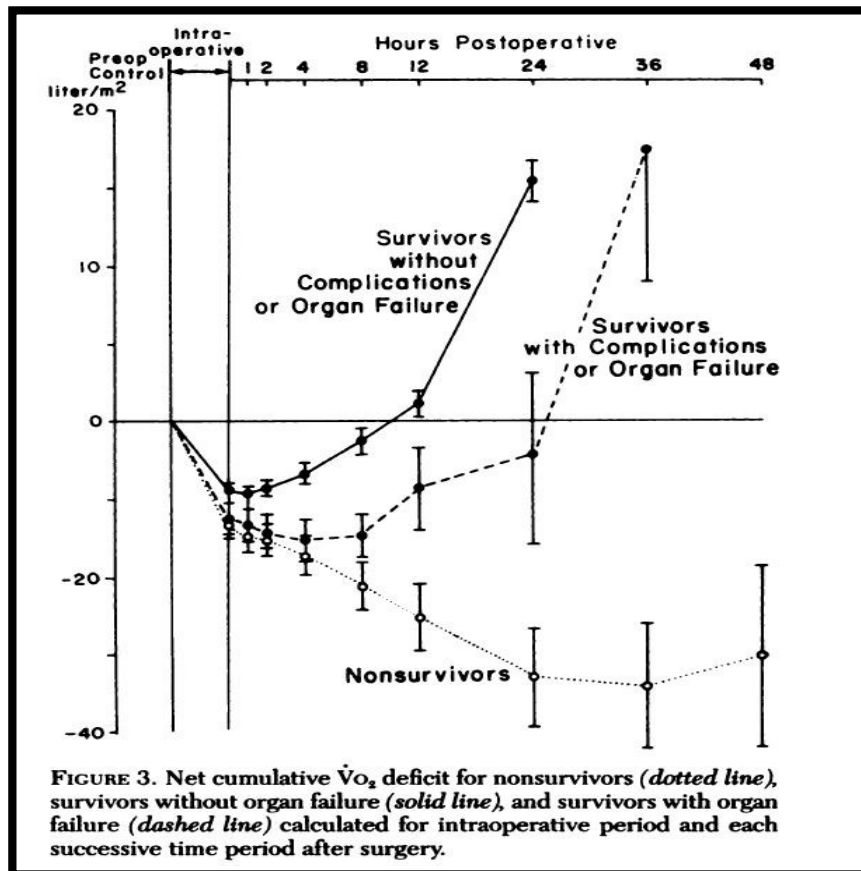


Figure 3 Temporal patterns of post-operative oxygen deficit/excess

From Shoemaker *et al.* (1992) [38]

In an RCT Wilson *et al.* [34] demonstrated that both length of stay and mortality rates were improved with pre-operative optimisation of patients with fluids and inotropes compared with standard care, based on the hypothesis that these improved DO_2 [34]. Citing previous work that had shown that if DO_2 was less than $390 \text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$, then tissue oxygenation was inadequate [39], they concluded that optimisation of DO_2 was beneficial in high-risk surgery. They advocated the use of close monitoring as intraoperative blood loss, reductions in haemoglobin concentration and CO could cause consequent falls in tissue

oxygenation [34]. These interventions would later be called goal directed therapy (GDT, *section 1.5 page 28*).

1.3.2 CARDIOPULMONARY EXERCISE TESTING (CPET)

In addition to the work by Shoemaker and Wilson, a complementary stream of research investigated the utility of pre-operative testing of patients` functional capacity to increase DO_2 (for example cardiopulmonary exercise testing, CPET) to predict clinical outcome and thus to triage allocation of resources such as post-operative critical care [31]. Risk stratification based on CPET is gaining in popularity [40], and usually occurs at dedicated pre-assessment clinics prior to admission for surgery and can facilitate shared decision making with the patient, the planning of appropriate peri-operative care, and allow pre-operative optimisation.

CPET is a comprehensive objective assessment of cardiopulmonary function, examining the ability of a patient to meet the oxygen demands seen during times of tissue stress such as that seen during and after major surgery. Studies have suggested that CPET is able to identify patients with poor functional reserve that may be less able to maintain peri-operative DO_2 , and are therefore at risk of morbidity and mortality after surgery [31, 33, 35, 41, 42]. CPET derived variables include anaerobic threshold (AT), the point at which aerobic metabolism is inadequate to meet the energy demand in exercising muscles, thus requiring anaerobic metabolism to make up the deficit; $\dot{V}\text{O}_2$ peak, the maximum $\dot{V}\text{O}_2$ achievable by an individual, and the ventilatory equivalent of CO_2 , calculated as $\dot{V}\text{E}/\dot{V}\text{CO}_2$, where $\dot{V}\text{E}$ = pulmonary ventilation (amount of air moved in and out of the lungs per minute), and $\dot{V}\text{CO}_2$ = CO_2 production.

However, in reality the mechanisms defining “fitness” for an individual i.e. their resilience to physiological stress, are likely to be complex and multifactorial including neurohumoral pathways [43].

In a study on 116 patients following major elective general surgery, Snowden *et al.* demonstrated that an AT of 10.1 mlO₂/kg/min was able to distinguish between those at increased risk of developing post-operative complications with a sensitivity of 88% and specificity 79% [35]. Those with >1 complication had a significantly longer length of stay (LOS, 26 vs. 10 days; p<0.001) and worse AT (9.1 vs. 11.9 mlO₂/kg/min; p=0.001). More recently, West *et al.*, in a study of 703 patients from 6 centres, also showed that a pre-operative CPET derived AT ≤11.1 ml/kg/min, and VO₂ peak ≤18.2 ml/kg/min were able to identify patients at risk of developing post-operative morbidity [44].

Not only are CPET variables able to predict morbidity, but they are also able to predict mortality after surgery. In addition it is the CPET variables that predict the outcome rather than the age of patients. In a study of 389 patients undergoing hepatobiliary surgery, patients were divided into groups according to age (</> 75 yrs) and fitness (AT </>10ml/kg/min), with only fitness being the independent predictor of mortality and length of stay (*Figure 4*) [45]. That is to say that “fit” older patients, as measured by CPET, do better after major surgery than “unfit” younger patients. Moreover, Older *et al.* [33] demonstrated in 548 >60 yrs of age undergoing major intra-abdominal surgery it was the AT as determined by CPET rather than age that was a discriminator of mortality.

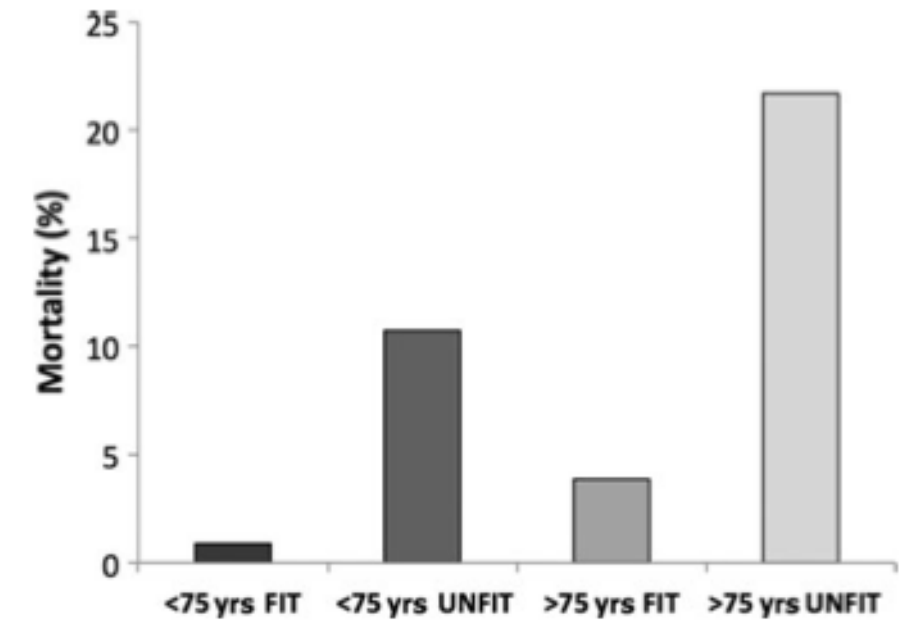


Figure 4 Age, fitness, and mortality rates from hepatobiliary surgery in 389 patients

From Snowden *et al.* (2013) [45]. (Fit = AT >10ml/kg/min, unfit = AT <10ml/kg/min)

In addition, Wilson *et al.*, in a retrospective analysis of 843 patients who underwent major elective colorectal or urological surgery found that $\dot{V}E/\dot{V}CO_2 >34$, an AT ≤ 10.9 ml/kg/min, and a clinical history of ischaemic heart disease were all significant predictors of all cause 30 and 90-day mortality [42]. Interestingly the effect of a reduced AT was most pronounced in patients without cardiac risk factors, which might suggest some clinical management bias with closer monitoring in critical care for those with cardiovascular risk factors rather than for those deemed unfit by CPET. Furthermore, in a novel study looking at a cohort of patients unable either to perform a CPET test and/or demonstrate an AT on CPET, Lai and colleagues demonstrated that these patients had longer LOS and higher early and medium-term mortality than either patients stratified as fit (AT ≥ 11.0 ml/kg/min) or unfit (AT <11.0ml/kg/min) by CPET [46].

Work from Torbay Hospital has demonstrated that even just attending a specialised pre-operative assessment clinic (during which CPET is performed) is independently associated with a 58% lower mortality rate after major colorectal surgery [47]. This was thought to be in part explained by more frequent planned post-operative admission to the critical care unit. Indeed, in a further study of 156 patients undergoing open colorectal surgery from the same group [48], patients with an AT ≤ 11 ml/kg/min had fewer cardiac events when managed in the critical care unit than when managed on the surgical ward (*Figure 5*). Carlisle *et al.* also found that the net income generated by the high-risk pre-operative clinic (including CPET) reduced the cost of post-operative critical care compared to those not seen at the clinic [47].

Anaerobic threshold (ml oxygen per kg per min)	Postoperative destination	Cardiac event
≥ 11	Ward	0 of 55
< 11	CCU	0 of 51
< 11	Ward	7 of 39

Table 2 Postoperative cardiac events.

From Swart & Carlisle (2012) [48] CCU, Critical Care Unit

1.4 STRESS RESPONSE TO SURGERY

The stress response to surgery refers to a series of interlinked physiological changes that occur in response to a surgical (or traumatic) insult. These include a cascade of endocrine, metabolic and immunological responses that evolved to improve the chances of survival following injury, however, in modern surgical and anaesthetic practice aspects of the response may become maladaptive.

Cuthbertson classically described the biphasic hypermetabolic response to injury [49]: The initial “ebb” phase begins soon after the injurious stimulus and typically lasts 2-3 days and is characterised by a reduction in metabolic activity. The subsequent “flow” phase, lasting from days to weeks depending on the severity of the traumatic insult, is characterised by a catabolic and hypermetabolic response. In reality the two phases are less clearly defined and the biphasic concept may not adequately describe the metabolic responses induced following surgical insults, however, the correlations established between injury and hypermetabolism and the modulation of the physiological responses continue to guide advancements in surgical care.

As a direct consequence of local tissue injury, somatic and visceral afferent neuronal signals are transmitted via the ascending spinal pathways to the central nervous system. These activate both the sympathetic nervous system and the hypothalamic pathways characterised by the increased secretion of pituitary hormones [7]. The changes in pituitary secretion have secondary effects on hormonal secretion from various target organs, principally the adrenals, kidneys, liver and pancreas. *Figure 5* summarises the systemic responses to surgery. The overall metabolic effect is increased catabolism and subsequent substrate mobilisation of carbohydrate (secondary to raised glucagon secretion, decreased insulin together with peripheral insulin resistance), fat (in response to cortisol and growth hormone) and protein (cortisol), and salt and water retention (due to up-regulation of the renin-angiotensin-aldosterone axis in combination with the effect of antidiuretic hormone on the kidney).

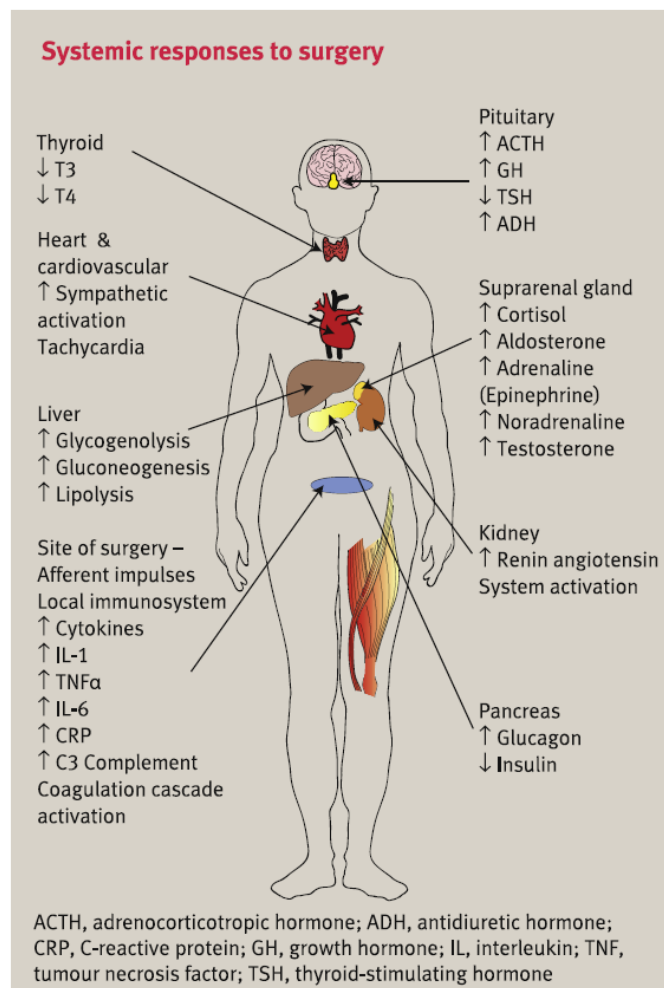


Figure 5. The systemic responses to surgery

taken from Moor et al. (2017) [50]

Tissue damage also leads to the local release of chemical mediators by activated macrophages, fibroblasts and endothelial cells, principally the cytokines, which have both pro- and anti-inflammatory effects. Pro-inflammatory cytokines include interleukin (IL)-1, IL-6 and tumour necrosis factor- α (TNF- α), which activate acute-phase response protein production from the liver e.g. C-reactive protein (CRP) and complement factors, which are inflammatory mediators, anti-proteinases and in tissue repair. Anti-inflammatory cytokines include IL-4, IL-10 and transforming growth factor- β (TGF- β). They can reduce

the severity and duration of any systemic inflammatory response, but if unregulated can predispose to immunodeficiency and sepsis [51]

In general, the magnitude and duration of the stress response are proportional to the surgical injury and the development of complications. An unregulated response, can lead to the systemic inflammatory response syndrome (SIRS) and ultimately multi-organ failure and death. Conversely, modulation of the stress response by various interventions is the central tenet of enhanced recovery after surgery (ERAS) programmes (Section 1.5, Enhanced recovery after surgery, *p28*), which seeks to diminish the stress response and promote a faster recovery time with improved morbidity and short and long term mortality [52]. In particular neuroaxial blockade by local anaesthetic agents in epidural or spinal anaesthesia prevents afferent activation of the hypothalamus and efferent stimulation of the adrenals, liver and pancreas, thus attenuating the stress response [7]. Regional anaesthesia has no effect on cytokine levels as this is mediated and initiated locally by direct tissue damage. However, this effect can be decreased by reducing the duration and magnitude of the surgical intervention e.g. with laparoscopic surgery [52].

The concept of the stress response to surgery and our understanding of it continue to evolve. What remains clear is that it remains a complex multisystem phenomenon involving the endocrine, immune and metabolic systems.

1.5 ENHANCED RECOVERY AFTER SURGERY

Enhanced recovery after surgery (ERAS) pathways, since their inception in the 1990s by Henrik Kehlet [53], have gained widespread acceptance as the standard of care for patients having major surgery. Much of the evidence for the

practice has come from colorectal surgery, but the ERAS Society has published guidelines for multiple specialties (*Table 3*). The concept behind ERAS is to attenuate the stress response to surgery and improve recovery. It accomplishes this via a multimodal approach to the perioperative care of the surgical patient (*Figure 6*), which requires input from multiple members of the multidisciplinary team. The key principles are pre-operative counselling, pre-operative nutrition, avoidance of perioperative fasting, carbohydrate loading up to 2 hours pre-operatively, standardised anaesthetic and analgesic protocols, and early mobilisation. When applied to colorectal surgery, ERAS pathways have been shown to reduce LOS, complication rates and 30-day mortality [54, 55]. However, in a meta-analysis of 38 trials covering GI, GU, orthopaedic, thoracic and vascular surgery, with a total of 5099 patients, ERAS pathways were only shown to reduce LOS (standardised mean difference -1.14 (-1.45 to -0.85)) and reduce the risk of all complications within 30 days (RR 0.71 (0.60 to 0.86)), with no reduction in mortality (RR 0.69 (0.34 to 1.39)), major complications (RR 0.95 (0.69 to 1.31)) or readmission rates (RR 0.96 (0.59 to 1.58)) [56]. No individual components of the ERAS pathway were identified as independently improving outcomes, which suggests that the multi-modal approach of ERAS is akin to British Cycling's Dave Brailsford's concept of "marginal gains":

"The whole principle came from the idea that if you broke down everything you could think of that goes into riding a bike, and then improved it by 1%, you will get a significant increase when you put them all together" [57].

Table 3. ERAS Society Guidelines^a

Procedure and Topic	Year of Publication
Colonic resection	2012
Rectal resection	2012
Pancreaticoduodenectomy	2012
Cystectomy	2013
Gastric resection	2014
Anesthesia protocols	2015
Anesthesia pathophysiology	2015
Major gynecology (parts 1 and 2)	2015
Bariatric surgery	2016
Liver resection	2016
Head and neck cancer surgery	2016
Breast reconstruction	2017
Hip and knee replacement	Under production
Thoracic noncardiac surgery	Under production
Esophageal resection	Under production

Abbreviation: ERAS, Enhanced Recovery After Surgery.

^a For updates and free download, go to <http://www.erassociety.org>.

Table 3 ERAS Society Guidelines by specialty and year of publication

From Ljungqvist *et al.* (2017) [58].

Compliance to ERAS protocols also seems to be important. In a study on 953 consecutive patients with colorectal cancer in Sweden, >70% adherence to the ERAS protocol significantly reduced adverse outcomes in terms of 30-day morbidity, LOS, and readmissions compared with low (<50%) ERAS adherence [59]. Moreover, long-term survival seems to be improved with increasing adherence, with patients with ≥70% adherence to ERAS pathways, the risk of 5-year cancer-specific death was lowered by 42% (HR 0.58 (0.39 to 0.88)) [60].

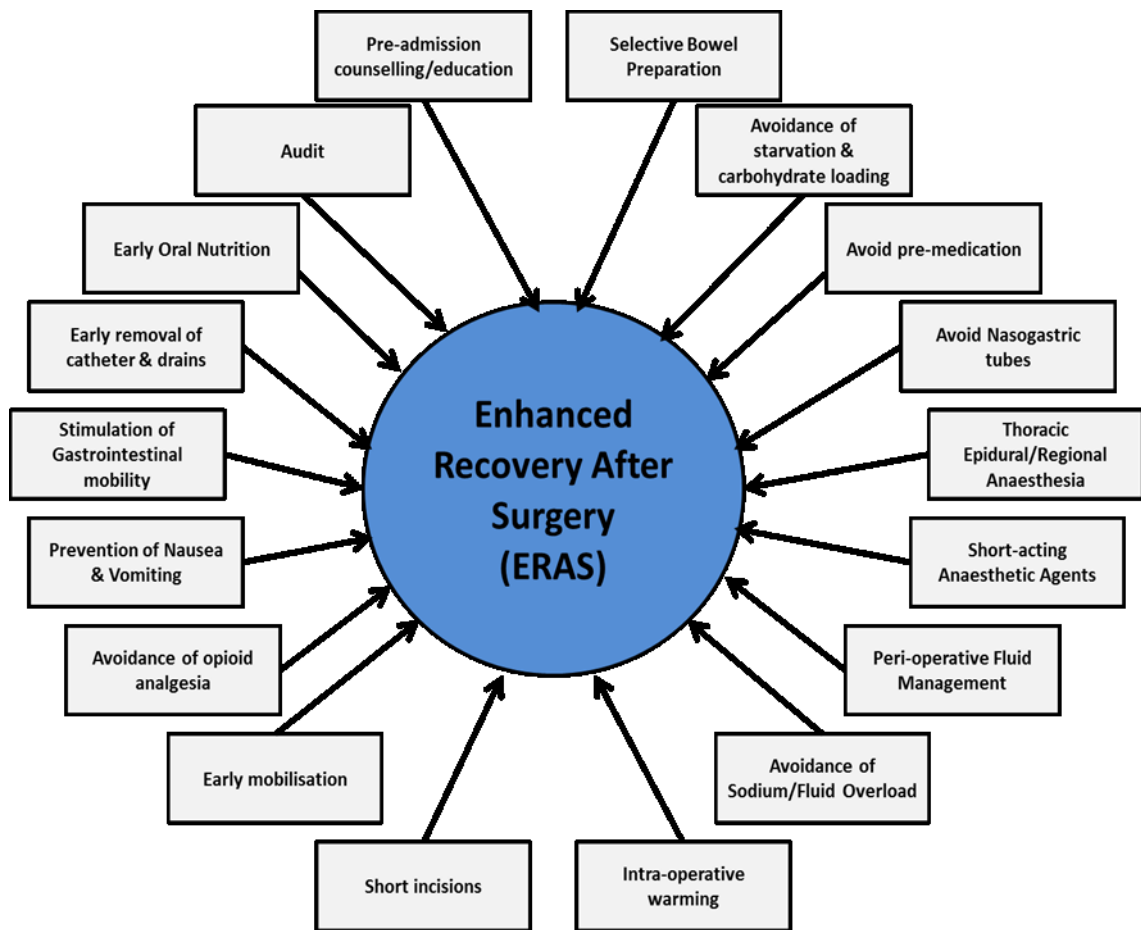


Figure 2 Enhanced Recovery After Surgery

The multimodal approach

ERAS represents a paradigm shift in the delivery of surgical care, with both short and long-term benefits for patients. Contrary to the beliefs of early detractors who suggested that the impressive early results showing 2-day hospital stays after sigmoid resection [61] was due to careful patient selection, similarly impressive results have been seen in high-risk patients with complex medical co-morbidities undergoing major surgery [62]. Fit patients having laparoscopic colonic resections within an established ERAS protocol can even be discharged within 23 hours of surgery without adverse events [63].

1.6 GOAL DIRECTED THERAPY (GDT)

There is perhaps no more controversial subject in perioperative medicine than that of fluid therapy. What can be said with any certainty is that the literature is inconsistent. Any meta-analysis that has been performed has noted the heterogeneity of studies in terms of fluid regimes and outcome definitions [64-69]. Too little fluid and hypovolaemia can develop, resulting in decreased CO and thus impaired tissue perfusion, reduced DO_2 and increased morbidity [70], an important part of which could be explained largely due to hypoperfusion of various tissue beds, most importantly for GI surgery, the splanchnic circulation [71, 72]. This can be compounded in GI surgery by prolonged peri-operative fasting and mechanical bowel preparation [73], although this has in part been offset by the introduction of ERAS pathways [53]. Equally, too much fluid can lead to tissue oedema, compromised cardiac and pulmonary function, and increase the risk of post-operative ileus [65, 74, 75]. Many hope that the well designed RELIEF trial [67] will give the definitive answer as to whether a liberal (10ml/kg bolus of balanced crystalloid at initiation of surgery followed by 8ml/kg/hr until the end of surgery, followed by a maintenance infusion of 1.5ml/kg/hr for 24 hours), or restrictive (≤ 5 ml/kg bolus of balanced crystalloid at induction of anaesthesia followed by 5ml/kg/hr until the end of surgery, followed by a postoperative infusion rate of 0.8ml/kg/hr until cessation of iv fluids within 24 hours) fluid regime is optimum for patients undergoing major abdominal surgery.

What is clear is that peri-operative fluid management follows what could be termed the “Goldilocks principle”: not too much, and not too little, but just right

(*Figure 7*)! In their systematic review of peri-operative fluid therapy Bundgaard-Nielsen *et al.* make the point that “a fixed volume regimen is unlikely to both prevent hypovolaemia and the risk of hypervolaemia for every patient”, and that “rational perioperative fluid management may include a combination of fixed crystalloid administration to replace extra-vascular losses and individualized goal-directed colloid administration to maintain a maximal cardiac stroke volume” [64].

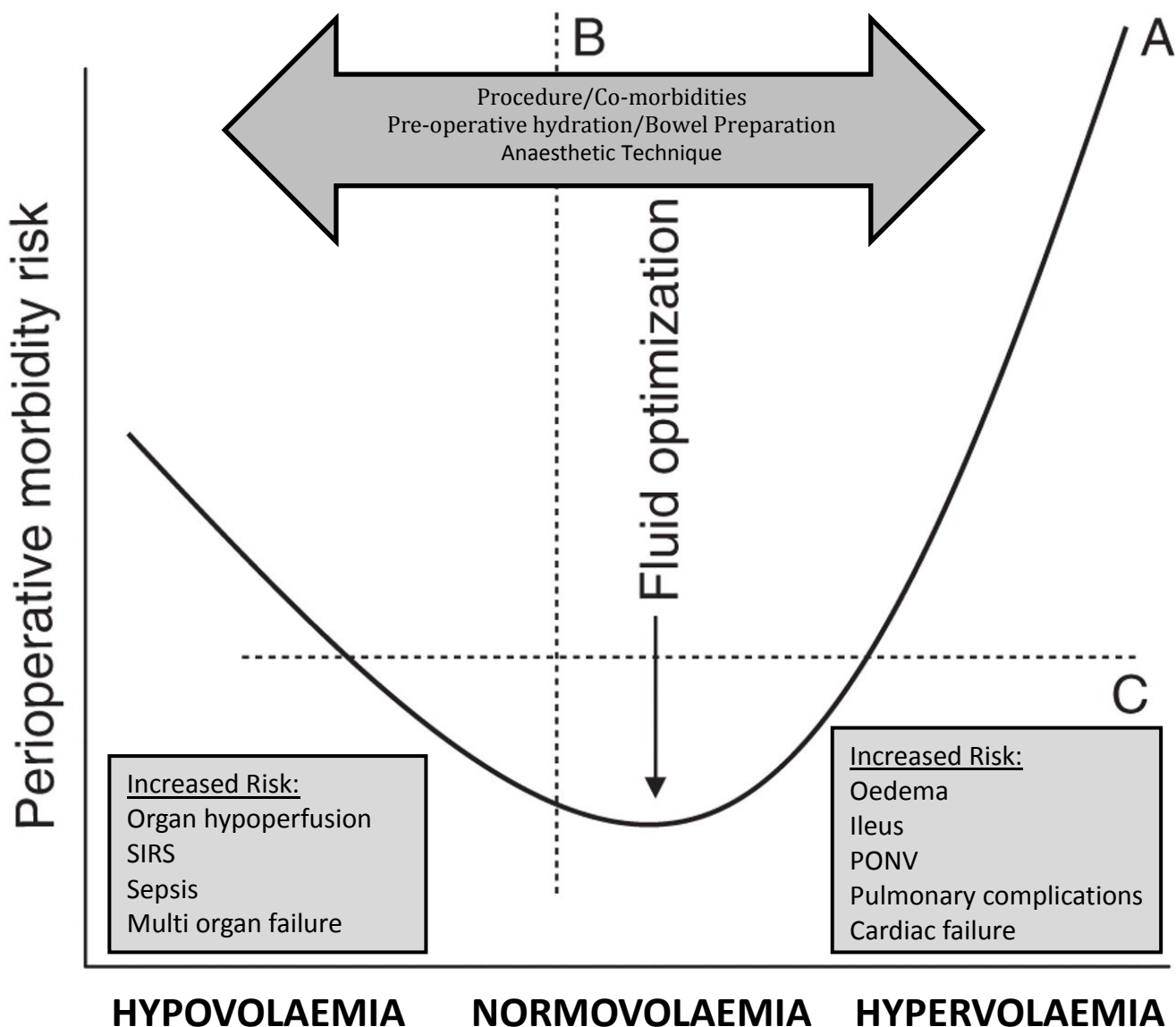


Figure 7 The optimal fluid administration curve

From Bellamy (2006) [76] & Bundgaard-Nielsen *et al.* (2009) [64]. Relationship between perioperative administered fluid volume and post-operative morbidity and factors influencing shift of the curve (arrow). *Curve A* represents the hypothesized line of risk. *Broken line B* represents a division between patient groups in a 'restrictive vs. liberal' study. *Broken line C* represents a division between patient and groups in an 'optimised vs. non-optimised' study. Boxes indicate the risk of complications associated with deviation from normovolaemia.

As previously discussed, Shoemaker *et al.* were the first to develop the concept of GDT. They described the increase in $\dot{V}O_2$ in patients after major surgery and presented evidence that the inability to meet this demand was associated with severe post-operative complications and mortality [14, 37, 38]: Shoemaker estimated patients' postoperative oxygen consumption requirement (using their measured preoperative baseline $\dot{V}O_2$ corrected for temperature) and suggested that oxygen deficit was present when this figure exceeded measured $\dot{V}O_2$. The temporal pattern of post-operative oxygen deficit appears to differ according to whether patients survive, develop complications or not (*Figure 3*). They then optimised patients with intravenous fluids, inotropes and O_2 therapy to so-called "supra-normal values" for CO and tissue DO_2 , demonstrating a reduction in mortality from 28% to 4% ($p < 0.02$) [14]. Further RCTs were performed, and meta-analyses carried out, of protocols which included various methods of measuring CO, different fluid regimes and either using vasoactive drugs or not. These early studies showed strong benefits in terms of a reduction in postoperative morbidity and reduced LOS with GDT compared with "conventional" fluid therapy [71, 77-80].

As described above with meta-analyses of liberal vs. restrictive perioperative fluid therapy, meta-analysis of GDT is hampered by heterogeneity of study design [81, 82]. Despite this, in 2011 NICE issued guidance recommending the use of individualised GDT through stroke volume optimisation as a standard of care during major surgery [83]. However, more recent trials have not demonstrated any benefit to GDT [84-86], which questions the recommended ubiquity of stroke volume optimisation by NICE. Indeed, two recent trials from

our group in the era of routine ERAS pathways in colorectal surgery, suggest that GDT in this patient population may actually cause adverse effects [87, 88]. The recent meta-analysis of GDT in colorectal surgery by Srinivasa *et al.* has shown that GDT did not influence LOS or complication rate in the context of ERAS pathways, or when compared with fluid restriction [89]. Moreover, in the context of bowel function, although GDT results in a shortened time to first bowel movement, a shortened time to oral intake and reduced post-operative nausea and vomiting, this was only seen outside ERAS pathways and colorectal surgery [90]. The most recent meta-analysis of intra-operative GDT in elective major abdominal surgery concluded that any historical advantage of GDT was attenuated by its combination with ERAS pathways, and that GDT may only be of use in the intraoperative care of the high-risk patient [91].

1.7 THE NEED FOR FURTHER RESEARCH

Since the 1980's major advances in perioperative care have greatly reduced the risk of dying after surgery and complication rates (reflected in shorter length of stay). Recent studies of GDT and CPET suggest that the assumptions made from 1980's studies may not hold – most less fit patients survive surgery and go home promptly [35] and GDT may not have the impact of previous studies [84, 87, 88, 92]. There is the strong possibility that modern care does not trigger as much of an inflammatory response as that seen in the 1980's and 90's and that patients do not need to develop the same increases in $\dot{V}O_2$ and DO_2 . Indeed, in a recent study of patients undergoing major vascular surgery using non-invasive techniques to determine $\dot{V}O_2$, Royds *et al.* did not observe any rise in postoperative $\dot{V}O_2$ [93].

Earlier studies used invasive techniques to measure and calculate oxygen delivery variables - primarily the pulmonary artery catheter (PAC) – in the setting of Intensive Care Units. Thus these studies included only those patients who were considered to be at sufficiently high risk to justify the insertion of a PAC and admission to a high dependency environment (in general those having surgery with a likelihood of extensive tissue trauma and fluid shifts, or those with co-morbidities severe enough to potentially impair their ability to generate a sustained increase in $\dot{V}O_2$). Consequently the pattern of postoperative $\dot{V}O_2$ and DO_2 in fitter patients or those having less extensive body cavity surgery is not known. In addition, these methods are not easily applicable to modern care, which aims to reduce the impact of surgical and anaesthetic interventions on return to normal function and has reduced the number of “lines” being inserted.

Our long-term aim is to use indirect calorimetry to measure resting $\dot{V}O_2$ and non-invasive technology to measure DO_2 after surgery – replicating measurements made 20 – 30 years ago, but in a broader group of patients. However, a crucial preliminary step is to validate non-invasive measurement of oxygen consumption and oxygen delivery against an accepted standard – presented in the first study of this thesis.

Oxygen consumption patterns after “modern” abdominal surgery are not known. The second study was designed to help assess the feasibility of non-invasive measurement techniques of $\dot{V}O_2$ and DO_2 in the perioperative setting. Ultimately non-invasive techniques might be applicable to determine which

patients are developing “oxygen debt” as a trigger to alter clinical care and potentially improve outcome.

CHAPTER 2

METHODS

This chapter describes the methods used during the studies. Sections 2.1 and 2.2 describe the general principles of the devices used and Sections 2.3 and 2.4 describe in detail the individual patient journey for the 2 studies and detailed descriptions of data collection including flow diagrams.

2.1 OXYGEN CONSUMPTION

2.1.1 Non-invasive measurement

The GEM (GEMNutrition, Daresbury, UK) is an open-circuit flow-through indirect calorimeter [94]. The compact bedside unit measures gas exchange volumes, respiratory quotient and energy expenditure. It does this by alternately measuring O_2 and CO_2 concentrations of inspired and expired air. Flow rate is continually measured to determine the dilution factor. Gas collection is via a comfortable transparent perspex hood placed over the patient's head and chest (*Figure 8*).

GEM is inaccurate above an F_iO_2 of 30%, and the system is incompatible with ventilators. For this study measurements were conducted on spontaneously breathing patients at an F_iO_2 of 21% (room air), however, for pragmatic patient safety reasons, if the patient's SpO_2 fell below 92% an F_iO_2 of 28% was employed and the reading repeated. Further de-saturation on 28% oxygen mandated abandoning the recordings at that time point. A recent study of post-operative $\dot{V}O_2$ in patients undergoing major vascular surgery had similar readings taken with a Douglas Bag on room air without adverse effects reported [93].



Figure 3 The GEM indirect calorimeter gas collection hood.

(Picture used with consent of subject)

Laboratory performance tests for the GEM using reference gas injections show a mean error of $0.3 \pm 2.0\%$ for the measurement of $\dot{V}O_2$ and $1.8 \pm 1.0\%$ for that of VCO_2 , which compares favourably to those of other commercially available indirect calorimeters, and indicate a clinically insignificant mean relative error when measuring these variables [94]. Furthermore, when compared to the DeltatracTM Metabolic Monitor (Datex-Ohmeda Inc.), although GEM reported higher values of resting metabolic rate (RMR), there were no significant differences within repeated measures [95] and therefore when used to track changes in $\dot{V}O_2$ could be considered a reliable alternative

to Deltatrac, which is no longer commercially available, but has been considered as the standard reference tool in indirect calorimetry [96].

According to the manufacturers recommendations, the GEM was calibrated after a 30-minute warm-up. Calibrations were also performed when the cart had been idle for more than 20 minutes or after 2 hours of continuous use. Calibration utilised two pressurized cylinders of reference gas (BOC): high-purity N₂ for the zero and a gas mixture of nominal composition 20% O₂, 1% CO₂, balance N₂ for the span. Monthly ethanol burning tests were performed as a quality check, and the manufacturer calibrated the mass flow meter annually (*Appendix 6*). Minute-by-minute $\dot{V}O_2$ averages are displayed on a monitor and it typically takes a subject between 5 and 10 minutes to acclimatise and for the $\dot{V}O_2$ to settle to a baseline ($\Delta\dot{V}O_2 < 5\%$ on 2 consecutive readings) - *personal communication*: Dr A Jeffery, Research Nurse, EarlyBird Diabetes Study, which used the GEM to measure RMR in 300 children every 6 months for 12 years between 2000 and 2012 [97]. This was followed by a 5-minute recording period. A mean $\dot{V}O_2$ was then calculated for the 5-minute recording period.

2.1.2 Invasive measurement

The reverse Fick equation was used to calculate $\dot{V}O_2$.

$$\dot{V}O_2 = CO \times (C_aO_2 - C_vO_2),$$

$$C_aO_2 = (Hb \times S_aO_2 \times 1.34) + (0.023 \times P_aO_2)$$

$$C_vO_2 = (Hb \times S_vO_2 \times 1.34) + (0.025 \times P_vO_2)$$

Where CO = Cardiac Output, C_aO_2 = Oxygen concentration of arterial blood and C_vO_2 = Oxygen concentration of mixed venous blood, Hb = haemoglobin concentration, P_aO_2 = partial pressure of Oxygen in arterial blood, P_vO_2 = partial pressure of Oxygen in mixed venous blood.

In our institution pulmonary artery catheterisation is rarely performed. However, patients undergoing liver resection surgery routinely have arterial and central venous catheters inserted which remain in situ for at least 24 hours post-operatively to guide post-operative management in the critical care setting.

Continuous arterial pulse contour analysis (following calibration by thermodilution) using the PiCCOplus (Pulsion Medical Systems, Munich, Germany) monitor was initially employed to measure cardiac output. PiCCOplus has acceptable agreement and bias in the measurement of cardiac output compared with intermittent thermodilution via a PAC provided a repeat calibration is performed after any major haemodynamic changes [98-

100]. PiCCOplus requires a specific proprietary arterial catheter to be placed with the transducer tip in either the femoral or axillary artery.

In the early stages of the validation study (n=4) the method of estimating the CO was changed due to an adverse event and a near miss. (*Appendix 5*). All adverse event reporting, and changes to the study protocol, adhered to NRES and ICH GCP guidelines. Subsequently the LiDCOrapid (LiDCO Ltd, London) was used as the CO monitor. LiDCOrapid is a proprietary unit that interrogates the arterial trace from a standard arterial line (typically in the radial artery) and provides an estimated/nominal CO based on the PulseCO algorithm [99]. In the original LiDCO monitor nominal CO can be calibrated against a known CO e.g. lithium dilution method, to give an actual CO. LiDCOrapid uses the validated algorithm without calibration, as a result in this study rather than an absolute value for CO, we utilised an uncalibrated nominal value. This is the major limitation of the device and should be considered when interpreting results, however, LiDCOrapid has the advantage of being minimally invasive, with no potential for direct harm to patients. LiDCOrapid has been shown to be within acceptable limits of agreement with intermittent thermodilution via PAC [99, 101, 102]. CO was transcribed directly onto the case report form (CRF) every minute over the same 5-minute period as the GEM measured $\dot{V}O_2$ and a mean CO calculated.

Simultaneous arterial and central venous blood samples were drawn at the beginning and end of the 5-minute recording period and placed on ice and

immediately analysed in order of time drawn at the end of the 5-minute recording period. Thus the maximum time for being stored on ice was 10 minutes. This allowed measurement and calculation of average arterial and central venous oxygen saturations, haemoglobin concentrations, PaO_2 and the partial pressure of central venous O_2 (PcvO_2). Central venous oxygen saturations (ScvO_2) have been shown to correlate well with those of mixed venous saturations [103], therefore in the absence of mixed venous readings, central venous values were substituted in the above equations to calculate $\dot{V}\text{O}$

2.2 OXYGEN DELIVERY

2.2.1 Non-invasive measurement

DO₂ is calculated according to the following equation:

$$DO_2 = CO \times C_aO_2$$

Where CO = Cardiac Output, C_aO₂ = Oxygen concentration of arterial blood

EsCCO technology (Nihon Kohden, Japan) utilises a proprietary algorithm to provide a real-time estimation of CO from pulse wave transit time i.e. the time interval between the R wave of the ECG and the arrival of the arterial pulsation wave at an oximeter probe placed on the finger. It has been validated against intermittent thermodilution via a PAC as a method to characterise CO in critically ill patients [104]. After an interval of approximately 3 minutes, CO and stroke volume, as well as routine haemodynamic variables, are continuously displayed on a monitor. No data is available from the manufacturers detailing the time delay from measurement of CO to its display on the monitor. Readings were transcribed directly onto the CRF every minute over the 5-minute recording period and an average CO calculated.



Figure 9 The esCCO cardiac output monitor

The Pronto-7 pulse co-oximeter (Masimo Corp, Irvine, CA, USA), is a non-invasive haemoglobin and oxygen saturation spot-check device. It has a spectrophotometric sensor that senses multiple wavelengths of light to acquire blood constituent data i.e. different haemoglobin species, and determines total haemoglobin levels by applying proprietary algorithms based on light absorption [105]. It has been shown to have similar accuracy as the HemoCue (HemoCue, Sweden) point-of-care device when compared with a laboratory haematology analyser in the outpatient setting, with bias \pm standard deviation of -0.1 ± 1.1 g/dL and -0.1 ± 1.6 g/dL respectively [106], and comparable accuracy in the trauma patients [107]. The Pronto-7 finger probe was placed on the opposite side to the arterial line catheter and readings were taken at the beginning and end of the 5-minute GEM recording period and a mean value calculated.



Figure 10 The Pronto-7 pulse co-oximeter

Non-invasive C_aO_2 was calculated as follows:

$$C_aO_2 = (Hb \times SaO_2 \times 1.34) + (0.023 \times PaO_2)$$

The amount of oxygen dissolved in arterial blood ($0.023 \times PaO_2$) was disregarded in the calculation, as PaO_2 could not be determined non-invasively. In an average adult male with an Hb = 15 g/dL, an $SaO_2 = 100\%$, a $PaO_2 = 13.3$ kPa, and a CO = 5 l/min, the difference in $CaO_2 = 0.3$ ml/100ml (20.1 vs 20.4 ml/100ml), which equates to a difference in $DO_2 = 15$ ml/min (1005 vs 1020 ml/min), or a reduction of < 1.5%, which was deemed acceptable on pragmatic grounds.

2.2.2 Invasive measurement

CO and C_aO_2 were measured as described in Section 2.1.2 using the PiCCOplus, and subsequently the LiDCOrapid, monitor, combined with

arterial blood gas analysis drawn from the arterial catheter in situ. Average values were calculated for the 5-minute GEM recording period.

2.3 VALIDATION STUDY

2.3.1 STUDY DESIGN

This was a prospective observational study of paired minimally invasive (standard) and non-invasive measurements of $\dot{V}O_2$ and DO_2 at 6 time points in the first 24 hours postoperatively in a cohort of 20 patients undergoing elective major liver resections between October 2013 and July 2014 at the Peninsula Hepatopancreatobiliary (HPB) Surgical Unit, Derriford Hospital, Plymouth, UK. Ethical approval was obtained from the NRES Committee South West - Cornwall & Plymouth (ref: 13/SW/0177). This study was adopted by NIHR (UKCRN ID: 15072).

2.3.2 HPB SURGERY CLINIC

Patients having major surgery for colorectal liver metastases receive this diagnosis at a consultant led clinic and have an opportunity to discuss the management of their disease, including an operation, with their surgeon.

An appointment is made for a full pre-operative assessment, and often a date for surgery is decided. Patients receive an information pack regarding the procedure for pre-assessment. Included within this is information regarding the tests they may undergo. At the same clinic they are counselled by a cancer nurse specialist regarding potential implications of the diagnosis. During this discussion the nurse specialist may inform the patient about pre-operative risk assessment using cardiopulmonary exercise testing (CPET), if deemed necessary.

2.3.3 PRE-OPERATIVE ASSESSMENT

All patients scheduled for elective liver resections undergo a pre-operative assessment at a dedicated clinic. For the majority of patients, this includes functional assessment with CPET on a stationary bicycle performed by a consultant anaesthetist. Anaerobic threshold (AT) was determined by the V-slope method with correlation by ventilatory equivalents.

On the basis of the result of the CPET and other factors patients were categorised as "normal" risk or "high" risk for peri-operative cardiac or respiratory complications. They had an opportunity to discuss the results and their implications immediately with a consultant anaesthetist. The results influenced the scheduled surgery as follows: they suggested an acceptable risk for the particular patient; alternatively a less radical operation, or non-operative management was chosen. Such decisions were made by the patient and surgeon.

Those patients who did not have a CPET i.e. those considered "fit" by their consultant surgeon, still attended a nurse-led preoperative assessment clinic.

During the conduct of the pre-operative assessment, patients who met the eligibility criteria were informed about the study by an investigator. Those patients who expressed an interest were provided with a patient information sheet (*Appendix 1*). A screening number was then issued and this number, date, hospital identification number and patient's initials were entered onto a screening database stored on a secured network drive along with an

indication of whether they were agreeable for an investigator to telephone later to discuss the study. A telephonic discussion then followed at least 24 hours later. This provided an opportunity to answer any questions and allow assent to proceed with the study.

2.3.4 ELIGIBILITY CRITERIA

Inclusion and exclusion criteria are shown in *Table 4*.

Inclusion Criteria	<ul style="list-style-type: none"> • Aged \geq 18years
	<ul style="list-style-type: none"> • Elective major liver resection
	<ul style="list-style-type: none"> • Post-operative admission to High Dependency Unit (HDU)
	<ul style="list-style-type: none"> • Arterial line and central venous pressure line in situ
Exclusion Criteria	<ul style="list-style-type: none"> • Age <18 years
	<ul style="list-style-type: none"> • Refusal to participate
	<ul style="list-style-type: none"> • Requirement for post-operative ventilation
	<ul style="list-style-type: none"> • Requirement for inspired O₂ concentrations (F_IO₂) >28% to maintain O₂ saturations \geq92%

Table 4 Eligibility Criteria for Validation Study

Patients were excluded if they required post-operative mechanical ventilation or an F_IO₂ >28% as the GEM metabolic cart is inaccurate above an F_IO₂ of 30% and is incompatible with ventilators. An oxygen saturation \geq 92% was chosen on a pragmatic patient safety basis.

2.3.5 CONSENT

On the day of surgery, an investigator met with the patient to provide an opportunity for further discussion. Formal written consent was then obtained on NRES-approved forms (*Appendix 2*) from those patients willing to proceed with the study.

2.3.6 PERIOPERATIVE MANAGEMENT

All interventions were at the discretion of the operating surgeon and/or consultant anaesthetist responsible for the patient. During the conduct of the study a locally established Enhanced Recovery After Surgery (ERAS) pathway was introduced for patients undergoing liver resections (*Figure 11*), which included pre-operative nutritional supplements (Ensure/Enlive™) and carbohydrate drinks (Pre-Op™; Nutricia, UK), and standardised post-operative care.

Patients received a volatile-based general anaesthetic with standard monitoring as per AAGBI guidelines [108] along with invasive continuous monitoring of arterial and central venous pressure and hourly monitoring of urine output. Local guidelines suggest low thoracic intraoperative and postoperative epidural analgesia, but other regional techniques were also utilised according to anaesthetist discretion. Fluid management, at the discretion of the attending anaesthetist, was typically permissive hypovolaemia during dissection and resection phases of surgery, then fluid resuscitation to euvolaemia using isotonic crystalloid, colloid, blood products and inotropes/vasopressors infusion as indicated.

During the early phases of the study a specific brachial arterial line for the PiCCOplus™ monitoring system was used, however, following an adverse event, and a near miss (*Appendix 5*), the study protocol was changed to employ the LiDCOrapid as the CO monitor. All adverse event reporting and changes to the study protocol adhered to NRES and ICH GCP guidelines. The LiDCOrapid interrogates the arterial trace from a standard arterial line and provides an estimated CO based on the PulseCO algorithm [99].

OPEN EXTENDED & HEMI-HEPATECTOMY +/- ROUX-EN-Y

Actions	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Discharge
Monitoring	Hourly obs (minimum) Cardiac monitoring Oxygen via mask	2-4 hourly obs (min) STOP oxygen and cardiac monitoring	4 hourly obs (min)	4 hourly obs (min)	6 hourly obs (min)	6 hourly obs (min)	6 hourly obs (min)	6 hourly obs (min)	Obs stable
DVT Prophylaxis	TED Stockings Clexane 6hrs post-op	TEDs Clexane	TEDs Clexane	TEDs Clexane	TEDs Clexane	TEDs Clexane	TEDs Clexane	TEDs Clexane	Home with Clexane for 28 days
Pain Control	PCA IV paracetamol	As per day 0 plus Oral analgesia	STOP PCA Oral analgesia	Oral analgesia	Oral analgesia	Oral analgesia	Oral analgesia	Oral analgesia	Pain controlled
NG Tube	In place	Spigot if <500ml in 24hrs	REMOVE if <500ml in 24hrs						
Abdominal Drain	In place	In place	REMOVE if no bile/enteric contents in drain						
Urinary Catheter	In place	REMOVE unless contra- indicated							
Central line	In place	REMOVE unless contra- indicated							
IV Fluids	In place	STOP							
Investigations	CXR in recovery/HDU FBC, LFTs, U&Es, Monitor lactate & Clotting screen - APTT & PT	FBC, LFTs, U&Es, Monitor lactate & Clotting screen - APTT & PT		FBC, LFTs, U&Es, Clotting screen - APTT & PT		FBC, LFTs, U&Es			All results acceptable level Bilirubin <3x normal and/or LFTs improving
Eating and Drinking	Sips of water	Sips of water	Free fluids	Normal diet and free fluids	Normal diet and free fluids	Normal diet and free fluids	Normal diet and free fluids	Normal diet and free fluids	Eating and Drinking
Wound Care	None	Check wound, only change dressing if leaking	If wound is dry, REMOVE dressing						Wound satisfactory Wound care advice given
Exercise	Keep head of bed raised to at least 30° Show & encourage deep breathing & leg exercises	Keep head of bed raised to >30° Assist pt to sit out and mobilise 2-4 times Encourage breathing & leg exercises	Keep head of bed raised to >30° Assist pt to sit out and mobilise 4 times Encourage breathing & leg exercises	Keep head of bed raised to >30° Assist pt to sit out and mobilise 4 times Encourage breathing & leg exercises	Mobilise fully	Mobilise fully	Mobilise fully	Mobilise fully	Independently mobilising to pt's norm
Personal Care	Assist pt with personal care	Assist pt with personal care	Encourage pt to self-care and dress in day clothes	Encourage pt to self-care and dress in day clothes	Pt dressed in day clothes	Pt self-caring as normal	Pt self-caring as normal	Pt self-caring as normal	Independent as patients normal

Comments are closed.

Figure 11 Local hemi-hepatectomy ERAS pathway.

Reproduced from www.erasapp.co.uk

It is standard practice to allow patients to wake at the conclusion of surgery, with only those patients having complicated (e.g. intra-operative haemorrhage), or prolonged (typically >6 hours) surgery admitted to the intensive care facility ventilated; these patients were excluded from the study. Patients typically spent between 30 minutes to several hours in the Recovery Area in the main theatre complex where haemodynamic observations are taken as well as objective measures of postoperative pain scores. Once stable, patients were taken to the High Dependency Unit (HDU), which is an area within the main ITU complex. Occasionally patients bypassed the Recovery Area and were admitted straight to HDU.

Standardised post-operative care was provided by a dedicated HPB surgical team and the ITU medical staff according to a locally introduced ERAS pathway (*Figure 11*).

2.3.7 STUDY OBSERVATIONS

Paired minimally invasive and non-invasive measurements of $\dot{V}O_2$ and DO_2 were commenced at 1 hour after admission to the HDU and then at a further 5 time points in the first 24 hours post-operatively at least 2 hours apart. All observations were made with patients lying in bed with a 30° head up tilt. All monitors were placed in the immediate bedside environment of the patient.

1. The GEM metabolic cart was switched on at least 30 minutes prior to any recording taking place and calibrated according to the manufacturers instructions.
2. The esCCO finger probe, ECG dots and arm cuff (*Figure 9*) and the Pronto-7 pulse co-oximeter finger probe (*Figure 10*) were attached to the patient on the opposite side to the arterial line. After an interval of approximately three to five minutes haemodynamic variables are obtained from the esCCO monitor including estimated CO.
3. A tympanic measurement of body temperature using a Braun Thermoscan® PRO 4000 was taken just prior to the GEM hood being placed over the head and chest of the patient (*Figure 8*). Measurements were taken with the patient breathing room air ($F_iO_2 = 21\%$), however, if the patient's SpO_2 fell below 92%, an F_iO_2 of 28% was employed. Further desaturation on 28% O_2 mandated abandoning the recordings at that time-point. Minute-by-minute $\dot{V}O_2$ averages are displayed on a monitor, and once the subject had acclimatised (which typically takes between 5 and 10 minutes) and the $\dot{V}O_2$ settled to a baseline ($\Delta\dot{V}O_2 < 5\%$ on 2 consecutive readings), a 5-minute recording period ensued and a mean value calculated.

4. At the beginning and end of the 5-minute recording period 2ml blood samples were drawn from the arterial and CVP lines and placed on ice for a maximum of 10 minutes. These were subsequently analysed in time order using the ABL800 FLEX benchtop blood gas analyser (Radiometer Medical ApS, Denmark) at the end of the recording period and values for Hb, PaO₂, PcvO₂, SaO₂ and ScvO₂ obtained and averaged over the recording period.
5. Spot Hb measurements were taken with the Pronto-7 pulse co-oximeter at the beginning and end of the 5-minute recording period and an average value calculated.
6. CO was directly transcribed at 1-minute intervals over the recording period from the esCCO monitor and LiDCOrapid monitor, derived from the in situ arterial line trace, and an average value for the recording period calculated. (Nb. For the first 4 patients in the study PiCCOplus was used to measure CO. This required calibration by 3 transpulmonary thermodilutions with 20ml of cold normal saline. This was performed prior to the GEM hood being placed over the head and chest of the subject.)
7. An estimation of any oral calorific intake in the preceding 1-hour was recorded.
8. At each time point paired mean minimally invasive and non-invasive $\dot{V}O_2$ and DO_2 were calculated from the recorded data.

Routine post-operative care was provided at the discretion of the surgical and HDU/ITU teams until patients were fit for discharge home. Teams were

encouraged to adhere to the locally agreed ERAS pathway. A flowchart for clinical data collection and each time point is given in *Figure 12*.

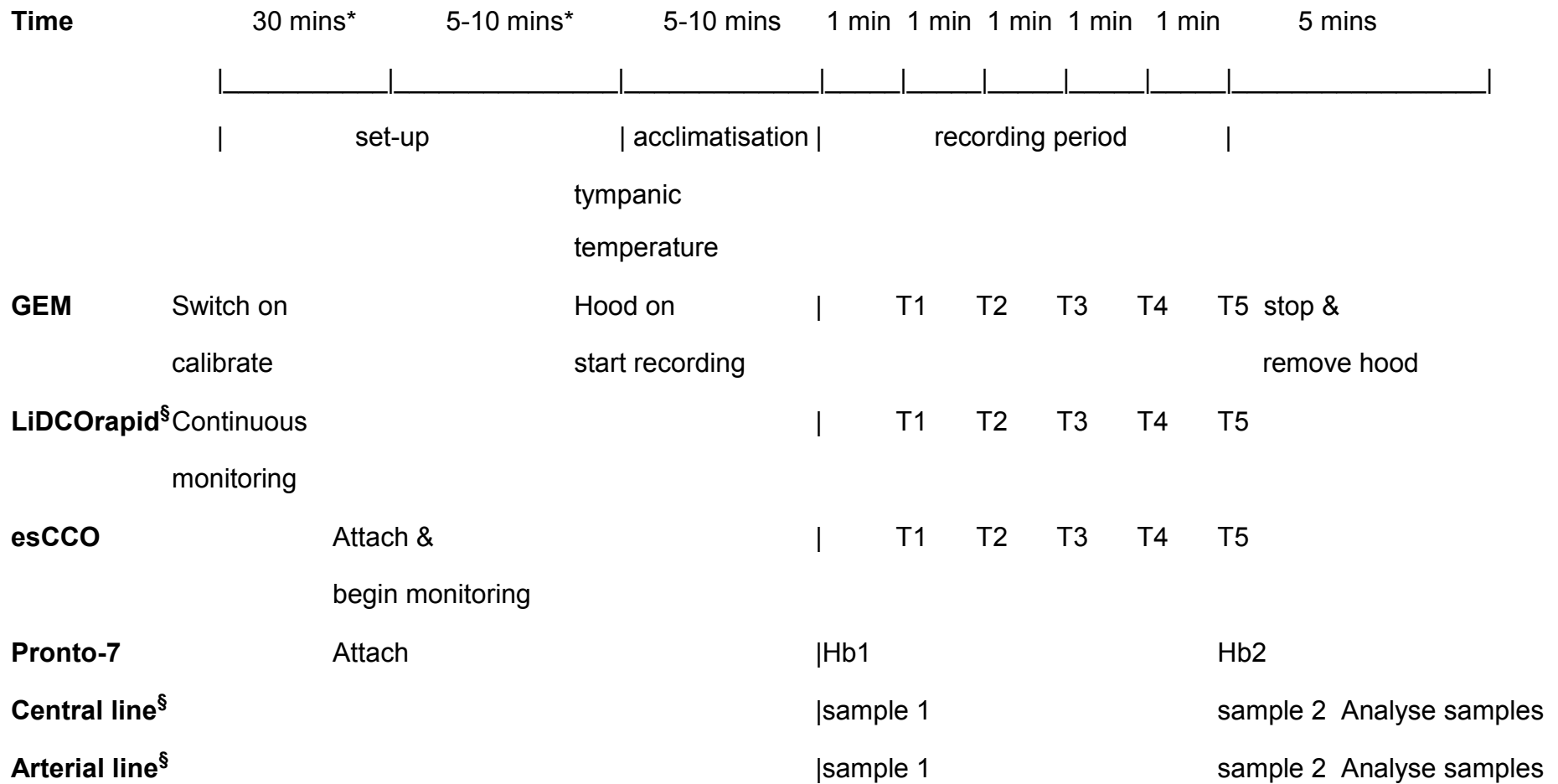


Figure 12 Flowchart for the acquisition of clinical data collection for validation study

2.3.8 STATISTICAL ANALYSIS

Previous studies of agreement between methods of CO measurement with multiple observations per individual have typically required approximately 100 paired observations [109], i.e. 6 observations performed on each of 17 participants. We expanded our sample size to allow for dropouts. In common with previous studies we used Bland-Altman analysis corrected for repeated measures [109] to compare absolute invasive and non-invasive measurements. Results are presented as bias (mean difference between measurements), precision (standard deviation, *SD*, of bias) and 95% limits of agreement (bias ± 1.96 *SD*) [109, 110]. The percentage error was calculated as $2SD$ of the bias divided by the mean of the invasive measurement. A percentage error of $<30\%$ is considered acceptable [111].

Trends of $\dot{V}O_2$, DO_2 and CO have more clinical relevance than point estimates, and therefore, the trending ability of the non-invasive techniques was assessed by analysing $\Delta_{\text{non-invasive}}$ values and Δ_{invasive} values on four-quadrant plots with concordance rates and polar plot analysis [112, 113].

In studies using thermodilution as the reference CO, concordance rates of 90-95% support good trending ability [112]. Four-quadrant plots are obtained by calculating the differences in consecutively obtained values (e.g. change in CO) for both the reference and studied technology and plotting them in a scatter plot. *Figure 13* shows an example 4-quadrant plot. Values on the x-axis refer to the change in the measured variable of the reference technology, and those on the y-axis for the change in the measured variable of the studied

technology. Data on the plot will fall within one of 4 quadrants. If there is a positive change in the measured variable in both technologies the data point will appear in the upper right quadrant. Correspondingly, a decrease in the measured variable in both technologies will result in a data point in the lower left quadrant i.e. both these quadrants represent concordant measurements of the two technologies and are subsequently shaded green in this example. Similarly data points in the quadrants coloured red in the example are discordant changes. If the changes in both technologies were identical then data points would lie on the line of identity ($y=x$, the light blue diagonal line on the example). The concordance rate is the proportion of data points in the green quadrants. Very small changes in a measured variable may be due to “noise”, and should not be included in any assessment of trending ability [112], therefore a central exclusion zone (typically 0.5 L/min, or 10%, for CO monitors) is employed. This is represented by the central light shaded box. Data points in this area are not included in the data analysis.

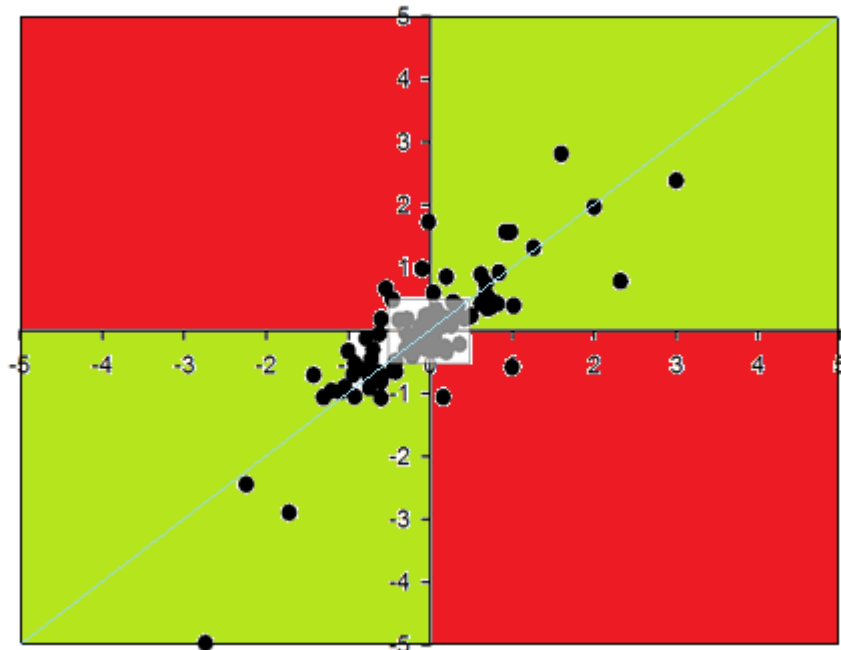


Figure 13 Example 4-quadrant plot

Values on the x-axis refer to the change in the measured variable of the reference technology, and those on the y-axis for the change in the measured variable of the studied technology. Data on the plot will fall within one of 4 quadrants. If there is a positive change in the measured variable in both technologies the data point will appear in the upper right quadrant. Correspondingly, a decrease in the measured variable in both technologies will result in a data point in the lower left quadrant i.e. both these quadrants represent concordant measurements of the two technologies and are subsequently shaded green in this example. Similarly data points in the quadrants coloured red in the example are discordant changes. If the changes in both technologies were identical then data points would lie on the line of identity ($y=x$, the light blue diagonal line on the example). The concordance rate is the proportion of data points in the green quadrants. Very small changes in a measured variable may be due to “noise”, and should not be included in any assessment of trending ability [112], therefore a central exclusion zone (typically 0.5 L/min, or 10%, for CO monitors) is employed. This is represented by the central light shaded box. Data points in this area are not included in the data analysis.

The polar plot was developed by Critchley *et al.* [112] and is methodologically derived from the 4-quadrant plot, but unlike concordance rates, polar plot analysis assesses agreement not only in direction of change, but also for the magnitude of that change. The x-y co-ordinates are converted to polar co-ordinates where the radial length of the polar vector represents the magnitude of the mean change in consecutive paired non-invasive and invasive

measurements. The polar angle represents agreement of the magnitudes of change between the methods (i.e. the line of identity) and the mean polar angle, or angular bias, indicates how well calibrated the test method is with the reference method. The radial limits of agreement is the radial sector that contains 95% of data points (analogous to the 95% limits of agreement in Bland-Altman analysis) and the 30° angular concordance rate is the percentage of data points in the $\pm 30^\circ$ sector. Critchley and colleagues set acceptance limits for good trending ability of an angular bias of $< \pm 5^\circ$, radial limits of agreement of $< \pm 30^\circ$, and a 30° concordance rate of $\geq 95\%$. However, in the meta-analysis by Peyton and Chong [114], the authors suggest percentage limits of agreement should be increased from $\pm 30\%$ to $\pm 45\%$, as there is a suggestion that in fact the precision error of thermodilution as a reference method is closer to $\pm 30\%$. Therefore, radial limits of $< \pm 30^\circ$ and $< \pm 45^\circ$ are reported in this study's results. An example polar plot is given in *Figure 14*. Mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. Data points in the red shaded area lie outside the $\pm 45^\circ$ angular concordant sector indicating poor trending ability. Data points within the green shaded area are within the 30° angular concordant sector and represent good trending ability. Data points in the yellow shaded area represent moderate trending ability. A central exclusion zone similar to that used in 4-quadrant plots is represented by the light shaded area.

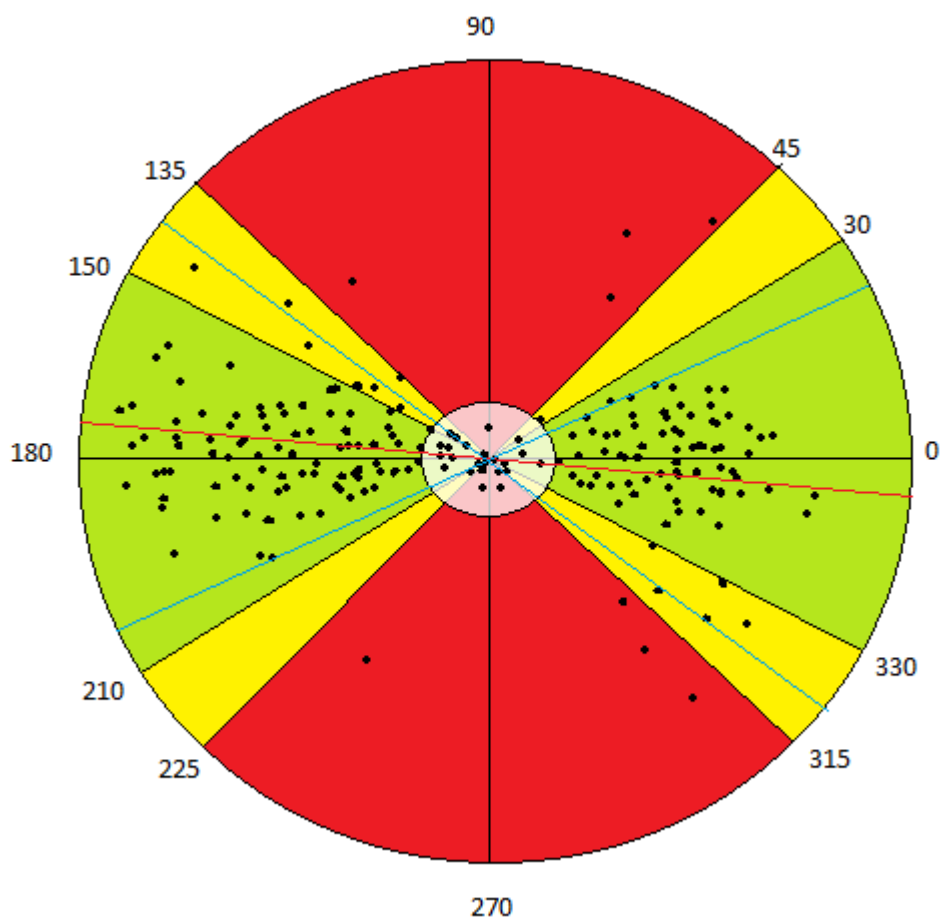


Figure 14 Example polar plot

Mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. Data points in the red shaded area lie outside the $\pm 45^\circ$ angular concordant sector indicating poor trending ability. Data points within the green shaded area are within the 30° angular concordant sector and represent good trending ability. Data points in the yellow shaded area represent moderate trending ability. A central exclusion zone similar to that used in 4-quadrant plots is represented by the light shaded area.

2.4 CO₂ST – A feasibility study

2.4.1 STUDY DESIGN

This was a prospective observational study of non-invasive measurements of $\dot{V}O_2$ and DO_2 pre-operatively and at 8 time points in the first 48 hours postoperatively in a cohort of 40 patients undergoing elective major colorectal surgery (both open and laparoscopic) between December 2014 and March 2015 at Derriford Hospital, Plymouth, UK. Ethical approval was obtained from the NRES Committee South West – Cornwall & Plymouth (ref: 14/SW/1109). It was registered on the ClinicalTrials.gov database (Identifier: NCT02238561).

2.4.2 COLORECTAL SURGICAL CLINIC

Patients having major abdominal surgery at Plymouth Hospitals NHS Trust (PHNT) receive this diagnosis at a consultant led clinic and have an opportunity to discuss the management of their disease, including an operation, with their surgeon.

An appointment is made for a full preoperative assessment, and often a date for surgery is decided. Patients receive an information pack regarding the procedure for pre-assessment, which may include pre-operative risk assessment using CPET, if deemed necessary.

2.4.3 PRE-OPERATIVE ASSESSMENT

By means of the pre-assessment literature patients may have been offered a CPET, conducted by a specialist physiologist or anaesthetist during the course of the pre-assessment clinic.

On the basis of the result of the CPET result, patients will be categorised as “normal” or “high” risk for peri-operative cardiac or respiratory complications. They had an opportunity to discuss the results and their implications immediately with a consultant anaesthetist. The patient’s surgeon and GP are informed by letter. These results may influence the scheduled surgery as follows: they may suggest an acceptable risk for the particular patient; alternatively a less radical operation, or non-operative management may be chosen. Such decisions are made by the patient and surgeon.

Those patients who did not have a CPET i.e. those considered “fit” by their consultant surgeon, still attended a nurse-led preoperative assessment clinic.

The above represents the desired standard of care for all patients scheduled for major elective colorectal surgery in PHNT. Up until this point the study is not relevant.

During the conduct of the discussion of the pre-operative assessment, patients who meet the inclusion criteria were informed about the study by an investigator. Those patients who expressed an interest were provided with a patient information sheet (*Appendix 4*). A screening number was then issued and this number, date, hospital identification number and patient’s initials were

entered onto a screening database stored on a secured network drive along with an indication of whether they were agreeable for an investigator to telephone later to discuss the study. A telephonic discussion then followed at least 24 hours later. This provided an opportunity to answer any questions and allow assent to proceed with the study.

2.4.4 ELIGIBILITY CRITERIA

Inclusion and exclusion criteria are shown in *Table 5*. Patients were excluded if they required post-operative mechanical ventilation or an $F_iO_2 >28\%$ as the GEM metabolic cart is inaccurate above an F_iO_2 of 30%, and is incompatible with ventilators. An oxygen saturation $\geq 90\%$ was chosen on a pragmatic patient safety basis. In the validation study only one patient desaturated to 90% (i.e. $<92\%$), without adverse sequelae therefore the lower value of 90% was chosen.

Inclusion Criteria	<ul style="list-style-type: none"> • Aged ≥ 18 years
Exclusion Criteria	<ul style="list-style-type: none"> • Elective major colorectal resection (open or laparoscopic) • Age <18 years • Refusal to participate • Requirement for post-operative ventilation • Requirement for inspired O_2 concentrations (F_iO_2) $>28\%$ to maintain O_2 saturations $\geq 90\%$

Table 5 Eligibility Criteria for CO₂ST Study

2.4.5 CONSENT

On the day of surgery, an investigator met with the patient to provide an opportunity for further discussion. Formal written consent was then obtained on NRES-approved forms (*Appendix 5*) from those patients willing to proceed with the study.

2.4.6 PERIOPERATIVE MANAGEMENT

All interventions were at the discretion of the operating surgeon and/or consultant anaesthetist responsible for the patient. Mechanical bowel preparation (MBP) was avoided where possible, and those patients receiving MBP routinely received an intravenous infusion of 1-2L of isotonic crystalloid prior to arrival in the operating theatre. Patients following the ERAS pathway were given pre-operative nutritional supplements (Ensure/Enlive™) and carbohydrate drinks (Pre-Op™; Nutricia, UK) according to local guidelines.

Patients received a volatile-based general anaesthetic with standard monitoring as per AAGBI guidelines [108], along with invasive continuous monitoring of arterial and central venous pressure in selected patients, and hourly monitoring of urine output. Local guidelines suggest low thoracic intraoperative and postoperative epidural analgesia for open procedures, but other regional techniques were also utilised according to anaesthetist discretion. Intra-operative fluid management was typically targeted fluid therapy, to maintain euvolaemia, with isotonic crystalloid. Blood products and inotropes/vasopressors were utilised as indicated at the discretion of the anaesthetist.

Standardised postoperative care was provided on a dedicated colorectal surgery ward. Daily ward rounds were conducted by surgical registrars or consultants. All patients were allowed free fluids and/or light diet on the evening of surgery if tolerated. There was no formal protocol for postoperative fluid administration, which was based on clinical need and/or assessment. The clinical team were encouraged to adhere to the local ERAS guidelines which recommended avoidance of excessive intravenous fluid administration (particularly 0.9% Normal Saline) and that they should be discontinued at the earliest opportunity. Early mobilisation was encouraged, epidurals were discontinued at 48-72 hours, and pain managed with oral analgesics at the earliest opportunity. Admission to the Critical Care Unit was at the discretion of the surgeon or anaesthetist.

2.4.7 STUDY OBSERVATIONS

All observations were made with patients lying in bed with 30 degrees head up tilt. Pre-operative observations were made on the morning of surgery after admission to the pre-operative surgical admission unit. Post-operative observations were made at 1, 2, 4, 8, 12, 24, and 48 hours after the completion of surgery.

1. The GEM metabolic cart was switched on at least 30 minutes prior to any recording taking place and calibrated according to the manufacturers instructions (see above).
2. The esCCO finger probe, ECG dots and arm cuff (*Figure 10*) and the Pronto-7 pulse co-oximeter finger probe (*Figure 11*) were attached to the patient. After an interval of approximately three to five minutes

haemodynamic variables are obtained from the esCCO monitor including estimated CO.

3. A tympanic measurement of body temperature using a Braun Thermoscan® **PRO4000** was taken just prior to the GEM hood being placed over the head and chest of the patient (*Figure 8*). Measurements were taken with the patient breathing room air ($F_iO_2 = 21\%$), however, if the patient's SpO_2 fell below 90%, an F_iO_2 of 28% was employed. Further desaturation on 28% O_2 mandated abandoning the recordings at that time-point. Minute-by-minute $\dot{V}O_2$ averages are displayed on a monitor, and once the subject had acclimatised (which typically takes between 5 and 10 minutes) and the $\dot{V}O_2$ settled to a baseline ($\Delta\dot{V}O_2 < 5\%$ on 2 consecutive readings), a 5-minute recording period ensued and a mean value calculated.
4. Spot Hb measurements were taken with the Pronto-7 pulse co-oximeter at the beginning and end of the 5-minute recording period and an average value calculated.
5. CO was directly transcribed at 1-minute intervals over the recording period from the esCCO monitor, and an average value for the recording period calculated.
6. An estimation of the oral calorific intake in the preceding 1-hour was recorded.
7. At each time point mean DO_2 was calculated..
8. On post-operative day 5, a Post-Operative Morbidity Survey (POMS) scale was determined (see section 2.4.8 Post-operative Morbidity Survey, p74). For patients who had been discharged earlier than this, a day 5 POMS score of 0 was assumed.

9. Routine post-operative care was provided at the discretion of the surgical and HDU/ITU teams until patients were fit for discharge home.

A flow chart for clinical data collection is given in *Figure 15*

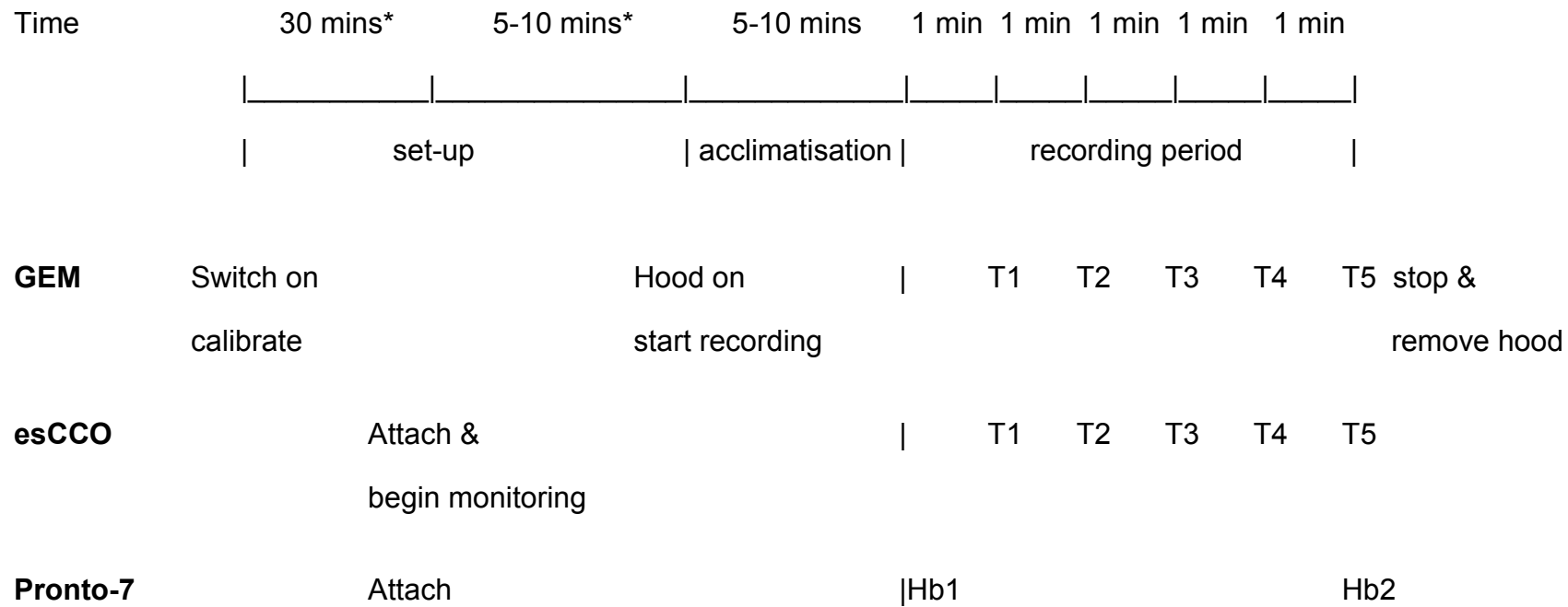


Figure 15 Flowchart for the acquisition of clinical data collection for feasibility study

2.4.8 POST-OPERATIVE MORBIDITY SURVEY

To explore the relationship between post-operative $\dot{V}O_2$ and complications in patients having contemporary major abdominal surgery, the severity of complications need to be graded. The Post-Operative Morbidity Survey (POMS, *Table 6*) is a simple outcome scale and was designed to produce an easy and reliable method of prospectively recording short-term morbidity after major surgery - specifically complications likely to keep a patient in hospital [25, 115]. The POMS only records complications by its effect on a system of the body rather than specify the actual complication. A POMS score performed on Day 5 is likely to be discriminative between patients who are recovering well, and those who are developing complications. POMS is easily performed, has good internal validity and is predictive of a prolonged length of stay [25]. POMS is not a simple additive scale; however, patients with a POMS score ≥ 1 are highly likely to remain in hospital, whereas those with a score of 0 are likely to be able to go home.

Morbidity Type	Criteria
Pulmonary	Has the patient developed a new requirement for supplemental oxygen or other respiratory support
Infectious	Currently on antibiotics and/or has a temperature >38°C in the last 24 hours
Renal	Presence of oliguria (<500 ml/24hr), increased serum creatinine (>30% from pre-operative level), or urinary catheter in place for non-surgical reason.
Gastrointestinal	Unable to tolerate enteral diet for any reason, including nausea, vomiting or abdominal distension (use of antiemetic)
Cardiovascular	Diagnostic tests or therapy within the last 24 hours for any of the following: new myocardial infarction or ischaemia, hypotension (pharmacological therapy or fluid therapy >200 ml/hr), arrhythmias, cardiogenic pulmonary oedema, thrombotic event (requiring anticoagulation)
Neurological	New focal neurological deficit, coma or confusion/delirium
Haematological	Requirement for any of the following within the last 24 hours: packed erythrocytes, platelets, fresh-frozen plasma or cryoprecipitate
Wound	Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms
Pain	New postoperative pain significant enough to require parenteral opioids or regional analgesia

Table 6 The Post-Operative Morbidity Survey (POMS)

Adapted from Grocott et al. (2007) J Clin Epidemiol; 60: 919-928 [25]

2.4.9 STATISTICAL ANALYSIS

This is a pilot study to investigate the feasibility of performing these observations on the target population and a preliminary investigation of $\dot{V}O_2$ and DO_2 after surgery. Thus many of the analyses are exploratory and in our cohort of patients we did not expect to see statistically significant correlations between

our measurements and outcomes. No power calculation was therefore performed.

Shoemaker's methodology was used to estimate oxygen requirement ($\dot{V}O_2$ 'need') at each time point [38]. This was estimated from the baseline pre-operative $\dot{V}O_2$ corrected for the effects of temperature (which assumed "metabolic activity increased or decreased 7 percent per degree Fahrenheit" and was calculated as follows:

$$\text{corrected } \dot{V}O_2 (\dot{V}O_{2c}) = \dot{V}O_2 \times 10^{-0.036667 \times (98.6 - T)},$$

where T is the patient's temperature in °F [38]).

The estimated $\dot{V}O_2$ deficit, or excess, at each time point was calculated as the difference between the measured $\dot{V}O_2$ and the pre-operative baseline $\dot{V}O_2$ corrected for temperature. The net cumulative O_2 balance at each given time-point was calculated as the area under the curve (AUC) described by the time - $\dot{V}O_2$ deficit/excess curve (*Figure 16*).

Patients were divided into those with or without major post-op morbidity (as quantified by Day 5 POMS score) to see whether differences were apparent in the overall AUC of $\dot{V}O_2$ and estimated oxygen debt, or at any of 7 specified time points postoperatively. If so, then the mean values & standard deviations of values of the groups would be useful to calculate sample size of a potentially larger observational study.

To determine if there was a difference in $\dot{V}O_2$, DO_2 , and cumulative O_2 balance between those patients who developed complications or not, we used a linear mixed model for repeated measures over time by group. This type of modelling is applicable to a repeated measures study in which there is unbalance in the study groups and makes it possible to prevent list-wise deletion due to missing data [116-118].

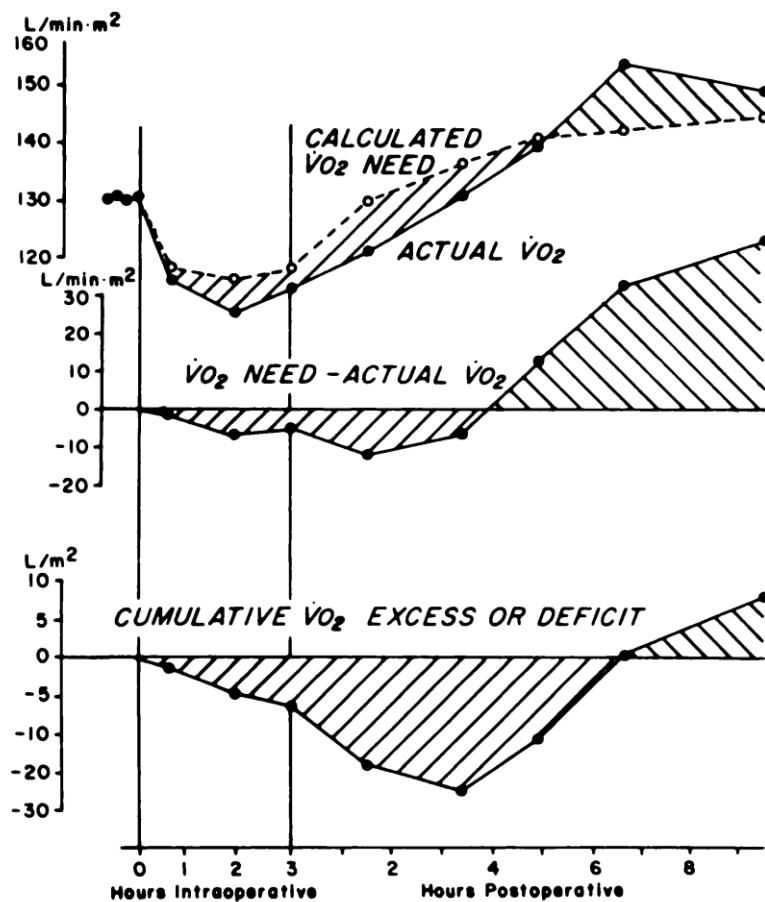


FIGURE 1. Upper section, serial measurements of $\dot{V}O_2$ (solid line) and estimated $\dot{V}O_2$ requirements (dashed lines) in illustrative case. Middle section, $\dot{V}O_2$ deficit measured as difference between actual measured $\dot{V}O_2$ and $\dot{V}O_2$ need. Lower section, cumulative $\dot{V}O_2$ deficit below or excess (above) zero line.

Figure 16 Calculation of net cumulative O_2 debt/excess.

Taken from Shoemaker *et al.* (1992) [38]

Chapter 3

A VALIDATION STUDY OF THE NON-INVASIVE MEASUREMENT OF OXYGEN DELIVERY AND CONSUMPTION AFTER ELECTIVE MAJOR ABDOMINAL SURGERY

3.1 INTRODUCTION

A physiological response to trauma has been recognised for many years [49]. The hypermetabolism and hypercatabolism that result is well documented [7, 119], and is ultimately manifested as an increase in $\dot{V}O_2$, which must be met by an increased DO_2 . Whilst this model is not universally accepted [32], several investigators have observed differences between the $\dot{V}O_2$ and DO_2 values of survivors, those who develop organ failure and those who die, and subsequently advocated the use of “supranormal” values of $\dot{V}O_2$, DO_2 and cardiac index (CI) as goals in the treatment of high risk surgical patients, or those with sepsis [14, 16, 37, 38, 120, 121] – so-called goal directed therapy (GDT), achieved by the administration of intravenous fluid therapy and/or inotropes.

Since these original studies were conducted there have been major advances in perioperative care that have greatly reduced the morbidity and mortality after surgery. Most less fit patients survive surgery and go home promptly [35], and GDT may not have the impact of previous studies [84, 87, 92]. There is the strong possibility that modern care does not trigger as much of an inflammatory response as that seen in the 1980’s and 90’s and that patients do not need to develop the same alterations in $\dot{V}O_2$ and DO_2 . In a recent study of patients undergoing major vascular surgery using non-invasive techniques to determine $\dot{V}O_2$, Royds *et al.* [93] did not observe any rise in postoperative $\dot{V}O_2$.

There are several techniques available for the measurement of $\dot{V}O_2$. Directly measured $\dot{V}O_2$ with a water-sealed spirometer remains the 'gold-standard' method [122], but is technically challenging outside of the laboratory setting. Indirect calorimetry, derived from the measurement of inspired and expired respiratory gases, can be performed either with metabolic gas monitors, or using mass spectrometry. However, until recently these methods were rather slow and cumbersome [123, 124], which meant that the only practical method available to clinicians and researchers was to calculate $\dot{V}O_2$ using the reverse Fick method. The Fick equation utilises CO, usually measured by thermodilution (with a pulmonary artery catheter, PAC), and arterial and mixed venous blood gases to calculate DO_2 and $\dot{V}O_2$:

$$\dot{V}O_2 = CO \times (C_aO_2 - C_vO_2),$$

$$C_aO_2 = (Hb \times S_aO_2 \times 1.34) + (0.023 \times P_aO_2)$$

$$C_vO_2 = (Hb \times S_vO_2 \times 1.34) + (0.025 \times P_vO_2)$$

$$DO_2 = CO \times C_aO_2$$

Where CO = Cardiac Output, C_aO_2 = Oxygen concentration of arterial blood and C_vO_2 = Oxygen concentration of mixed venous blood, Hb = haemoglobin concentration, P_aO_2 = partial pressure of Oxygen in arterial blood, P_vO_2 = partial pressure of Oxygen in mixed venous blood.

Thus studies included only those patients who were considered to be at sufficiently high risk to justify the insertion of a PAC and admission to a high dependency environment (in general those having surgery with a likelihood of extensive tissue trauma and fluid shifts, or those with co-morbidities severe enough to potentially impair their ability to generate a sustained increase in DO_2). Furthermore, in recent years PAC use has significantly reduced [125]

with no evidence of benefit to its routine use, and the risk of significant adverse events [126, 127]. Consequently the pattern of $\dot{V}O_2$ and DO_2 after contemporary high-risk surgery, or in fitter patients or those having less extensive body cavity surgery, is not known. Our long-term aim is to explore the feasibility of using non-invasive techniques to measure $\dot{V}O_2$ and DO_2 after surgery. This study describes the crucial preliminary step, which is to validate these methods in the perioperative setting against an accepted standard.

3.2 METHODS

For more detailed methods please refer to Chapter 2. This single-centre prospective observational study was conducted on patients undergoing elective major liver resections at the Peninsula Hepato-pancreato-biliary Surgical Unit, Derriford Hospital, Plymouth, UK, between October 2013 and July 2014. Ethical approval was obtained from the NRES Committee South West - Cornwall & Plymouth (ref: 13/SW/0177). This study was adopted by NIHR (UKCRN ID: 15072).

All patients scheduled for elective liver resections undergo a pre-operative assessment at a dedicated clinic. During the conduct of the pre-operative assessment, patients were provided with written information (*Appendix 1*) and invited to consider participation in the study. Written informed consent was obtained from all participants (*Appendix 2*).

All interventions were at the discretion of the operating surgeon and/or consultant anaesthetist responsible for the patient. Standardised post-operative care was provided by a dedicated HPB surgical team and the ITU medical staff, according to a locally introduced ERAS pathway. Patients were allowed to wake at the conclusion of surgery, with only those patients having complicated (e.g. intra-operative haemorrhage), or prolonged (typically >6 hours) surgery admitted to the intensive care facility ventilated; these patients were excluded from the study.

Paired minimally invasive and non-invasive measurements of $\dot{V}O_2$ and DO_2 were commenced at 1 hour after admission to the HDU and then at a further 5 time points in the first 24 hours post-operatively at least 2 hours apart. All observations were made with patients lying in bed with a 30° head up tilt. Measurements were taken simultaneously therefore there was no requirement to correct for temperature.

Measurement of $\dot{V}O_2$

Non-invasive measurement

The GEM (GEMNutrition, Daresbury, UK) is an open-circuit flow-through indirect calorimeter. The compact bedside unit measures gas exchange volumes, respiratory quotient and energy expenditure. It does this by alternately measuring O_2 and CO_2 concentrations of inspired and expired air. Gas collection is via a comfortable transparent perspex hood placed over the patient's head and chest (*Figure 9*). GEM is inaccurate above an F_iO_2 of 30%, and the system is incompatible with ventilators. For this study measurements were conducted on spontaneously breathing patients at an F_iO_2 of 21% (room air). Minute-by-minute $\dot{V}O_2$ averages are displayed on a monitor and it typically takes a subject between 5 and 10 minutes to acclimatise and for the $\dot{V}O_2$ to settle to a baseline ($\Delta\dot{V}O_2 < 5\%$ on 2 consecutive readings). This was followed by a 5-minute recording period. A mean $\dot{V}O_2$ was then calculated for the 5-minute recording period.

Invasive measurement

The reverse Fick equation was used to calculate $\dot{V}O_2$. In our institution pulmonary artery catheterisation is rarely performed. However, patients undergoing liver resection surgery routinely have arterial and central venous catheters inserted which remain in situ for at least 24 hours post-operatively to guide post-operative management in the critical care setting. CO was measured using the LiDCOrapid monitor (LiDCO Ltd, London, UK) and an average calculated for the 5-minute GEM recording period. Simultaneous arterial and central venous blood samples were drawn at the beginning and end of the 5-minute recording period and analysed with the ABL800 FLEX benchtop blood gas analyser (Radiometer Medical ApS, Denmark). This allowed measurement and calculation of average S_aO_2 , Central venous oxygen saturations ($S_{cv}O_2$), Hb concentration, P_aO_2 and the partial pressure of central venous O_2 ($P_{cv}O_2$). $S_{cv}O_2$ have been shown to correlate well with those of mixed venous saturations [103], therefore in the absence of mixed venous readings, central venous values were substituted in the Fick equation to calculate $\dot{V}O_2$.

Measurement of DO_2

DO_2 was calculated according to the following equation:

$$DO_2 = CO \times C_aO_2$$

$$C_aO_2 = (Hb \times SaO_2 \times 1.34)$$

The amount of oxygen dissolved in arterial blood ($0.023 \times PaO_2$) was disregarded in the calculation, as P_aO_2 could not be determined non-invasively (see *chapter 2.2.1*).

Non-invasive measurement

Non-invasive CO was measured using the esCCO (Nihon Kohden, Japan) monitor and an average calculated for the 5-minute GEM recording period. esCCO provides a real-time estimation of CO from pulse wave transit time i.e. the time interval between the R wave of the ECG and the arrival of the arterial pulsation wave at an oximeter probe placed on the finger.

Hb and S_aO_2 were measured with the Pronto-7 pulse co-oximeter (Masimo Corp, Irvine, CA, USA) at the beginning and end of the GEM recording period and an average calculated.

Invasive measurement

CO values were obtained from the LiDCOrapid monitor. Hb concentration and S_aO_2 values obtained from arterial blood gas analysis. Average values were calculated for the 5-minute GEM recording period.

Statistical analysis

Full details regarding the statistical analysis employed can be found in section 2.3.8 including an illustrated guide to interpretation for the 4 quadrant and polar plots. Brief details of statistical tests are provided here:

Previous studies of agreement between methods of CO measurement with multiple observations per individual have typically required approximately 100 paired observations [109], i.e. 6 observations performed on each of 17 participants. We expanded our sample size to allow for dropouts. In common

with previous studies we used Bland-Altman analysis corrected for repeated measures to compare absolute invasive and non-invasive measurements.

Trends of $\dot{V}O_2$, DO_2 and CO have more clinical relevance than point estimates, and therefore, the trending ability of the non-invasive techniques was assessed by analysing Δ non-invasive values and Δ invasive values on four-quadrant plots with concordance rates and polar plot analysis [112, 113].

Data was analysed and graphs produced using Microsoft® Excel® for Mac 2011 and SigmaPlot® version 13.0 (Systat Software Inc., San Jose, California, USA).

3.3 RESULTS

One hundred and eleven patients were screened during the study period between October 2013 and July 2014 (*Figure 17*). Twenty-seven patients were not for surgical intervention and 1 patient declined surgery. Of those who underwent pre-operative assessment (n=83), eleven were ineligible as they were not scheduled for a post-operative HDU admission, seven patients declined participation (six of these were due to claustrophobia), six were not recruited due to an investigator not being available, and one patient required a translator.

Fifty-eight patients were recruited. Nineteen subsequently did not meet the eligibility criteria (no admission to HDU, n=14, post-operative ventilation, n=5), six patients withdrew from the study, no investigator was available for three patients, and one patient was unable to tolerate the GEM hood due to post-operative confusion. Four patients had their scheduled date of surgery after the completion of the study (i.e. August 2014, or later). Four patients entered the study prior to a change in protocol (see *Appendix 3*) and are not included in the current analysis of $\dot{V}O_2$ and DO_2 .

A total of one hundred and nine paired minimally invasive and non-invasive measurements from twenty-one patients were collected for $\dot{V}O_2$, DO_2 , CO, Hb concentrations, and SpO_2 . Patient characteristics are shown in *Table 7*.

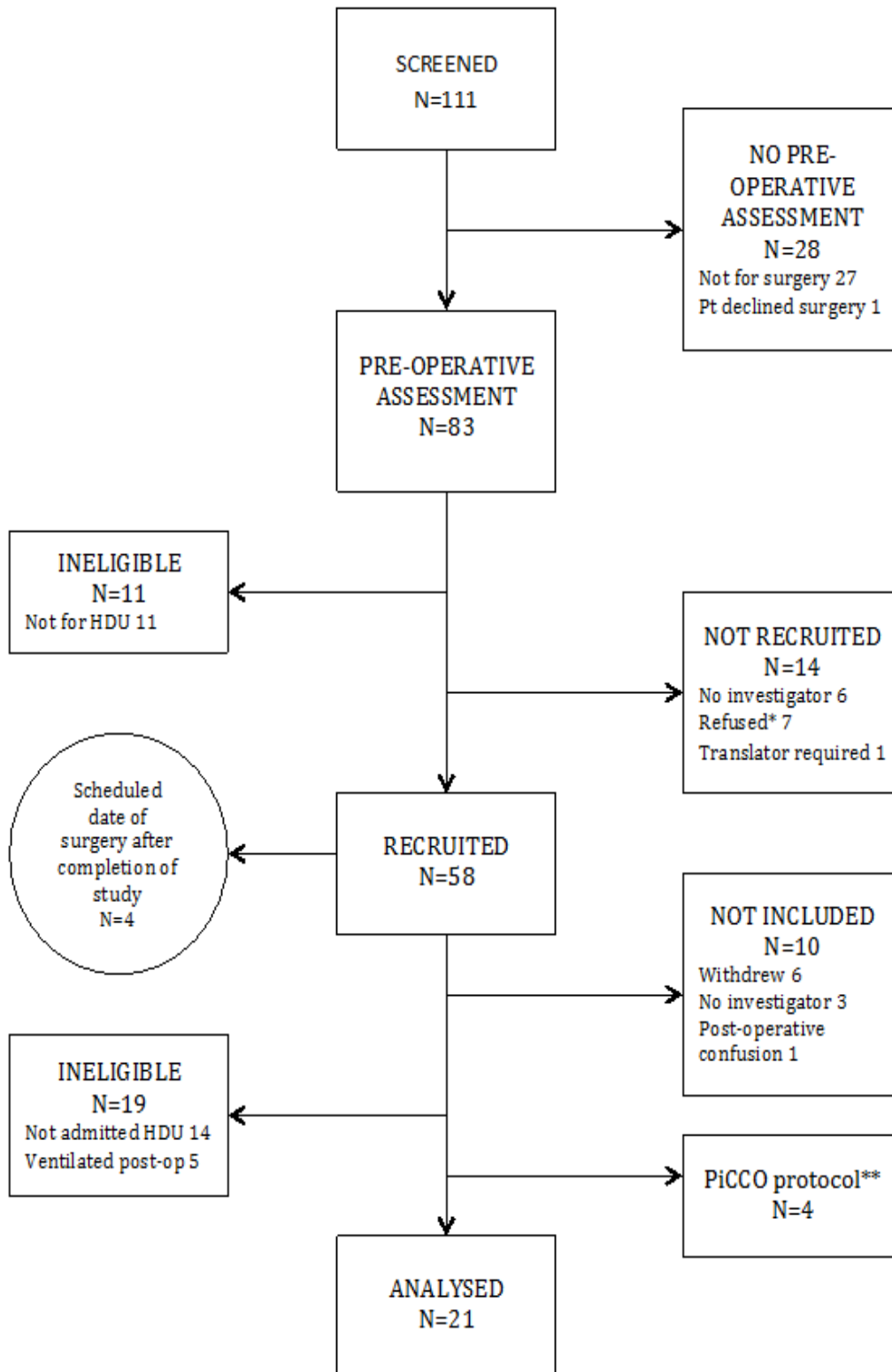


Figure 17 Validation Study population.

* 6/7 pts who refused suffered from claustrophobia. ** See Appendix 5

	All patients (n=21)
Age range (yr)	35-74
Sex (M/F)	17/4
Height (cm)	171.7 (7.0)
Body weight (kg)	79.4 (14.1)
Operation (laparoscopic)	
<i>Right hemihepatectomy ± wedge excision</i>	8 (4)
<i>Extended right hemihepatectomy ± wedge excision</i>	3 (2)
<i>Segmental liver resection</i>	2 (1)
<i>Left lateral sector resection ± radiofrequency ablation</i>	2 (1)
<i>Left hemihepatectomy ± wedge excision</i>	2 (1)
<i>Wedge excision</i>	2 (1)
<i>Left lateral sector liver resection & Anterior Resection</i>	1 (1)
<i>Extended right hemihepatectomy and small bowel resection</i>	1 (0)
Diagnosis	
<i>Colorectal metastases</i>	18
<i>Cholangiocarcinoma</i>	1
<i>Cholangiocarcinoma and synchronous neuroendocrine tumour</i>	1
<i>Breast metastases</i>	1

Table 7 Patient characteristics.

Data are expressed as mean (*SD*) or number

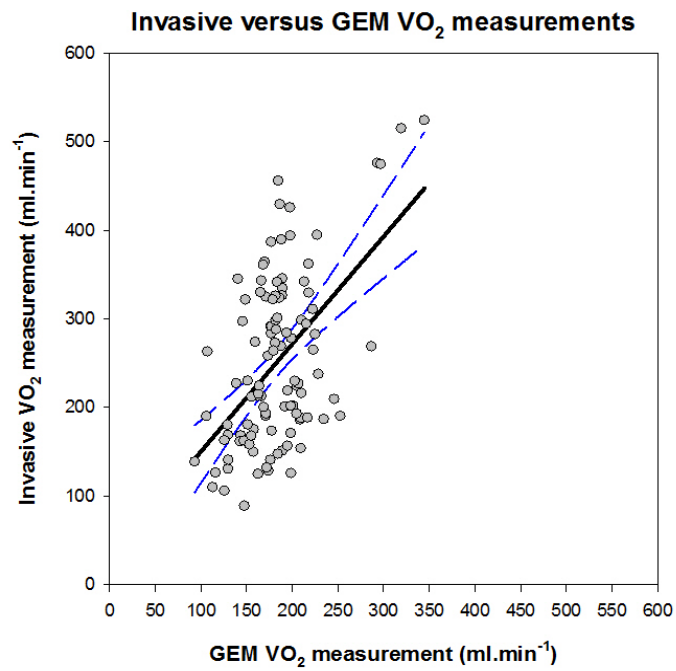
Bland-Altman analysis is the conventional method for comparing measurement methods. In this study we used repeated measures on each subject, therefore this was corrected for in the analysis as previously described [109]. Results are presented as bias (mean difference between measurements), precision (standard deviation, *SD*, of bias) and 95% limits of agreement (bias ± 1.96 *SD*) [109, 110]. The percentage error was calculated as $2SD$ of the bias divided by the mean of the invasive measurement. The tested method is considered interchangeable with the reference method when the percentage error is $<30\%$ [111]. This assumes a precision of $\pm 20\%$ for the reference method.

Bland-Altman plots of $\dot{V}O_2$, DO_2 , CO, Hb concentrations, and SpO_2 are presented in *Figures 18-24*, with bias, standard deviation (precision), 95% limits of agreement and percentage error shown in *Table 8*.

	VO₂ (ml.min ⁻¹)	DO₂ (ml.min ⁻¹)	CO (L.min ⁻¹)	Hb ABG/Pronto (g.L ⁻¹)	Hb CVBG/Pronto (g.L ⁻¹)	Hb ABG/CVBG (g.L ⁻¹)	Sats (%)
Bland-Altman analysis							
<i>n</i>	105	102	107	114	114	124	114
<i>Mean bias</i>	68.16	-18.98	-0.04	-3.49	-5.07	1.573	0.77
<i>standard deviation</i>	83.51	165.33	1.08	14.75	12.86	6.03	1.93
<i>95% limits of agreement</i>	-95.52 to 231.84	-343.00 to 305.07	-2.15 to 2.07	-32.40 to 25.43	-30.27 to 20.13	-10.25 to 13.40	-3.02 to 4.56
<i>Percentage error (%)</i>	66.3	39.6	36.5	25.9	22.9	10.6	4.1
Four Quadrant plots							
<i>n</i>	94	82	87	90	91	100	90
<i>exclusion zone</i>	10%	10%	0.5 L.min ⁻¹	10%	10%	10%	10%
<i>n after exclusion</i>	64	64	48	29	33	11	0
<i>Concordance (%)</i>	64.1	71.9	91.7	72.4	72.7	90.9	N/A
Polar plot analysis							
<i>n</i>	94	82	87	90	91	100	90
<i>exclusion zone</i>	10%	10%	0.5 L.min ⁻¹	10%	10%	10%	10%
<i>n after exclusion</i>	45	40	40	9	8	6	0
<i>mean angular bias (°)</i>	-15.56	1.98	-0.43	31.03	17.09	-3.96	N/A
<i>radial limits of agreement (°)</i>	50	48	27	48	58	28	N/A
<i>30° Angular concordance rate (%)</i>	60.0	82.5	95	33.3	25	100	N/A
<i>45° Angular concordance rate (%)</i>	86.7	92.5	97.5	88.9	75	100	N/A

Table 8 Statistical data from Bland-Altman analysis, four-quadrant plots and polar plots for VO₂, DO₂, CO, Hb and O₂ saturations when measured non-invasively compared to “standard” methods.

Highlighted data points demonstrate accuracy (mean bias), and trending ability (concordance from 4-quadrant plots, and angular concordance rates from polar plots) or the named technologies when compared with the reference devices.



Bland-Altman plot of invasive versus GEM VO₂ measurements

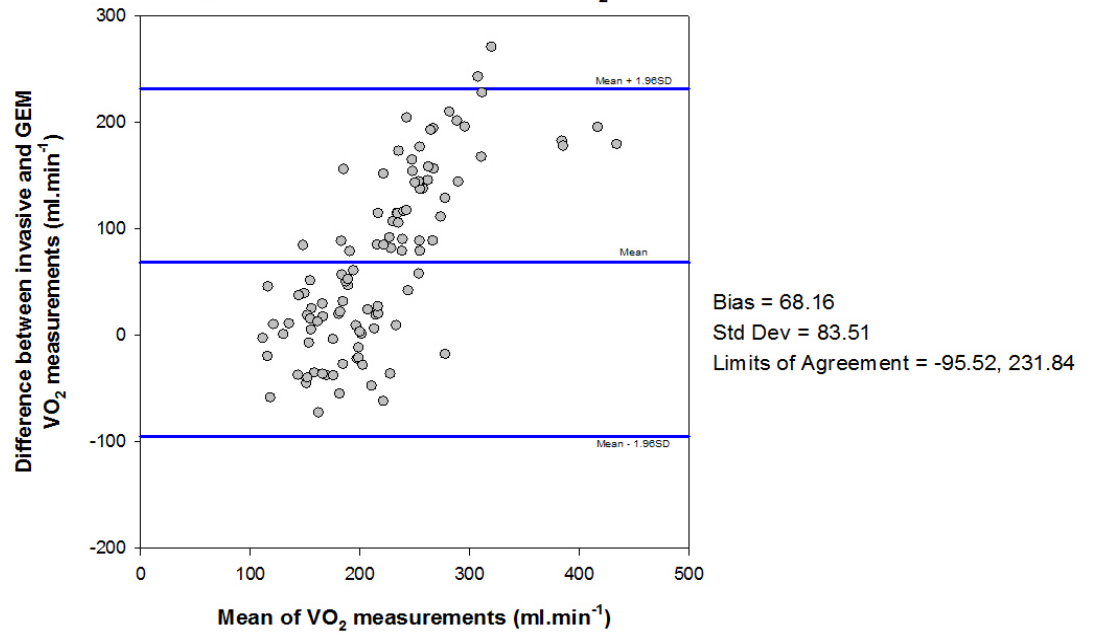
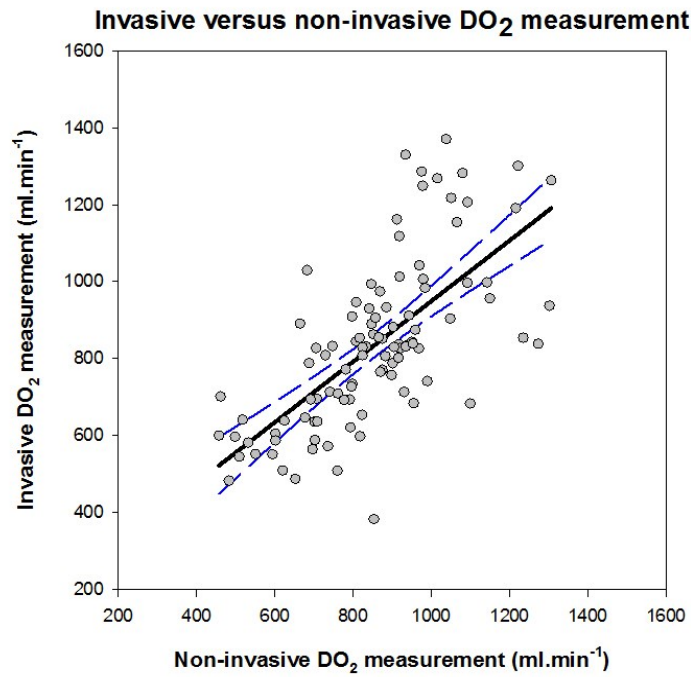


Figure 18 Scatter plot and Bland-Altman Plot for VO₂ measurements



Bland-Altman plot of invasive versus non-invasive DO₂ measurements

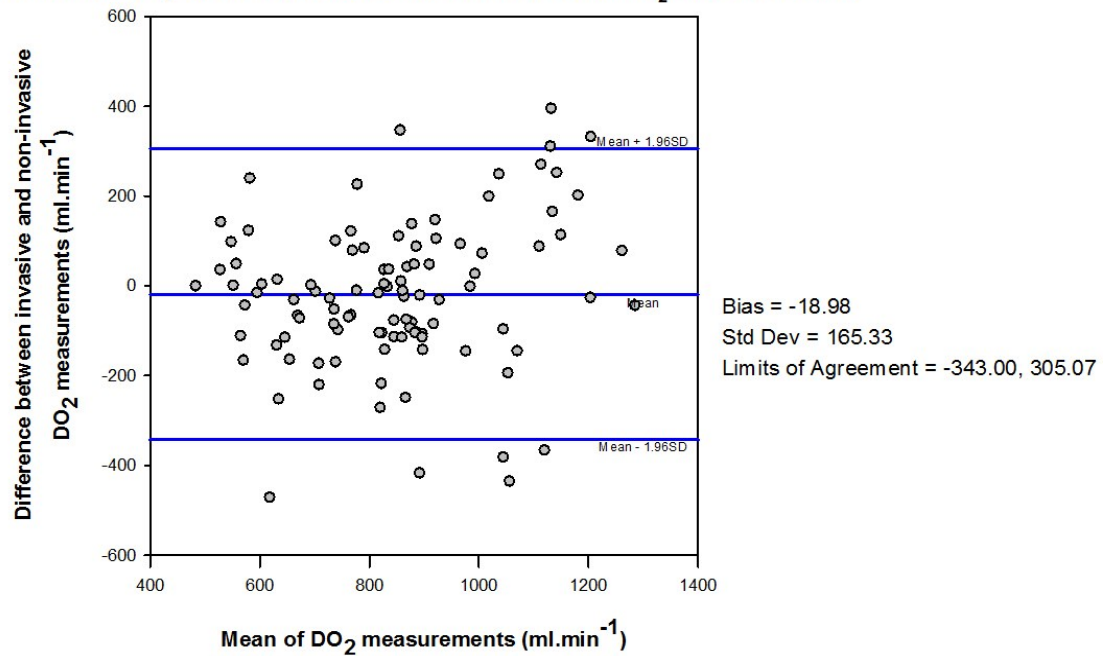
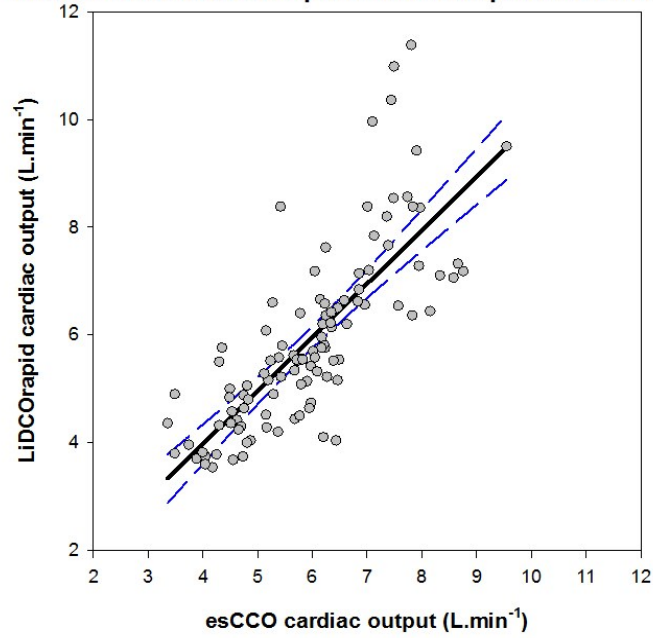


Figure 19 Scatter plot and Bland-Altman Plot for DO₂ measurements

esCCO versus LiDCOrapid cardiac output measurements



Bland-Altman plot of esCCO versus LiDCOrapid cardiac output measurements

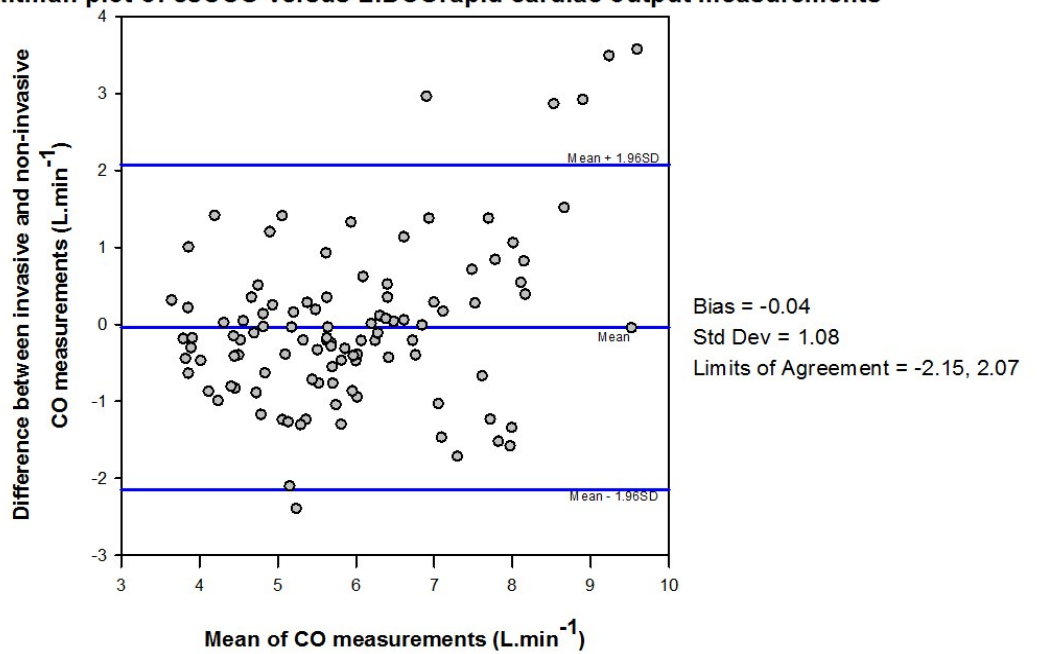
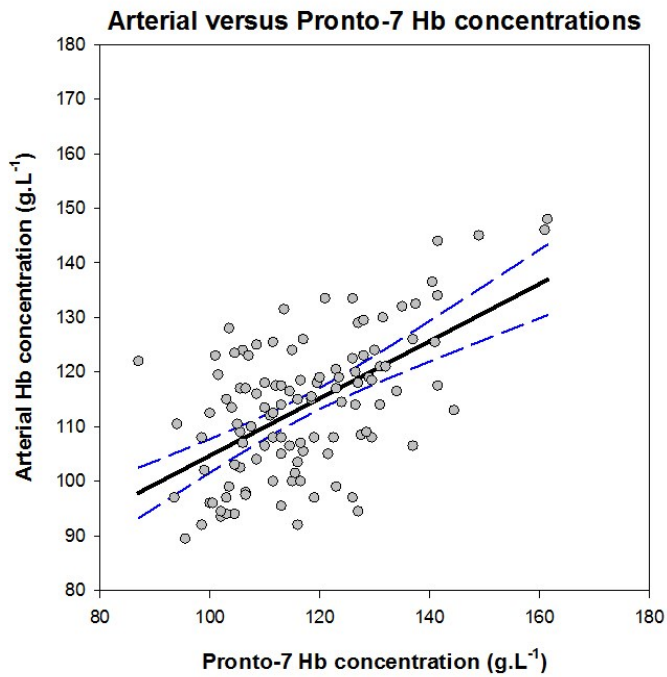


Figure 4 Scatter plot and Bland-Altman Plot for CO measurements



Bland-Altman plot of arterial versus Pronto-7 Hb concentrations

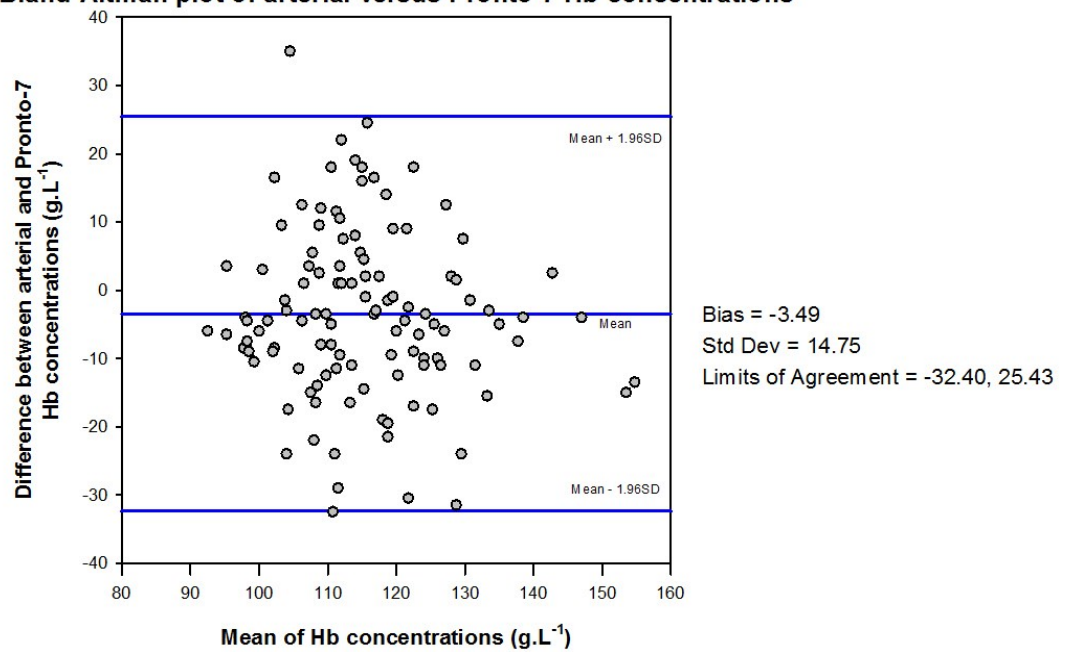
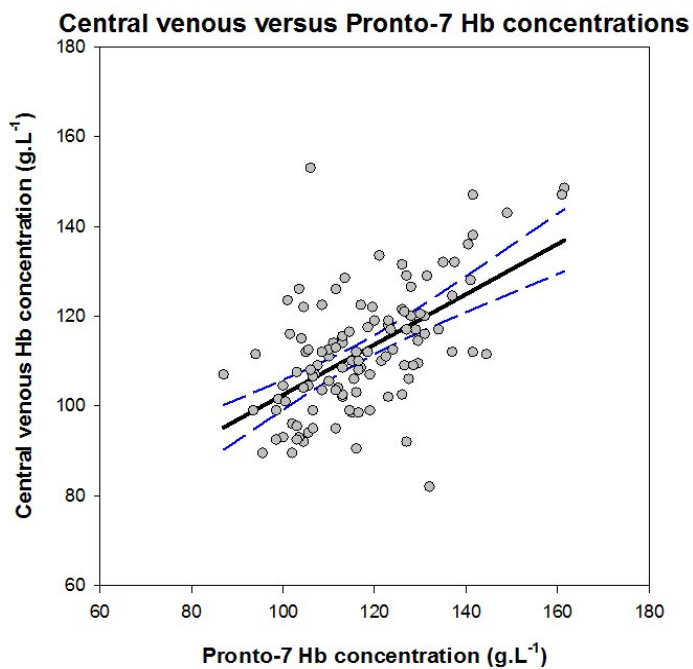


Figure 21 Scatter plot and Bland-Altman Plot for arterial versus Pronto-7 [Hb]



Bland-Altman plot of central venous versus Pronto-7 Hb concentrations

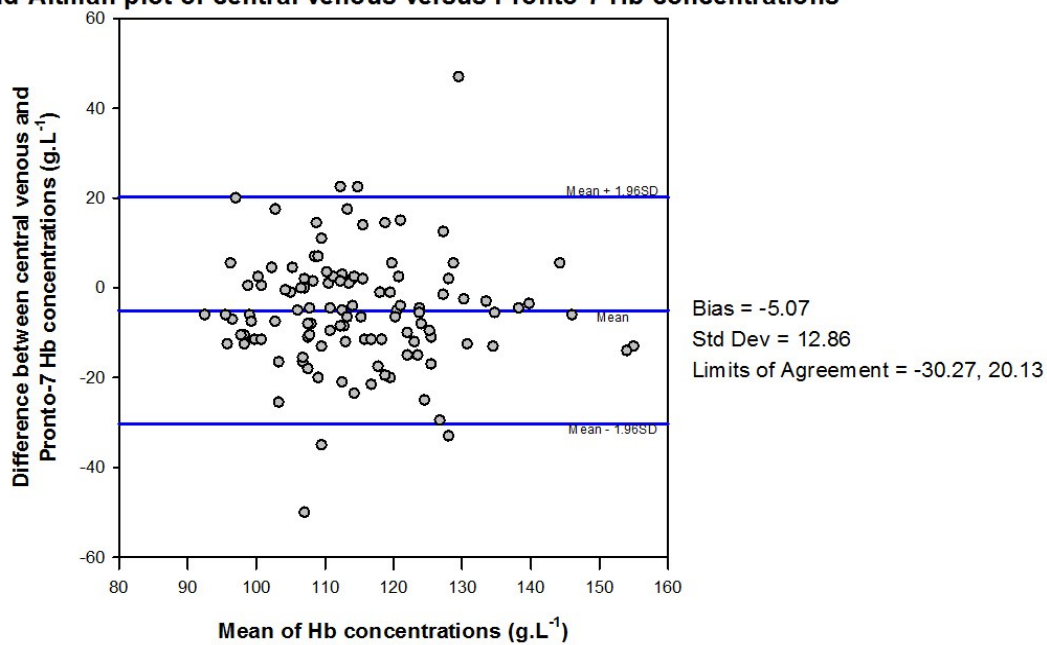
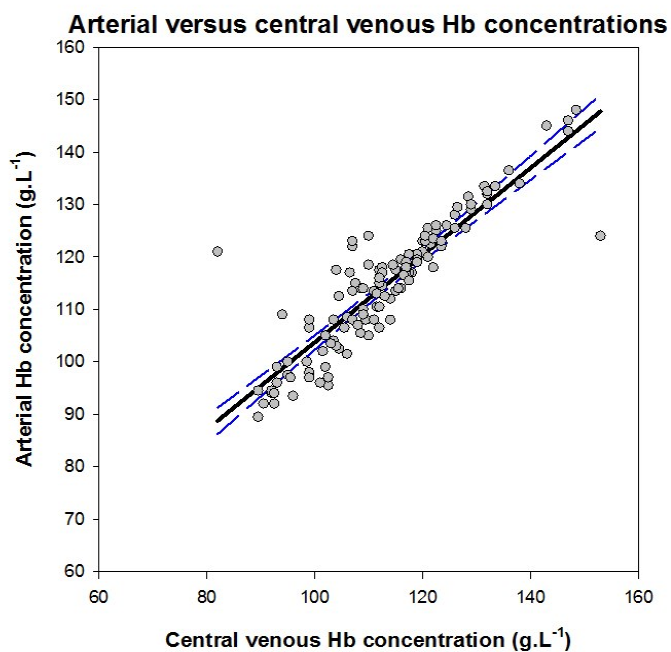


Figure 22 Scatter plot and Bland-Altman Plot for central venous versus Pronto-7 [Hb]



Bland-Altman plot of arterial versus central venous Hb concentrations

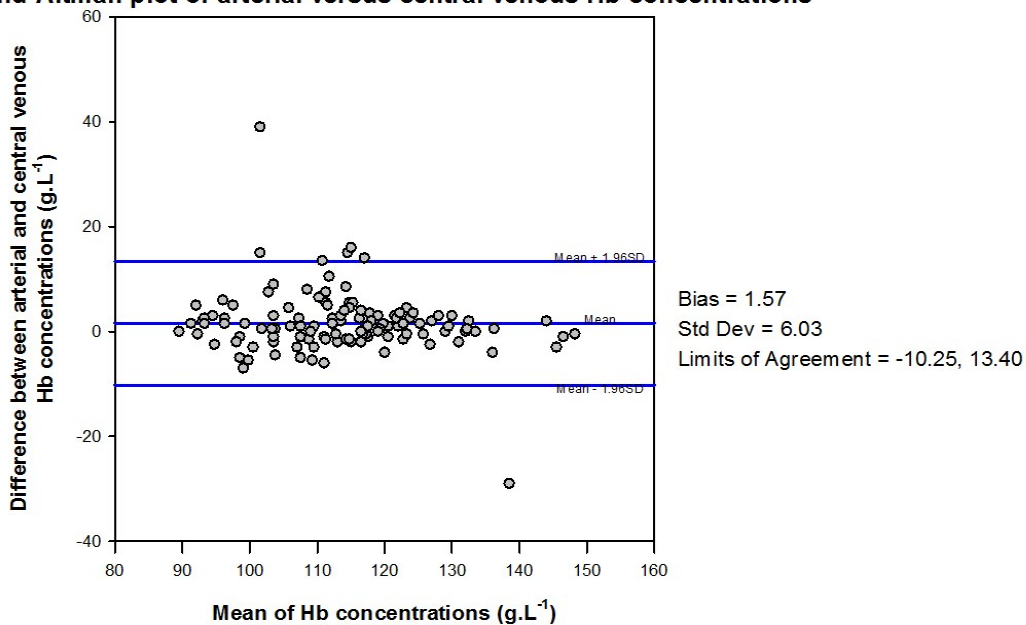
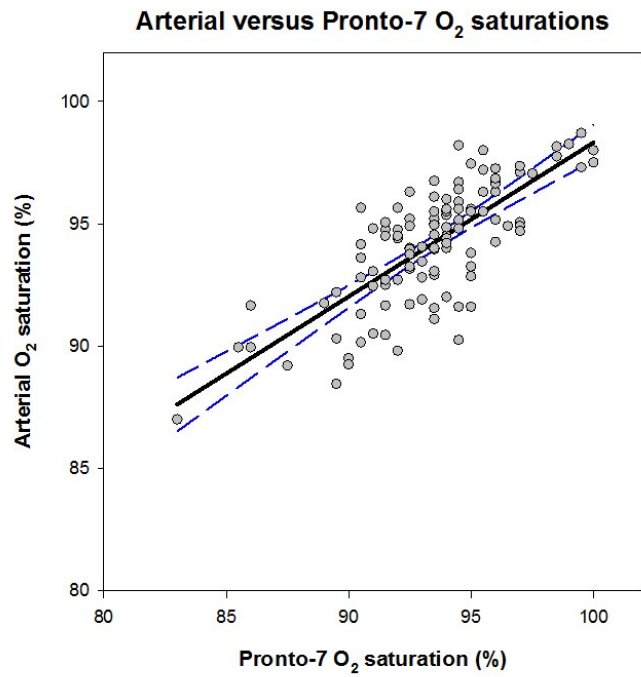


Figure 23 Scatter plot and Bland-Altman Plot for arterial versus central venous [Hb]



Bland-Altman plot of arterial versus Pronto-7 O₂ saturations

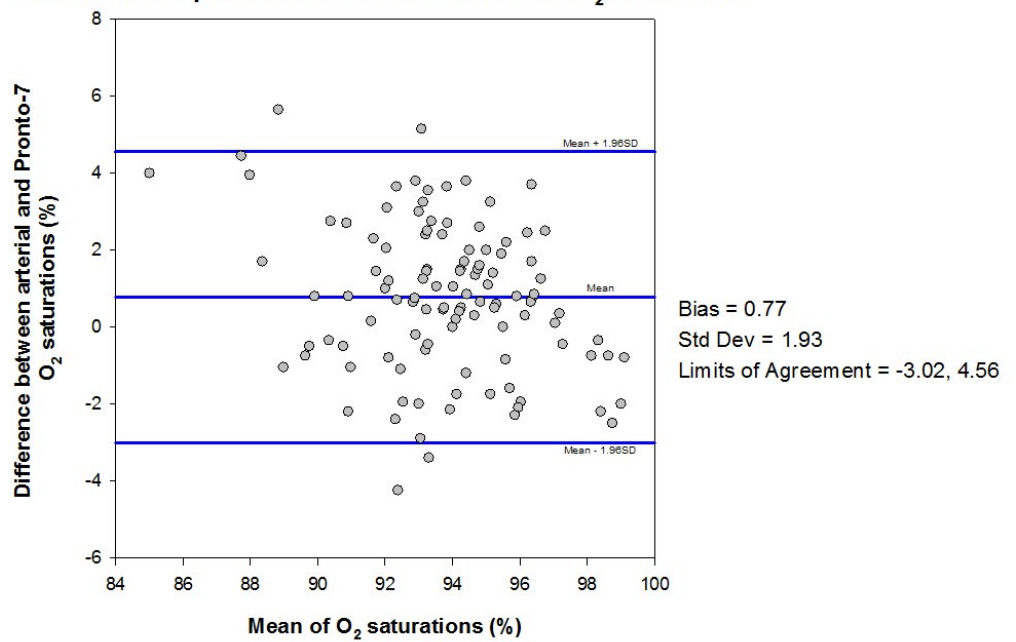


Figure 24 Scatter plot and Bland-Altman Plot for S_aO₂ versus Pronto-7 SpO₂

Trends of $\dot{V}O_2$, DO_2 and CO have more clinical relevance than point estimates, and therefore, the trending ability of the non-invasive techniques was assessed by analysing Δ non-invasive values and Δ invasive values on four-quadrant plots with concordance rates and polar plot analysis (*Figures 25-31, Table 8*) [112, 113]. In studies using thermodilution as the reference CO, concordance rates of 90-95% support good trending ability [112]. Unlike concordance rates, polar plot analysis assesses agreement not only in direction of change, but also for the magnitude of that change. The radial length of the polar vector represents the mean change in consecutive paired non-invasive and invasive measurements. The polar angle represents agreement of the magnitudes of change between the methods, and the mean polar angle, or angular bias, indicates how well calibrated the test method is with the reference method. The radial limits of agreement is the radial sector that contains 95% of data points (analogous to the 95% limits of agreement in Bland-Altman analysis) and the 30° angular concordance rate is the percentage of data points in the $\pm 30^\circ$ sector. Critchley and colleagues set acceptance limits for good trending ability of an angular bias of $< \pm 5^\circ$, radial limits of agreement of $< \pm 30^\circ$, and a 30° concordance rate of $\geq 95\%$. However, in the meta-analysis by Peyton and Chong [114], the authors suggest percentage limits of agreement should be increased from $\pm 30\%$ to $\pm 45\%$, as there is a suggestion that in fact the precision error of thermodilution as a reference method is closer to $\pm 30\%$. In addition, when methods of $\dot{V}O_2$ measurement with Fick have been compared, an error of 25% has been recognised due to the random error inherent in the calculation [122]. To

reflect this, *a priori*, radial concordance rates of $<\pm 30^\circ$ and $<\pm 45^\circ$ are reported in this study's results.

Four-quadrant concordance plot for changes in VO_2 measured invasively vs GEM

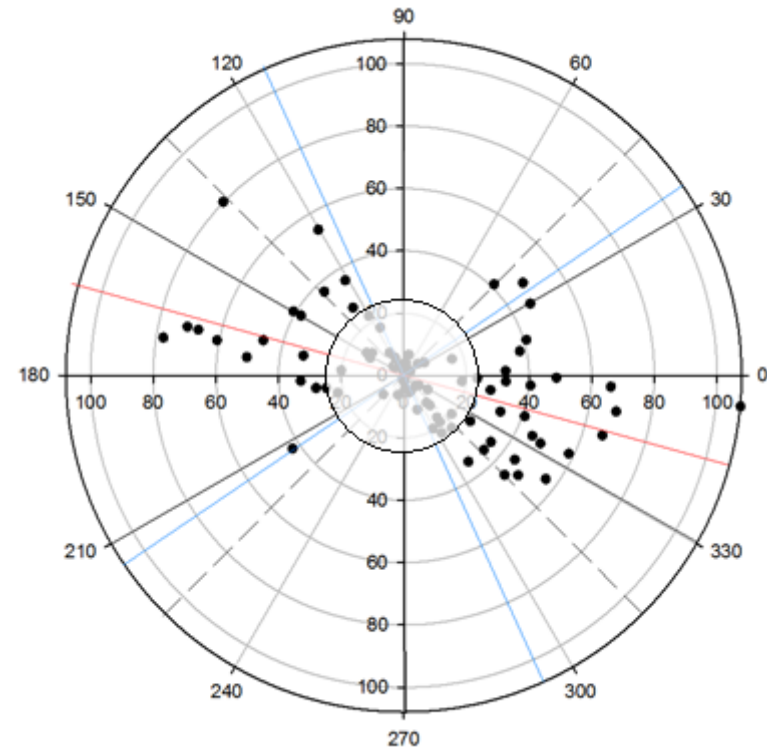
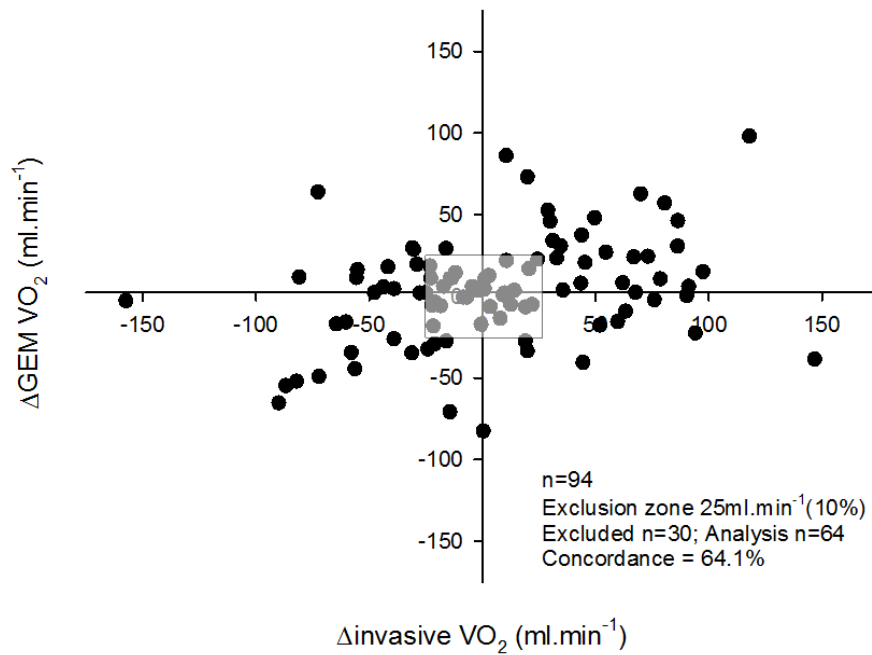


Figure 25 Four-quadrant concordance plot and polar plot for changes in VO_2 measured invasively compared to the GEM cart.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included.

Four-quadrant concordance plot for changes in DO_2 measured invasively vs non-invasively

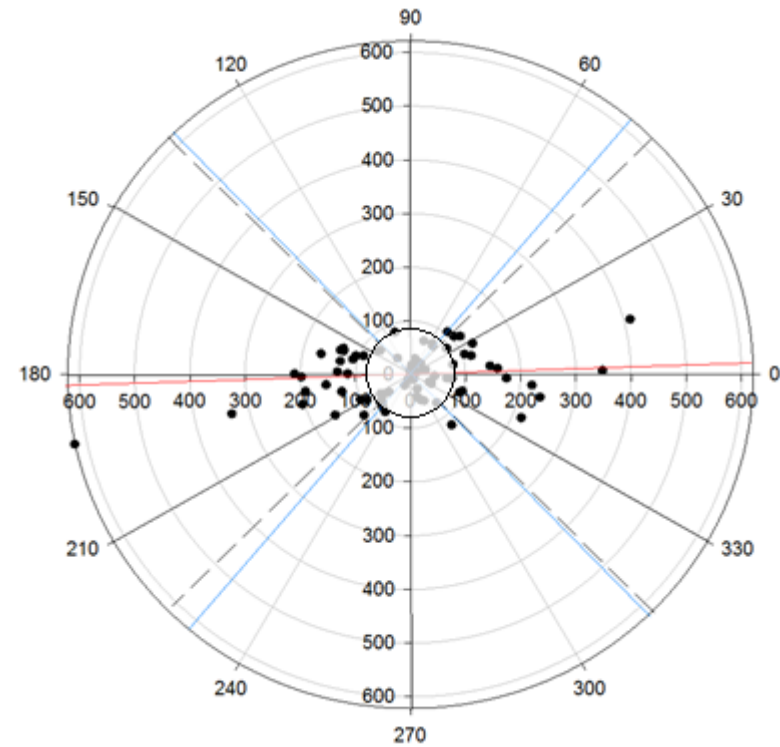
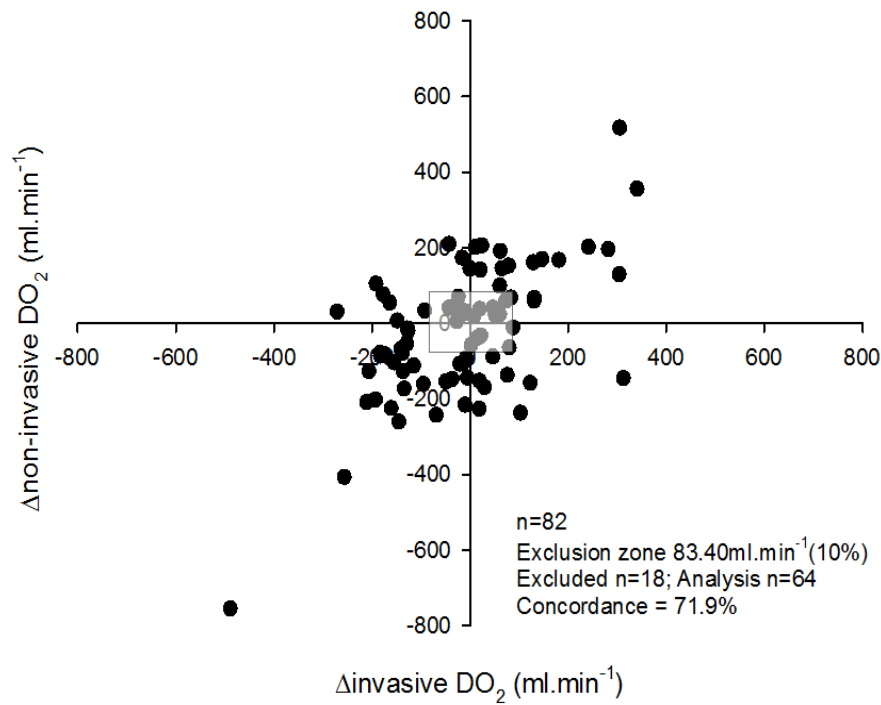


Figure 26 Four-quadrant concordance plot and polar plot for changes in DO_2 measured invasively and non-invasively.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included.

Four-quadrant concordance plot for changes in CO measured with esCCO vs LiDCOrapid

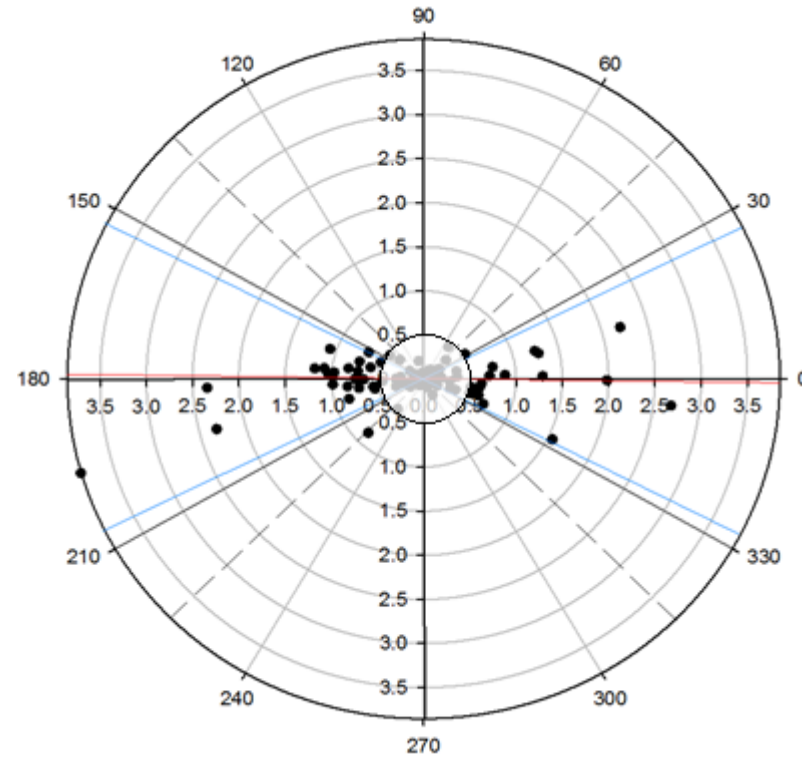
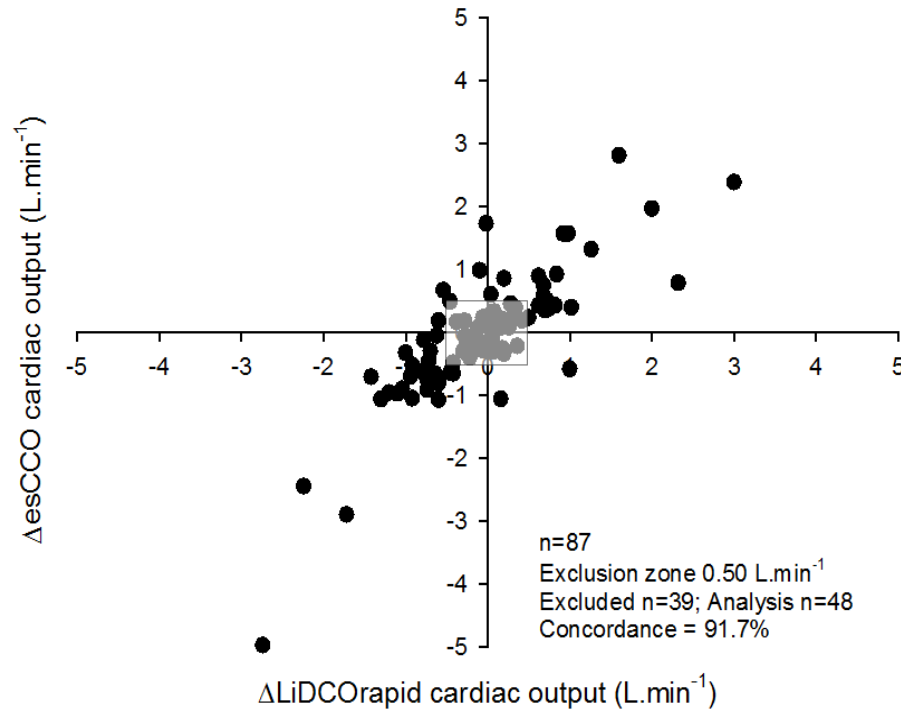


Figure 27 Four-quadrant concordance plot and polar plot for changes in CO measured with LiDCOrapid and the esCCO monitors.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included

Four-quadrant concordance plot for change in Hb measured arterially vs Pronto-7

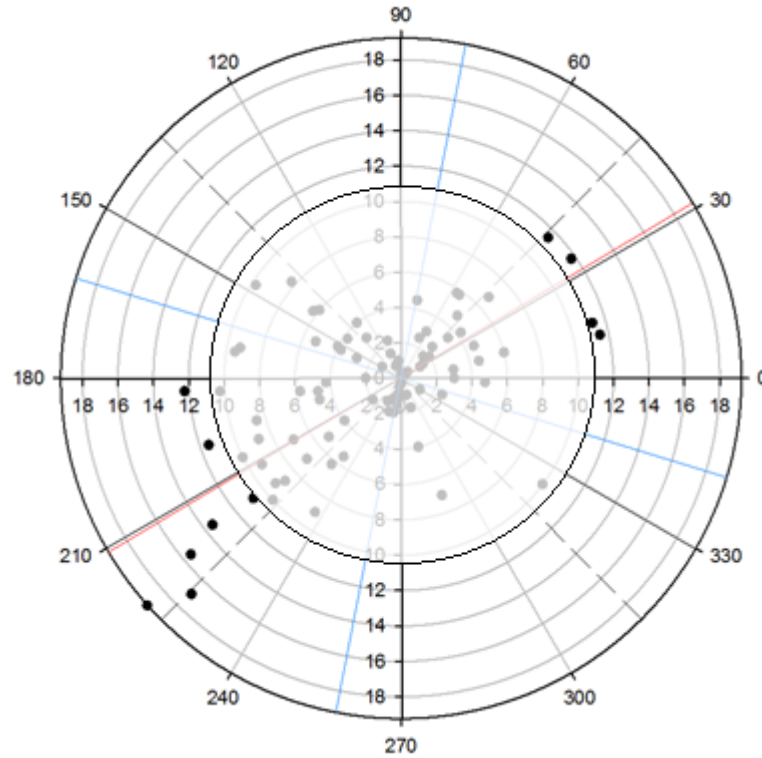
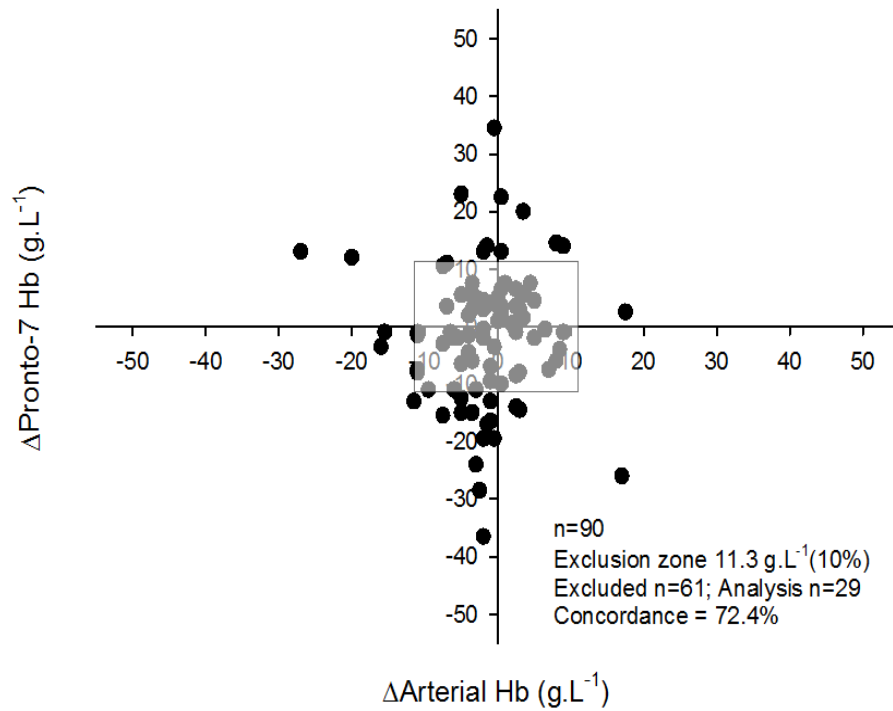


Figure 28 Four-quadrant concordance plot and polar plot for changes in Hb measured arterially compared to the Pronto-7 monitor.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included.

Four-quadrant concordance plot for change in Hb measured central venous vs Pronto-7

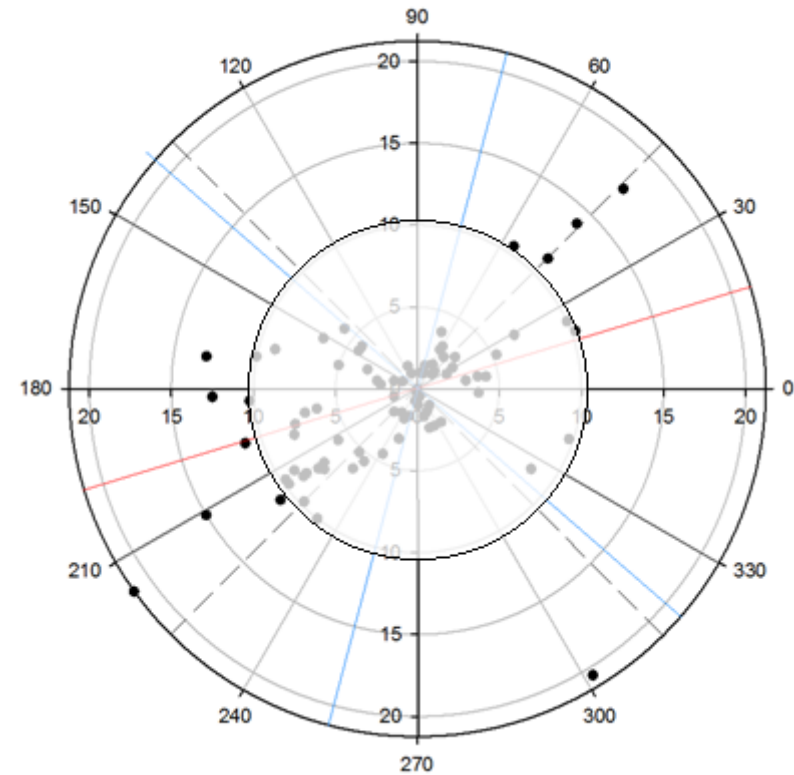
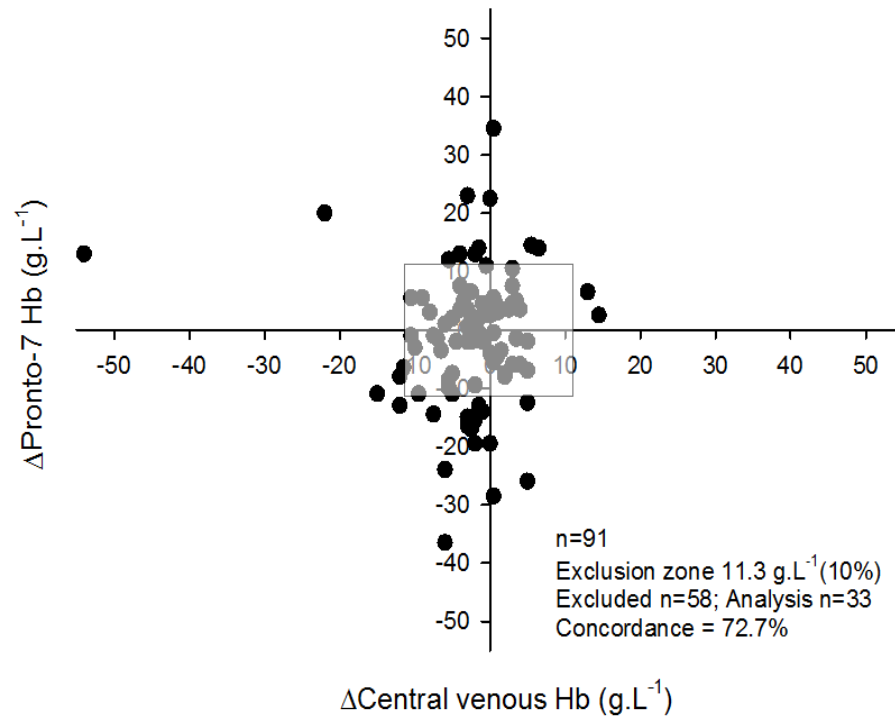


Figure 29 Four-quadrant concordance plot and polar plot for changes in Hb measured central venously compared to the Pronto-7 monitor.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included.

Four-quadrant concordance plot for change in Hb measured arterially vs central venous

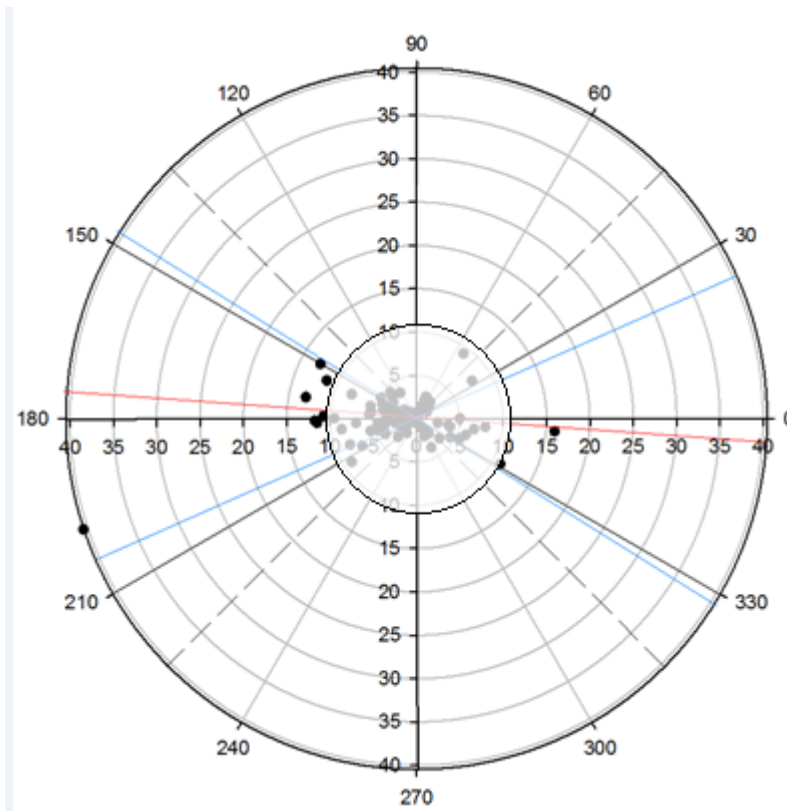
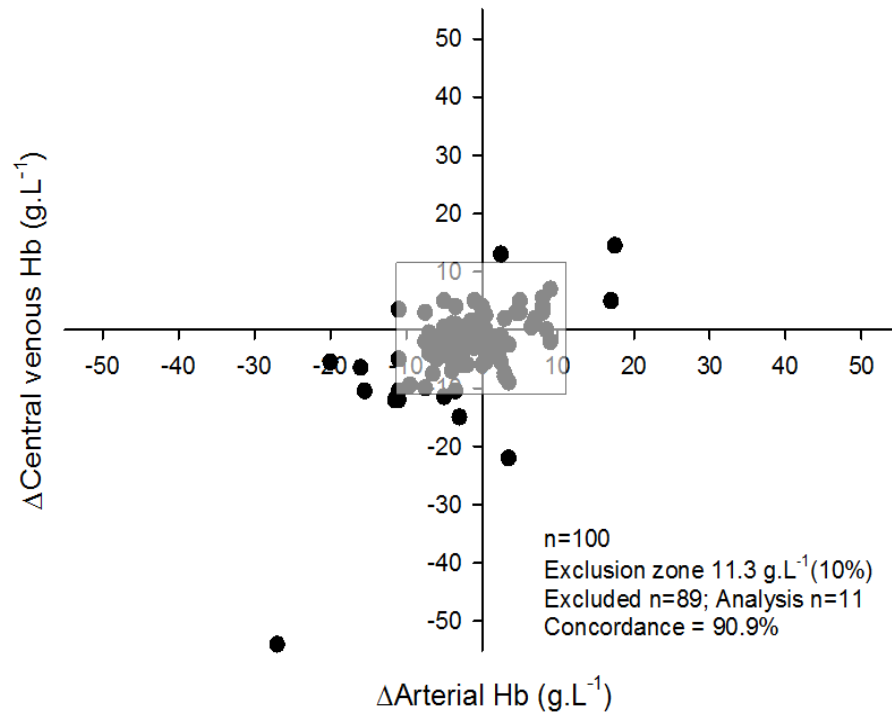


Figure 30 Four-quadrant concordance plot and polar plot for changes in Hb measured arterially compared to central venously.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included

Four-quadrant concordance plot for change in O₂ saturations measured arterially vs Pronto-7

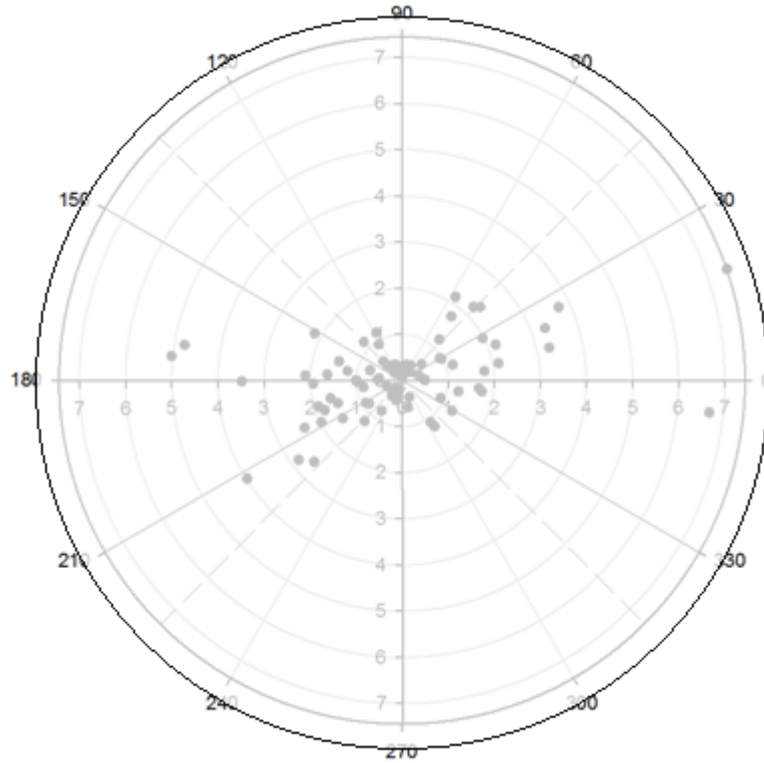
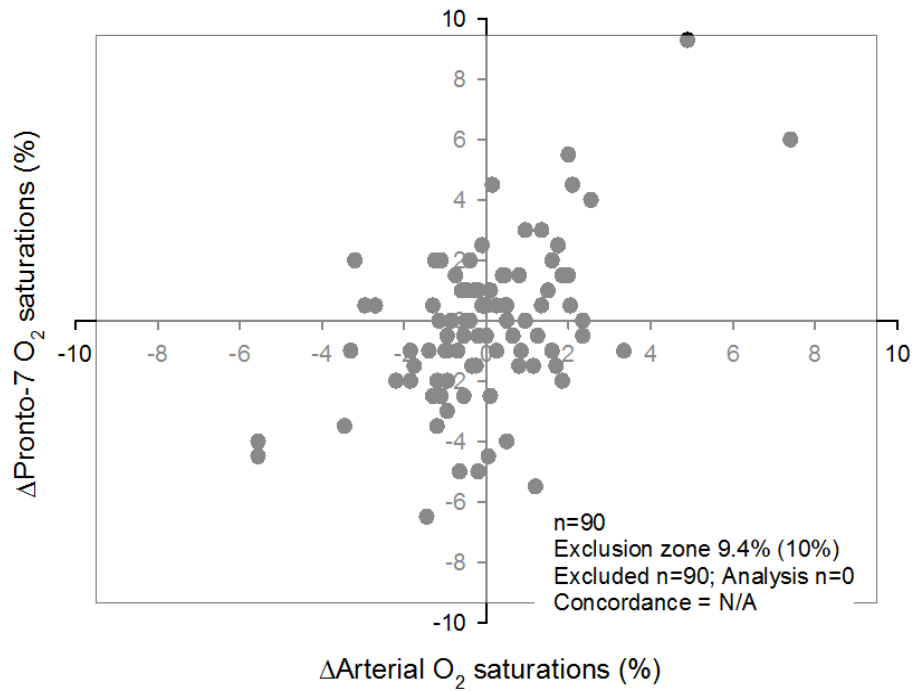


Figure 31 Four-quadrant concordance plot and polar plot for changes in O₂ saturations measured arterially compared to the Pronto-7 monitor.

Assessment for trending of data. In the left graph, the right upper and left lower quadrants the two technologies agree. The central square refers to the 10% exclusion zone. The concordance refers to the percentage of data points in these quadrants. On the right graph mean angular bias is represented by the red line and the radial limits of agreement are bounded by the light blue lines. The dashed line represents the $\pm 45^\circ$ angular concordant sector. A 10% central exclusion zone is included.

Figures 32-38 show the temporal patterns of post-operative $\dot{V}O_2$ and DO_2 when measure invasively and non-invasively for each individual patient. As the timing of each paired measurement was not consistent between individuals a population mean pattern is not possible to achieve. Although not formally tested, *Figures 32-38* do appear to demonstrate that non-invasive temporal patterns mirror those of the invasive measurements, and that there is a reduction in both $\dot{V}O_2$ and DO_2 in the early post-operative period followed by a subsequent increase.

A number of individual paired readings were not possible in eleven individuals.

Table 9 lists the reasons for the missed measurements.

Reason for missed reading	Readings affected	Number of readings affected	Number of patients
No arterial line trace/ <i>in situ</i>	All invasive readings	7	3
Pronto-7 reading not possible	Non-invasive Hb/O ₂ sats (non-invasive DO ₂ calculation)	6	1
Patient withdrew from study	All readings	5	1
Patient discharged from Critical care	All readings	3	2
Patient refused reading	All readings	2	1
Patient with OSA requiring CPAP	All readings	2	1
Leak from GEM tubing	Non-invasive VO ₂	2	2

Table 9 Reasons for missed readings in validation study

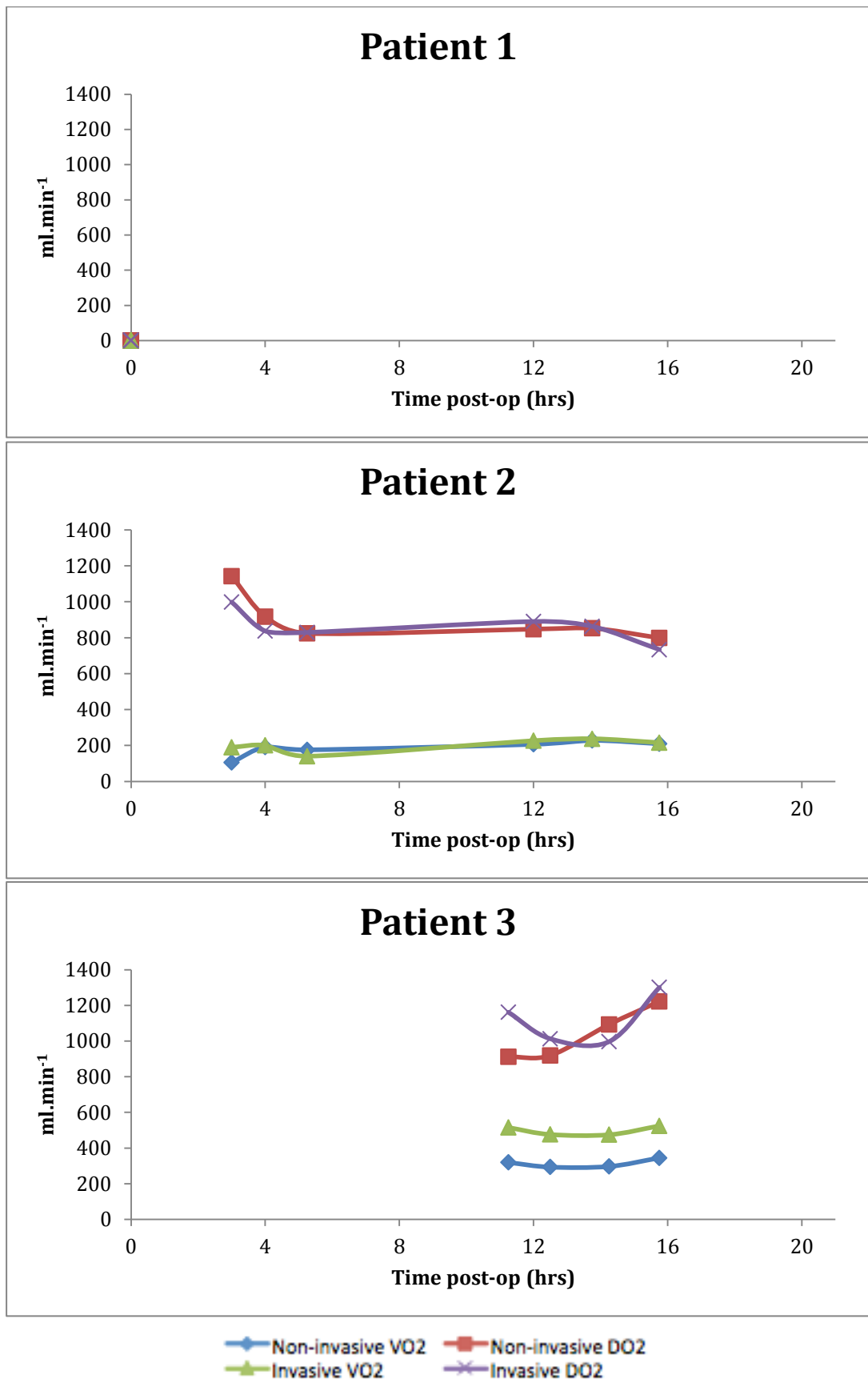


Figure 32 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

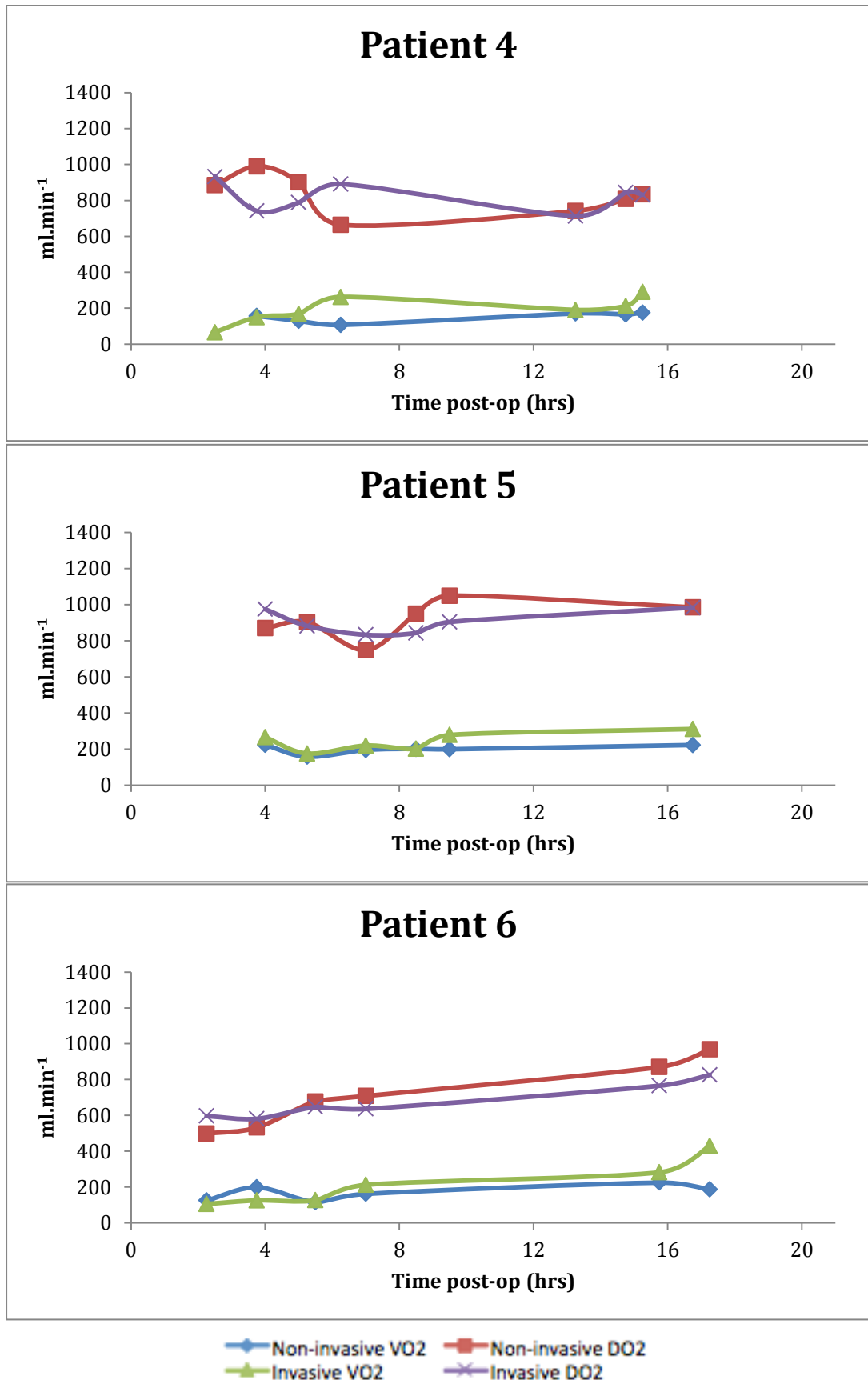


Figure 33 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

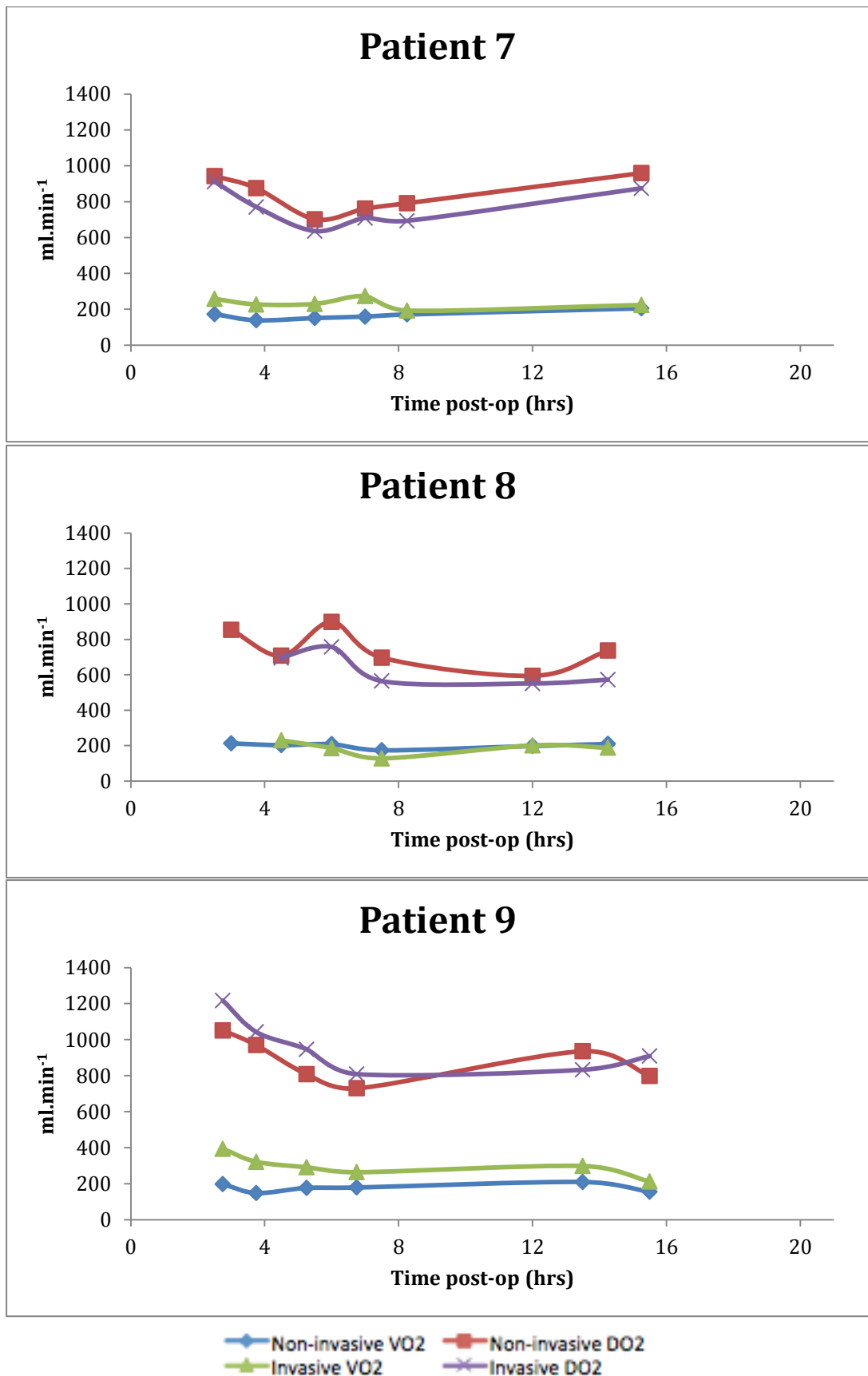


Figure 34 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

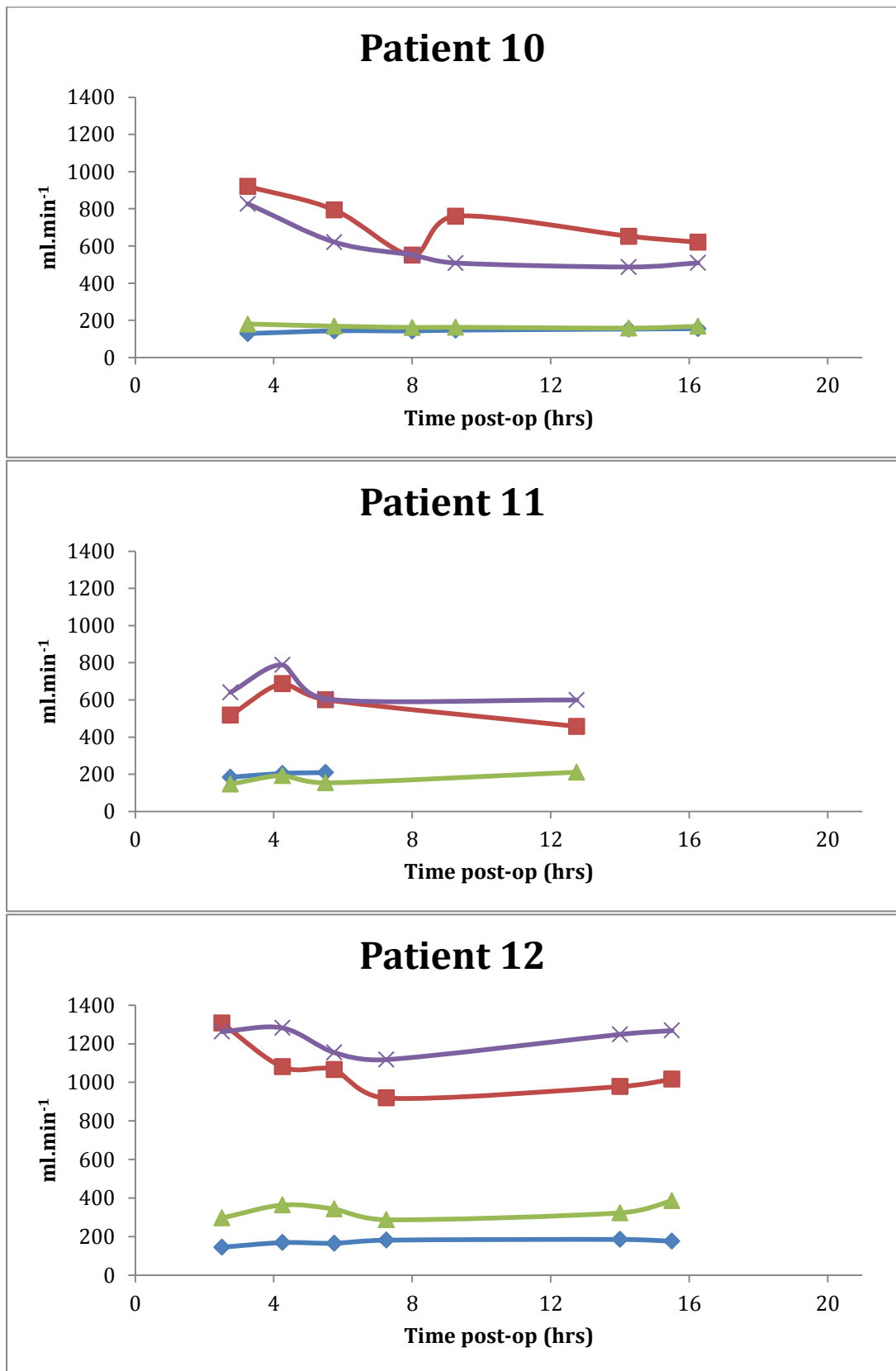


Figure 35 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

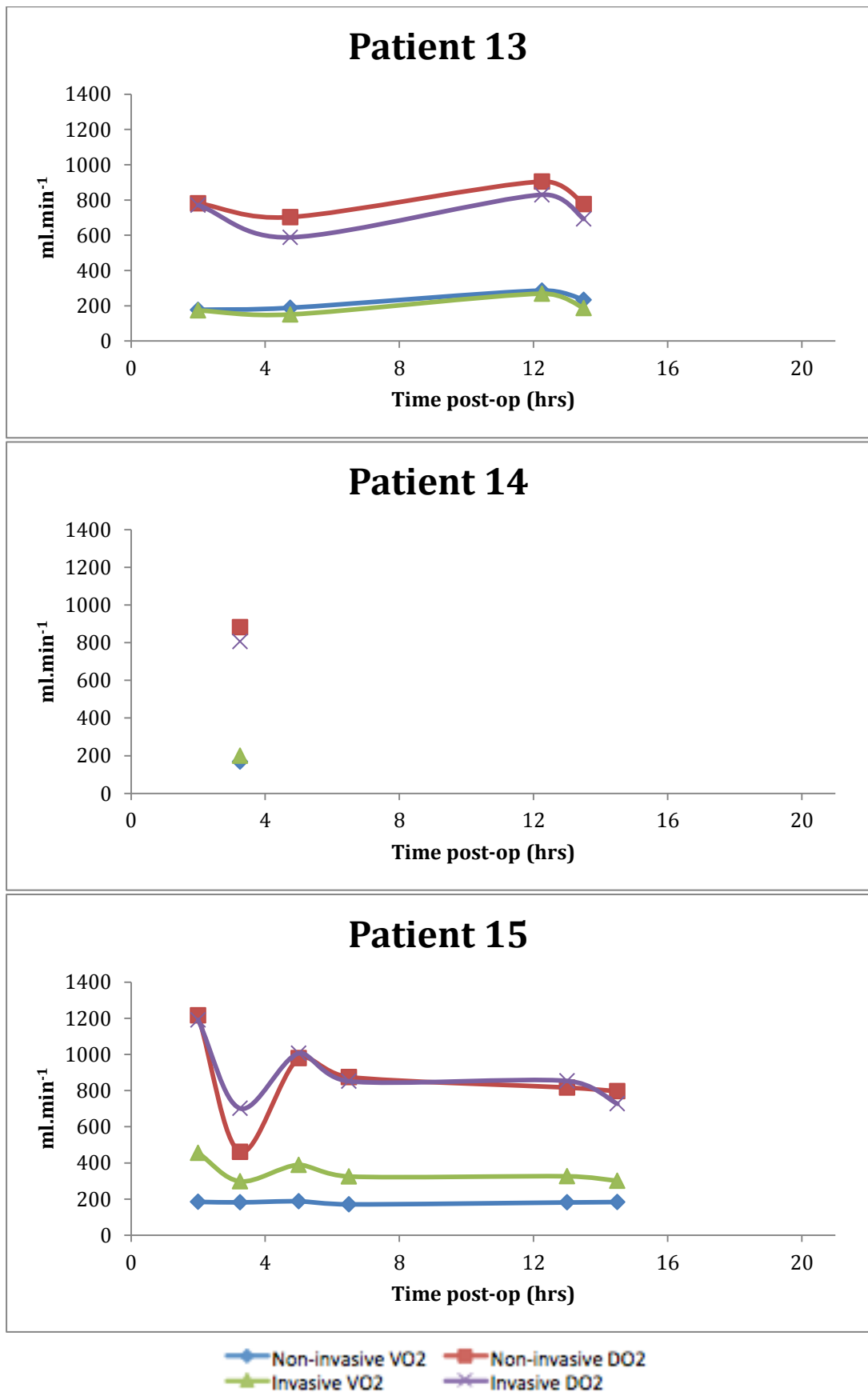


Figure 36 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

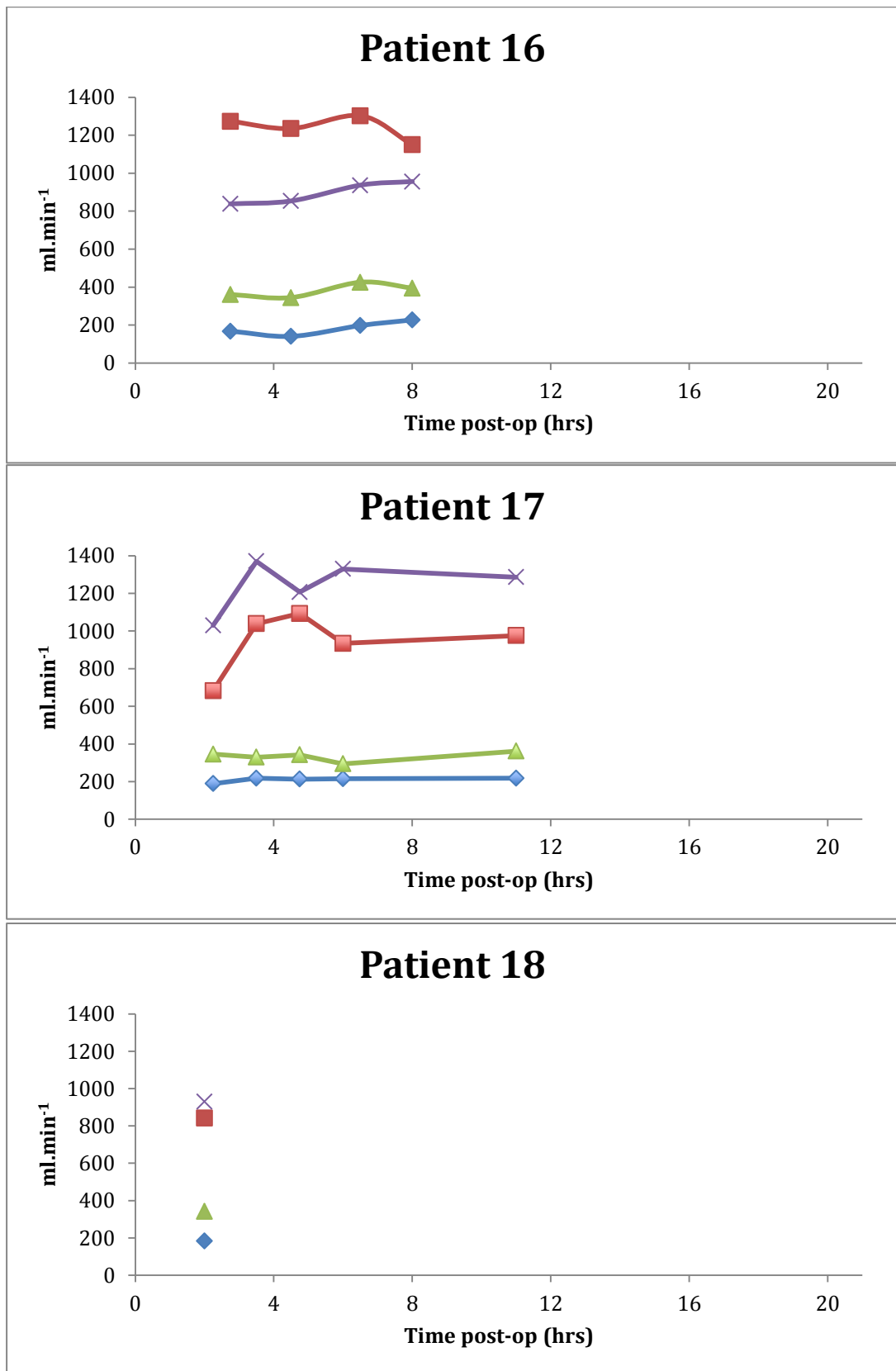
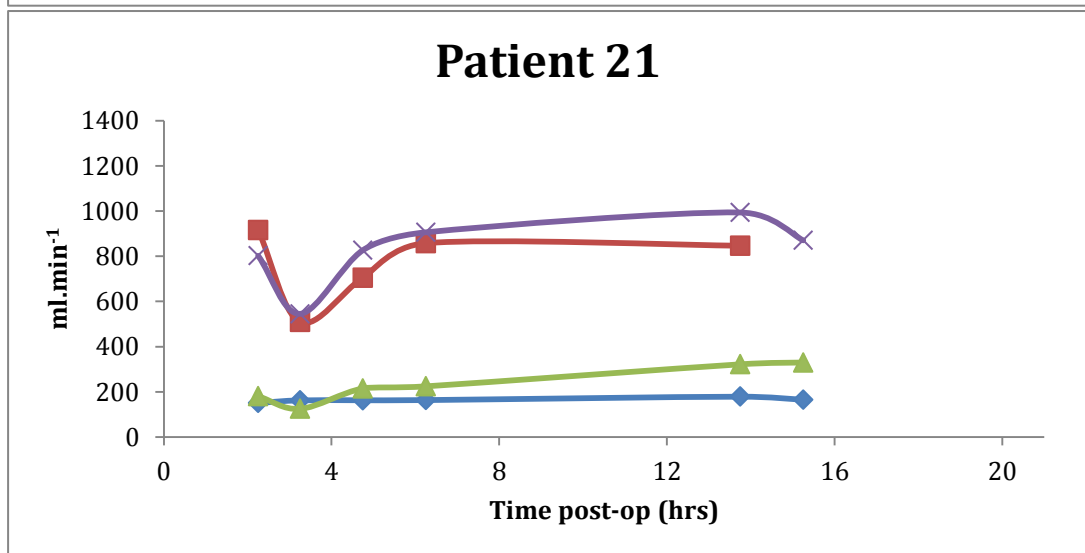
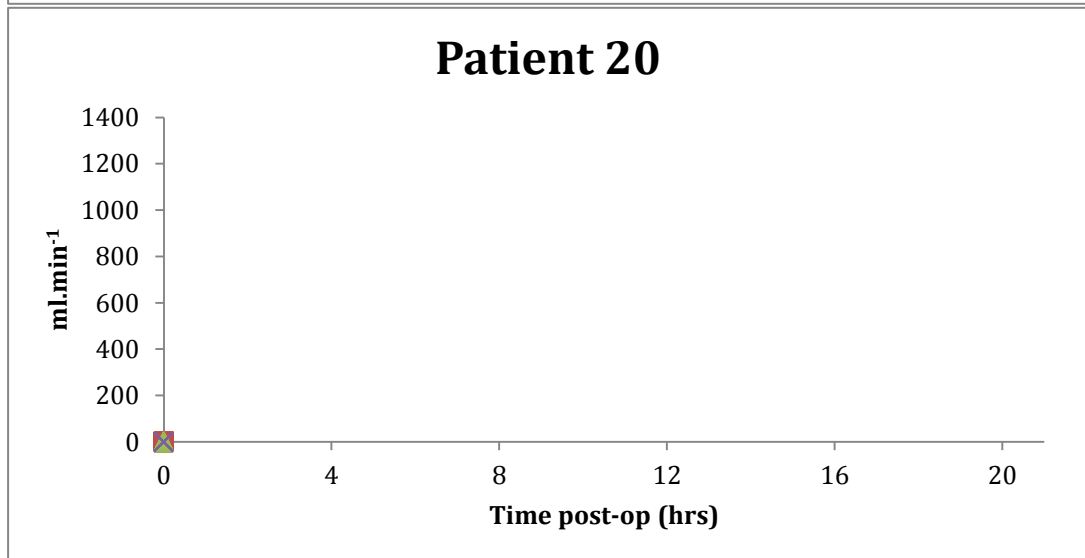
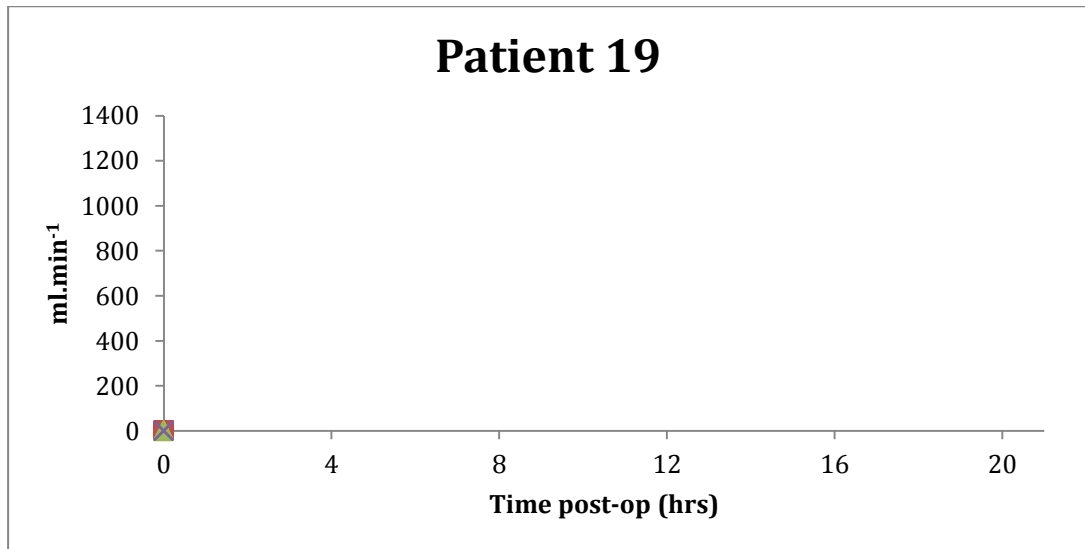


Figure 37 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.



◆ Non-invasive VO₂ ■ Non-invasive DO₂
▲ Invasive VO₂ ✕ Invasive DO₂

Figure 38 Individual patient patterns of post-operative VO₂ and DO₂ measured invasively and non-invasively.

Each data point represents one measurement. Time 0 = end of surgery. First measurement variable time post-operative.

3.4 DISCUSSION

To our knowledge, this is the first study to evaluate the ability of the GEM metabolic cart, and the esCCO and Pronto-7 derived variables, to measure and track changes in post-operative $\dot{V}O_2$ and DO_2 . As our reference technique we used variables obtained from the LiDCOrapid CO monitor, which is established in clinical practice and provides an estimated/nominal CO based on the PulseCO algorithm [99], and has been shown to be within acceptable limits of agreement with intermittent thermodilution via PAC [99, 101, 102] combined with arterial and central venous blood gas analyses, and calculated $\dot{V}O_2$ and DO_2 according to the Fick equation (Fick $\dot{V}O_2$ and invasive DO_2).

We found that the mean bias (\pm precision) between GEM $\dot{V}O_2$ and Fick $\dot{V}O_2$ was 68.16 (\pm 83.51) ml.min⁻¹, demonstrating that the GEM gave a systematically lower $\dot{V}O_2$ than the minimally invasively calculated Fick $\dot{V}O_2$. Conversely, the mean bias (\pm precision) between non-invasive DO_2 (NIDO₂) and invasive DO_2 (IDO₂) was -18.98 (\pm 165.33) ml.min⁻¹, showing a small, but systematically higher DO_2 when calculated from the non-invasive measurement techniques. Limits of agreement were wide for both $\dot{V}O_2$ and DO_2 (-95.52 to 231.84 ml.min⁻¹, and -343.00 to 305.07 ml.min⁻¹ respectively). The percentage error when comparing GEM $\dot{V}O_2$ and Fick $\dot{V}O_2$ was 66.3%, and 39.6% when comparing NIDO₂ and IDO₂. These findings suggest that GEM $\dot{V}O_2$ and Fick $\dot{V}O_2$, and NIDO₂ and IDO₂, are not interchangeable based on the criteria of Critchley and Critchley [111], who suggest a percentage error <30% is acceptable.

In a clinical setting, trends of $\dot{V}O_2$ and DO_2 have more relevance to patient management than absolute values. Trending ability was assessed with four-

quadrant concordance and polar plot analysis (*Figures 25 & 26, Table 8*). When comparing GEM $\dot{V}O_2$ and Fick $\dot{V}O_2$, there is a four-quadrant concordance rate of 64.1%, a mean angular bias of -15.56° , radial limits of agreement of $\pm 50^\circ$, and a 30° angular concordance rate of 60.0%. For DO_2 , these values are 71.9%, 1.98° , $\pm 48^\circ$, and 82.5% respectively. Based on the standards of Critchley and colleagues (who set acceptance limits for good trending ability of concordance rates of 90-95%, an angular bias of $<\pm 5^\circ$, radial limits of agreement of $<\pm 30^\circ$, and a 30° concordance rate of $\geq 95\%$) [112, 113], these methods demonstrate poor/moderate trending abilities. These limits were set based on Critchley and Critchley's theoretical scatter expected in agreement when two methods of CO are compared, each with a precision of $\pm 20\%$, with the reference method as thermodilution [111]. However, in their meta-analysis of 47 studies comparing four different methods for minimally invasive CO measurement with thermodilution, Peyton and Chong [114] found that none of the methods met Critchley and Critchley's criteria, but that they all achieved limits of agreement that were very similar (41.3-44.5%) despite using different physical and physiological principles suggesting that a "fundamental limitation exists to the precision of agreement with a given reference standard like thermodilution that can be achieved in clinical practice". They reasoned this was because the reference method (PAC derived CO via thermodilution) had a percentage error approaching $\pm 30\%$, rather than the oft-quoted $\pm 20\%$, and used the same mathematical theory applied by Critchley and Critchley to favour widening the acceptable percentage error in agreement to $\pm 45\%$. Furthermore, when methods of $\dot{V}O_2$ measurement with Fick have been compared, an error of 25% has been recognised due to the random error inherent in the calculation [122]. To reflect this, we have reported 45° angular concordance rates in our

polar plot analysis. These are 86.7% and 92.5% for GEM $\dot{V}O_2$ and NIDO₂ respectively, which may represent moderate/good trending ability when compared to our reference minimally invasive techniques.

There is a lack of published data validating the GEM against Fick $\dot{V}O_2$, but laboratory performance tests for the GEM show a mean error of $0.3 \pm 2.0\%$ for the measurement of $\dot{V}O_2$ [94]. This compares favourably to the mean error of $4 \pm 2.0\%$ demonstrated by Takala *et al.* [124] for the Deltatrac™ Metabolic Monitor (Datex-Ohmeda Inc.). Deltatrac is no longer commercially available, but has been considered as the standard reference tool in indirect calorimetry [96]. Furthermore, in their recent comparison study Kennedy and colleagues have shown GEM to be a reliable alternative to the Deltatrac based on measures of repeatability [95]. Previous studies comparing gas exchange methods with Fick $\dot{V}O_2$ have also concluded that the two methods are not interchangeable [122-124, 128-133]. Whilst the majority report that Fick (calculated) $\dot{V}O_2$ was less than that measured directly, and explain this in terms of lung $\dot{V}O_2$ which is not included in the Fick calculation [123, 124, 128, 132-134], others show no difference between the two methods [135, 136], or similar results to the present study [130, 137]. No previous study has attempted to formally address the trending ability of any method of $\dot{V}O_2$ measurement, however, Stock and colleagues, despite rejecting Fick $\dot{V}O_2$ as a research tool due to its inaccuracy when compared to $\dot{V}O_2$ measured with a water-sealed spirometer, suggest that the direction of change in true $\dot{V}O_2$ is likely reflected by Fick $\dot{V}O_2$, and may be useful clinically [122].

Fick $\dot{V}O_2$ and both IDO_2 and $NIDO_2$ are all calculated terms and so we have assessed the measurement of each variable (CO, Hb concentration, O_2 saturations) in terms of agreement and trending ability when compared to an accepted reference standard. The esCCO monitor had a mean bias of $-0.04L.min^{-1}$, a precision of $\pm 1.08L.min^{-1}$ with wide 95% limits of agreement of -2.15 to $2.07L.min^{-1}$, and a percentage error of 36.5% when compared to LiDCOrapid. This indicates that the two methods are not interchangeable in terms of absolute values. However, the trending ability of esCCO compared to LiDCOrapid is very good, as indicated by four-quadrant concordance rates of 91.7% and polar plot analysis giving a mean angular bias of -0.43° radial limits of agreements of $\pm 27^\circ$, and 30° and 45° angular concordance rates of 95% and 97.5% respectively. LiDCOrapid interrogates the arterial trace from a standard arterial line (typically in the radial artery) and provides an estimated/nominal CO based on the PulseCO algorithm [99]. LiDCOrapid has been shown to be within acceptable limits of agreement with intermittent thermodilution via PAC [99, 101, 102]. It has recently been used in 2 well-designed RCTs as the CO monitor to guide goal-directed fluid therapy [86, 88]. The esCCO is a novel non-invasive method for estimating continuous CO [138], and in a comparison to thermodilution derived CO Yamada *et al.* reported an acceptable bias of $0.13L.min^{-1}$ and small limits of agreement of 0.04 to $0.22 L.min^{-1}$, but a percentage error of 54%. Others have questioned the clinical utility of the esCCO, with large limits of agreement in comparison studies with thermodilution and transthoracic echocardiography [138-140]. However, like the present study, Ishihara and colleagues demonstrated comparable trending abilities with currently available arterial waveform analysis methods such as the FloTrac/Vigileo monitor [141].

Bland-Altman analysis of Pronto-7 determined Hb concentrations and O₂ saturations demonstrate good agreement between both arterial and central venous Hb measurements and standard oximetry values with acceptable bias, precision and 95% limits of agreement, and percentage errors of <30% (*Table 6*). Our statistical analysis, however, demonstrates the limitations of using both four-quadrant concordance plots and polar plot analysis for these measurements, as they are variables that would be expected to remain relatively stable even in the post-operative setting. This is reflected by the number of measurements (n) used in the analysis after the recommended 10% exclusion zone is instituted (to exclude small changes that might be expected due to random error [112]). In situations where there is significant expected blood loss, such as major neurosurgical procedures, the Masimo SpHb sensor (as used in the Pronto-7) has been shown to have good trending ability with arterial blood gas analysis [142]. Pronto-7 has also been shown to have similar accuracy as the HemoCue (HemoCue, Sweden) point-of-care device when compared with a laboratory haematology analyser in the outpatient setting, with bias \pm standard deviation of -0.1 ± 1.1 g/dL and -0.1 ± 1.6 g/dL respectively [106], and comparable accuracy in the trauma patients [107].

None of the methods we have used to measure $\dot{V}O_2$ or DO_2 can be considered a 'gold standard'. The poor agreement between the methods may be attributable to errors with either of the techniques themselves:

Indirect calorimetry usually requires patients to be in a steady state [128, 129, 143], which may limit its utility to track changes in $\dot{V}O_2$, however, the GEM was specifically designed to be used in either steady state or light exercise with its

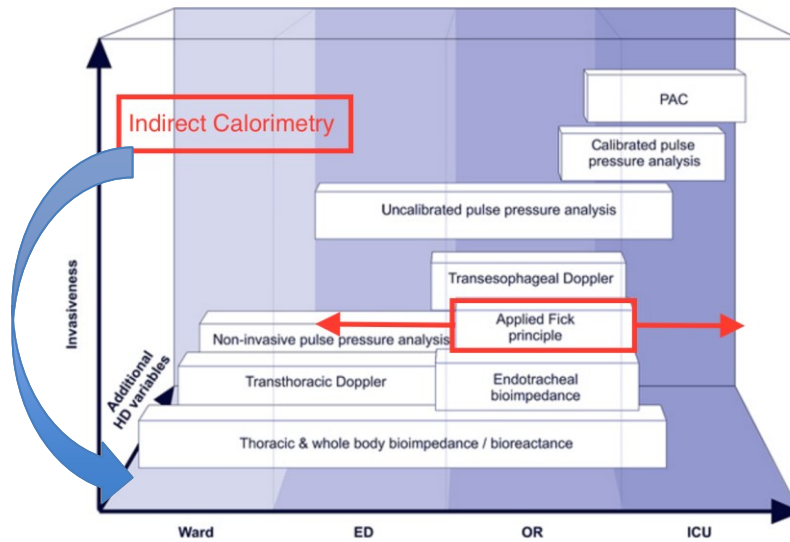
mixing chamber method for the collection of expired gases, and has proven highly reliable in these settings [94]. We carried out readings with all patients in the supine position with a 30° head-up tilt. No change in their haemodynamic status was evident within 30 minutes of any reading and there was no calorific intake 1 hour prior to any readings. In canopy indirect calorimeters such as the GEM, high gas flows in excess of 40 L.min⁻¹ are used to avoid CO₂ accumulation, resulting in dilution of expiratory gases, and the need to detect small differences in concentrations. Accuracy of O₂ measurement is reduced as F_iO₂ increases due to smaller differences in inspired and expired O₂ fractions. To mitigate against this we carried out all readings on room air (F_iO₂ = 0.21), with no patient de-saturating significantly. Any leaks from the system can also cause inaccuracies of gas collection. We had two readings abandoned due to system leaks (*Table 9*), which were identified following unexpectedly low $\dot{V}O_2$ readings. According to the manufacturers recommendations, the GEM was calibrated after a 30-minute warm-up. Calibrations were also performed when the cart had been idle for more than 20 minutes or after 2 hours of continuous use. Monthly ethanol burning tests were performed as a quality check, and the manufacturer calibrated the mass flow meter annually.

The precision of the Fick method for calculating $\dot{V}O_2$ and DO₂ is dependent on the accuracy of the CO and arterial and venous oxygen content measurements. These variables all have their own measurement error, which may be within the acceptable range, but when combined in a calculation these errors may be propagated and substantially greater than the sum of those errors [144]. In particular, some of the assumptions made in our Fick calculation could

introduce inaccuracy: The amount of oxygen dissolved in arterial blood ($0.023 \times \text{PaO}_2$) was disregarded in the calculation, as PaO_2 could not be determined non-invasively. In an average adult male with an $\text{Hb} = 15 \text{ g/dL}$, an $\text{SaO}_2 = 100\%$, a $\text{PaO}_2 = 13.3 \text{ kPa}$, and a $\text{CO} = 5 \text{ l/min}$, the difference in $\text{CaO}_2 = 0.3 \text{ ml/100ml}$ ($20.1 \text{ vs } 20.4 \text{ ml/100ml}$), which equates to a difference in $\text{DO}_2 = 15 \text{ ml/min}$ ($1005 \text{ vs } 1020 \text{ ml/min}$), or a reduction of $< 1.5\%$, which was deemed acceptable on pragmatic grounds. Furthermore, we chose 1.34 mL as the value of Hufner's constant for the O_2 combining capacity of Hb. Values between 1.31 mL and the theoretical value of 1.39 mL have been used in other studies, which can introduce a variability of around 6% for calculated values of $\dot{\text{V}}\text{O}_2$ and DO_2 [132], and would obviously affect any comparisons made in the present study. In addition, we substituted central venous oxygen saturations (ScvO_2) for mixed venous values in the Fick equation, which could potentially introduce further error into the calculation of our reference techniques. ScvO_2 has been shown to correlate well with those of mixed venous saturations [103], therefore in the absence of mixed venous readings it was our only alternative to calculate $\dot{\text{V}}\text{O}_2$. We attempted to reduce any further measurement errors in our invasive techniques by minimizing delays in analysis, calibrating analysers carefully, using a single investigator to take measurements, and averaging those measurements after a period of acclimatization. This was at the expense of making each data point acquisition very labour intensive.

When measuring post-operative $\dot{\text{V}}\text{O}_2$ and DO_2 , a variety of factors (institutional, device related, and patient specific) must be considered and influence the selection of the appropriate method, and clinicians must understand the underlying principles and inherent limitations of those methods. As is the case

with CO monitoring, an integrated approach is required, when the use of an invasive or a minimally or non-invasive technique is preferable (*Figure 39*).



Integrative concept for the use of cardiac output monitoring devices. ED: emergency department; HD: hemodynamic; ICU: intensive care unit; OR: operating room; PAC: pulmonary artery catheter.

Figure 39 An integrative concept for the use of cardiac output (and $\dot{V}O_2$ and DO_2) monitoring devices.

(Adapted from Alhashemi *et al.* [145]. Indirect calorimetry is non-invasive

Conclusion

Although there is a bias towards a lower $\dot{V}O_2$ and slightly higher DO_2 with wide limits of agreements when measured non-invasively and these methods may lack precision when compared to currently available minimally invasive measurements, these techniques demonstrate moderate to good trending ability and have the advantage of being safe, totally non-invasive, reliable and convenient. Moreover, Fick calculations of $\dot{V}O_2$ and DO_2 have the shared variables of CO and C_aO_2 , which raises the possibility of a systematic methodological error as a consequence of mathematical coupling [144, 146, 147], when supply dependency of O_2 is being investigated. Therefore, these non-invasive techniques could be useful for the bedside monitoring of post-operative $\dot{V}O_2$ and DO_2 patterns of ward patients.

The following chapter describes a further study into the feasibility of these non-invasive measurement techniques of $\dot{V}O_2$ and DO_2 in the perioperative setting and as pilot work examining the relationship between post-operative $\dot{V}O_2$ and complications in patients having contemporary major abdominal surgery. Ultimately non-invasive techniques might be useful as an early warning to determine which patients are developing “oxygen debt” [38], as a trigger to alter clinical care and potentially improve outcome.

Chapter 4

**CO₂ST: THE COST IN OXYGEN OF SURGICAL TRAUMA – A
FEASIBILITY STUDY OF THE NON-INVASIVE MEASUREMENT OF
OXYGEN DELIVERY AND CONSUMPTION AFTER MAJOR
ABDOMINAL SURGERY**

4.1 INTRODUCTION

More than 80 years ago Cuthbertson measured $\dot{V}O_2$ by external spirometry after orthopaedic injuries or operations in six patients [49]. He found initial decreases in $\dot{V}O_2$ followed by increased $\dot{V}O_2$; he termed this pattern the “ebb and flow” of oxygen. Later Cournand et al. [148] described oxygen transport and haemodynamic patterns in traumatic shock, and reporting reductions in CO, body metabolism, and blood volume in severe shock. In addition, Clowes and Del Guercio [149] described increased CO after surgery when associated with sepsis. Subsequently, the temporal patterns of haemodynamic and oxygen transport variables have been described following elective surgery in survivors and non-survivors [14, 16, 150-152]. In these patients, cardiac index (CI), DO_2 and $\dot{V}O_2$ were significantly higher in survivors than in non-survivors with comparable disorders. In 708 high-risk surgical patients, Shoemaker *et al.* demonstrated that survivors had greater postoperative increases in CI, DO_2 , $\dot{V}O_2$, and other haemodynamic variables than in the non-survivors [150], and that these variables were highly predictive of outcome. Indeed, several prospective studies, patient outcome was improved when “supra-normal” values, defined empirically by the median values of survivors, were attained early [14, 16, 150-152]. However, other studies showed no improvement in outcome by increasing DO_2 during the late postoperative period after organ failure was established [153, 154].

These studies used invasive techniques to measure and calculate $\dot{V}O_2$ and DO_2 ; primarily the pulmonary artery catheter (PAC). Thus, these studies

included only those patients who were considered to be at sufficiently high risk to justify the insertion of a PAC and admission to a high dependency environment - in general those having surgery with a likelihood of extensive tissue trauma and fluid shifts, or those with co-morbidities severe enough to potentially impair their ability to generate a sustained increase in $\dot{V}O_2$). Consequently the pattern of postoperative $\dot{V}O_2$ and DO_2 in fitter patients or those having less extensive body cavity surgery is not known.

More recently major advances in peri-operative care have greatly reduced the risk of dying after surgery and complication rates (reflected in shorter length of stay). Recent studies suggest that the assumptions from previous studies may not hold – most less fit patients survive surgery and go home promptly [35] and goal directed therapy may not have the impact of previous studies [84, 87, 92]. There is the strong possibility that modern care does not trigger as much of an inflammatory response as that seen previously and that patients do not need to develop the same alterations in $\dot{V}O_2$ and DO_2 . This was demonstrated in a recent small study of patients undergoing major vascular surgery using non-invasive techniques to determine $\dot{V}O_2$, where no rise in post-operative $\dot{V}O_2$ was observed [93].

We have previously evaluated the GEM indirect calorimeter (GEM Nutrition, Daresbury, UK), the esCCO (Nihon Kohden, Japan) CO monitor, and the Masimo Pronto-7 SpHb device against currently available minimally invasive devices and demonstrated a bias towards a lower $\dot{V}O_2$ and slightly higher DO_2

with wide limits of agreements when measured non-invasively (Chapter 3). These methods may lack precision but they demonstrate moderate to good trending ability and have the advantage of being safe, totally non-invasive, reliable and convenient. Therefore, we believe these techniques are useful for the bedside monitoring of post-operative O_2 and DO_2 , especially in the Level 1/0 ward setting [155].

This study aims to test the feasibility of these non-invasive measurement techniques in a cohort of patients and to explore the temporal patterns of $\dot{V}O_2$ and DO_2 measured by these techniques, and their relationship with post-operative complications, after contemporary major abdominal surgery.

4.2 METHODS

For more detailed methods please refer to the earlier Methods chapter. This prospective observational feasibility study was conducted on a cohort of 42 patients undergoing elective major colorectal surgery between December 2014 and March 2015 at Derriford Hospital, Plymouth, UK. Ethical approval was obtained from the NRES Committee South West – Cornwall & Plymouth (ref: 14/SW/1109), and was registered on the ClinicalTrials.gov database (Identifier: NCT02238561).

All patients scheduled for elective colorectal resections undergo a pre-operative assessment at a dedicated clinic. During the conduct of the pre-operative assessment, patients were provided with written information (*Appendix 4*) and invited to consider participation in the study. Written informed consent was obtained from all participants (*Appendix 5*).

All interventions were at the discretion of the operating surgeon and/or consultant anaesthetist responsible for the patient. Mechanical bowel preparation (MBP) was avoided where possible, and those patients receiving MBP routinely received an intravenous infusion of 1-2L of isotonic crystalloid prior to arrival in the operating theatre. Standardised peri-operative care was provided by a dedicated colorectal surgical team, and critical care as appropriate, according to a well-established local ERAS pathway.

Baseline $\dot{V}O_2$ and DO_2 measurements were made on the morning of surgery after admission to the pre-operative surgical admission unit. Post-operative measurements were taken at 1, 2, 4, 8, 12, 24, and 48 hours after the completion of surgery. All observations were made with patients lying in bed with a 30° head up tilt.

$\dot{V}O_2$ measurement

The GEM (GEMNutrition, Daresbury, UK) is an open-circuit flow-through indirect calorimeter. The compact bedside unit measures gas exchange volumes, respiratory quotient and energy expenditure. It does this by alternately measuring O_2 and CO_2 concentrations of inspired and expired air. Gas collection is via a comfortable transparent perspex hood placed over the patient's head and chest (*Figure 9*). GEM is inaccurate above an F_iO_2 of 30%, and the system is incompatible with ventilators. Measurements were taken with the patient breathing room air ($F_iO_2 = 21\%$), however, if the patient's SpO_2 fell below 90%, an F_iO_2 of 28% was employed. Further desaturation on 28% O_2 mandated abandoning the recordings at that time-point. Minute-by-minute $\dot{V}O_2$ averages are displayed on a monitor and it typically takes a subject between 5 and 10 minutes to acclimatise and for the $\dot{V}O_2$ to settle to a baseline ($\Delta\dot{V}O_2 < 5\%$ on 2 consecutive readings). This was followed by a 5-minute recording period. A mean $\dot{V}O_2$ was then calculated for the 5-minute recording period.

DO₂ measurement

DO₂ was calculated according to the following equation:

$$DO_2 = CO \times C_aO_2$$

$$C_aO_2 = (Hb \times SaO_2 \times 1.34)$$

The amount of oxygen dissolved in arterial blood ($0.023 \times PaO_2$) was disregarded in the calculation, as PaO_2 could not be determined non-invasively (see *chapter 2.2.1*).

CO was measured using the esCCO (Nihon Kohden, Japan) monitor and an average calculated for the 5-minute GEM recording period. The esCCO monitor provides a real-time estimation of CO from pulse wave transit time i.e. the time interval between the R wave of the ECG and the arrival of the arterial pulsation wave at an oximeter probe placed on the finger.

Hb and S_aO_2 were measured with the Pronto-7 pulse co-oximeter (Masimo Corp, Irvine, CA, USA) at the beginning and end of the GEM recording period and an average calculated.

Post-Operative Morbidity Survey

To explore the relationship between post-operative $\dot{V}O_2$ and complications in patients having contemporary major abdominal surgery, the severity of complications need to be graded. The Post-Operative Morbidity Survey (POMS) is a simple outcome scale and was designed to produce an easy and reliable method of prospectively recording the incidence of clinically important complications - specifically complications likely to keep a patient in hospital

[25, 115]. For patients who had been discharged prior to assessment, a day 5 POMS score of 0 was assumed. Patients were then divided into 3 groups: those without major post-operative morbidity, as defined by a POMS day 5 score = 0, those with major post-operative morbidity (POMS day 5 ≥ 1), and those who died within 30 days of surgery.

Statistical analysis

This is a pilot study to investigate the feasibility of performing these observations on the target population and a preliminary investigation of $\dot{V}O_2$ and DO_2 after surgery. Thus many of the analyses are exploratory and in our cohort of patients we did not expect to see statistically significant correlations between our measurements and outcomes. No power calculation was therefore performed.

Oxygen requirement at each time point was estimated from the baseline pre-operative $\dot{V}O_2$. This was corrected for the effects of temperature (which assumed a “metabolic activity increased or decreased 7 percent per degree Fahrenheit” [38], and was calculated as follows:

$$\text{corrected } \dot{V}O_2 (\dot{V}O_{2c}) = \dot{V}O_2 \times 10^{-0.036667 \times (98.6 - T)}, \text{ where } T \text{ is the patient's temperature in } ^\circ\text{F}.$$

Values were indexed to body surface area to allow comparisons to be made between groups.

The estimated $\dot{V}O_2$ deficit, or excess, at each time point was calculated (as previously described [38]) as the difference between the measured $\dot{V}O_2$ and the pre-operative baseline $\dot{V}O_2$ corrected for temperature. The net cumulative O_2 balance at each given time-point was calculated as the area under the curve (AUC) described by the time - $\dot{V}O_2$ deficit/excess curve (*Figure 16*). This was calculated using the trapezium methodology.

To determine if there was a difference in $\dot{V}O_2$, DO_2 , and cumulative O_2 balance between those patients who developed complications or not, we used a linear mixed model for repeated measures over time by group. This type of modelling is applicable to a repeated measures study in which there is unbalance in the study groups and makes it possible to prevent list-wise deletion due to missing data [116-118].

Data was analysed and graphs produced using Microsoft® Excel® for Mac 2011 and SPSS® v23.0 (SPSS, Chicago, Illinois, USA). We compared baseline characteristics using χ^2 or Student's t-test as appropriate.

4.3 RESULTS

4.3.1 Study Population

Eighty-seven patients were screened during the study period between December 2014 and March 2015 (*Figure 37*). Seven patients were not for surgical intervention, and four patients were admitted as an emergency prior to their planned pre-operative assessment date. Of those who underwent pre-operative assessment (n=76), twelve were not recruited due to an investigator not being available, seven patients declined participation (two of these were due to claustrophobia and one patient suffered panic attacks), and one patient had dementia and was therefore unable to consent.

Fifty-six patients were recruited. Nine patients had their scheduled date of surgery after completion of the study (i.e. April 2015, or later). Three patients withdrew before commencement of the study. Six patients had measurements taken pre-operatively but subsequently withdrew (n=2), did not meet the eligibility criteria (n=2, post-operative ventilation, no resection performed), or had their operation cancelled (n=2). Therefore, thirty-eight patients were included in the analysis (*Figure 40*).

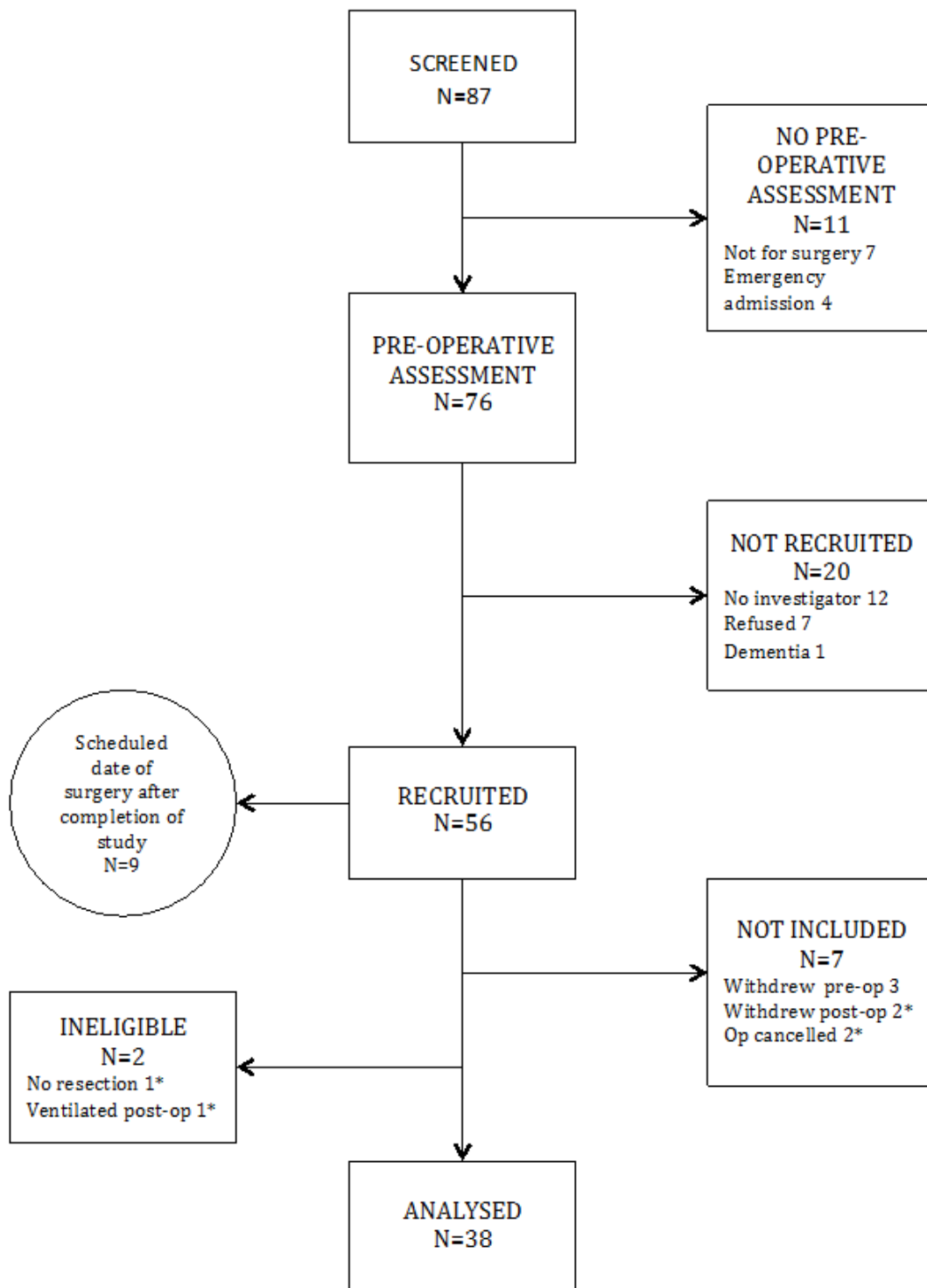


Figure 40 CO₂ST Study population

*Pre-operative measurements included in analysis

4.3.2 Patient Characteristics

Seventeen patients made an uneventful recovery from surgery. Twenty patients developed complications as defined by POMS ≥ 1 on day 5 post-operatively. One patient died 21 days post-operatively of a pulseless electrical activity (PEA) cardiac arrest after developing mechanical small bowel obstruction requiring further surgery.

Patient demographic data and preoperative values according to patient group are shown in *Table 10* and *Table 11*. There were no significant differences in age, male:female, or type of surgery (colonic vs. rectal) between those who developed complications or not. However, patients who developed complications had a significantly longer length of stay (13.9 ± 5.0 vs. 6.9 ± 4.8 , mean \pm SD, $p = 0.0001$), and were more likely to have had an open procedure (18/20 vs. 8/17, $p = 0.004$).

There were no significant differences between survivors and those who developed complications in any measured pre-operative variable, although pre-operative DO_2 values of those who developed complications tended to be lower than those who made an uneventful recovery (525.91 ± 26.67 vs. 599.06 ± 30.35 ml.min⁻¹.m⁻², mean \pm SD, $p = 0.07$).

	All	Survived	Survived with complications	<i>p</i>	Died
n	38	17	20		1
Age*	67.5(13.7) range 36.6-90.7	62.8(14.5) range 38.5-90.7	71.0(12.4) range 36.6-87.3	0.07	75.8
Sex (m:f)	22:16	9:8	12:8	0.67	1:0
LOS* (days)	10.7(6.0) range 2-23	6.9(4.8) range 2-22	13.9(5.0) range 6-23	0.0001	21 [§]
Procedure					
Rectal**	22(6)	10(5)	11(1)	0.82	1(0)
<i>AR</i>	11(4)	7(3)	4(1)		
<i>Hartmann's</i>	8(1)	1(1)	6(0)		1(0)
<i>Pan Proctocolectomy</i>	2(0)	1(0)	1(0)		
<i>APER</i>	1(1)	1(1)			
Colonic**	16(5)	7(4)	9(1)	0.82	
<i>Right hemi</i>	9(3)	4(3)	5(0)		
<i>Left hemi</i>	2(0)	1(0)	1(0)		
<i>Ext Right hemi</i>	2(1)	1(1)	1(0)		
<i>Ileo-caecal resection</i>	2(0)	1(0)	1(0)		
<i>Subtotal</i>	1(1)		1(1)		
Laparoscopic	11	9	2	0.004	0

Table 10 Demographic data of survivors, survivors with complications and non-survivor

*Values are mean (SD). **Values are total (number laparoscopic). Data was compared with Student's t-test or χ^2 test as appropriate. [§]Patient died on day 21. LOS: length of stay

	Survived	Survived with complications	p	Died
n	17	20		1
VO₂ (ml.min ⁻¹ .m ⁻²)	122.62 (3.49)	117.31 (3.74)	0.31	109.77
DO₂ (ml.min ⁻¹ .m ⁻²)	599.66 (30.35)	525.91 (26.67)	0.07	444.37
BSA (m ²)	1.93 (0.05)	1.91 (0.04)	0.76	2.19
CI (L.min ⁻¹ .m ⁻²)	6.56 (0.35)	5.91 (0.32)	0.17	5.67
Hb (g.L ⁻¹)	137.06 (4.32)	132.60 (4.23)	0.47	133.00
SpO₂ (%)	96.06 (0.40)	95.98 (0.46)	0.89	96.00
Temp (°C)	36.6 (0.10)	36.7 (0.09)	0.59	36.70

Table 11 Pre-operative values of survivors, survivors with complications and non-survivor

Values are mean (SD). Data was compared with student's t-test.

4.3.3 Post-operative $\dot{V}O_2$ and DO_2

The patterns of post-operative $\dot{V}O_2$ and DO_2 are shown in *Table 12* and *Figures 41* and *42*. The linear mixed model found that $\dot{V}O_2$ is suppressed in the immediate post-operative period and does not rise back to pre-operative levels until more than 4 hours post-operatively ($p < 0.001$). There was no difference in the temporal pattern between survivors and those patients who developed complications ($p = 0.882$). These patterns are similar to those seen previously [38].

The linear mixed model found no statistically significant temporal pattern to post-operative DO_2 , and no difference between groups ($p = 0.459$ and 0.156 respectively). If the pre-operative DO_2 values are excluded, there were still no statistically significant differences over time or between groups.

Time	Group			Mixed Model Analysis*	
	Survived	Survived with complications	Died	Effect	<i>p</i> [§]
VO₂ (ml.min⁻¹.m⁻²)					
Pre-operative	122.6 (3.49) (n=17)	117.3 (3.74) (n=20)	109.8		
1 hour	118.3 (8.02) (n=15)	105.8 (5.61) (n=17)	96.1		
2 hours	111.6 (6.34) (n=17)	111.9 (4.86) (n=19)	64.9	Group	0.882
4 hours	125.5 (5.76) (n=17)	124.6 (4.82) (n=18)	148.1		
8 hours	122.1 (4.91) (n=16)	126.3 (5.37) (n=18)	148.0	Time	<0.001
12 hours	126.6 (5.82) (n=16)	128.5 (4.48) (n=19)	150.4		
24 hours	130.7 (5.41) (n=17)	129.9 (7.39) (n=19)			
48 hours	133.6 (3.58) (n=13)	140.6 (7.56) (n=13)			
DO₂ (ml.min⁻¹.m⁻²)					
Pre-operative	599.7 (30.35) (n=17)	524.9 (26.67) (n=20)	444.4		
1 hour	510.7 (36.46) (n=16)	466.4 (20.16) (n=18)	299.9		
2 hours	520.34 (33.29) (n=17)	427.1 (19.56) (n=19)	388.6	Group	0.156
4 hours	505.2 (30.84) (n=17)	446.8 (19.79) (n=19)	383.9		
8 hours	436.8 (28.23) (n=16)	438.5 (20.15) (n=19)	455.4	Time	0.459
12 hours	433.2 (20.33) (n=16)	424.62 (19.75) (n=19)	355.6		
24 hours	485.5 (25.99) (n=17)	450.3 (29.55) (n=18)			
48 hours	498.4 (34.41) (n=14)	507.6 (23.63) (n=13)			

Table 12 VO₂ and DO₂ patterns by group and results of mixed model analysis

Values are mean (SEM). *Analysis compared survived and survived with complications groups only.
[§]*p* values associated with Type III tests of fixed effects.

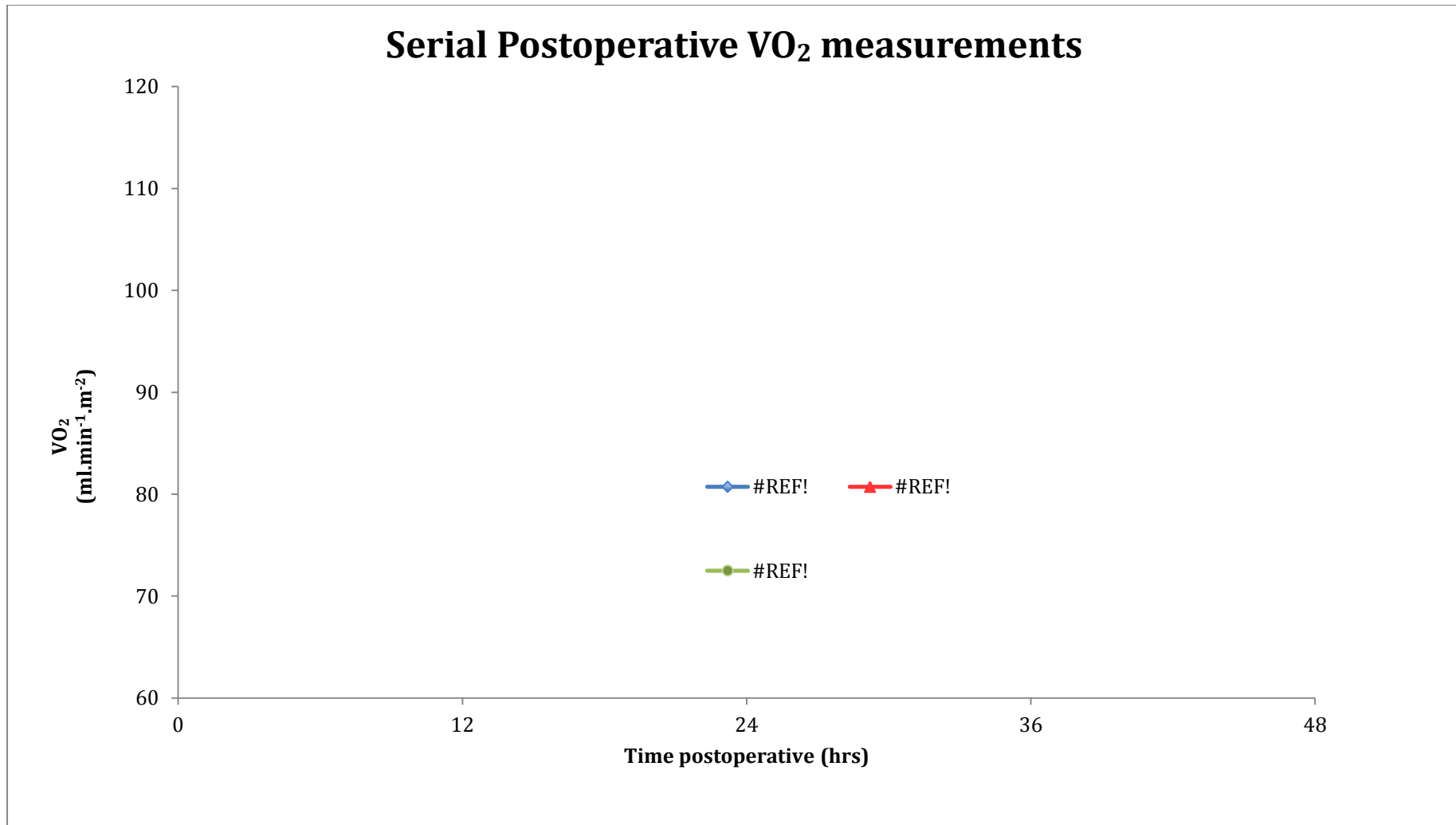


Figure 41 Serial measurements of mean $\dot{V}O_2$. Time 0 = pre-operative values. Error bars are SEM. Survived n=17, survived with complications n=20, died n=1.

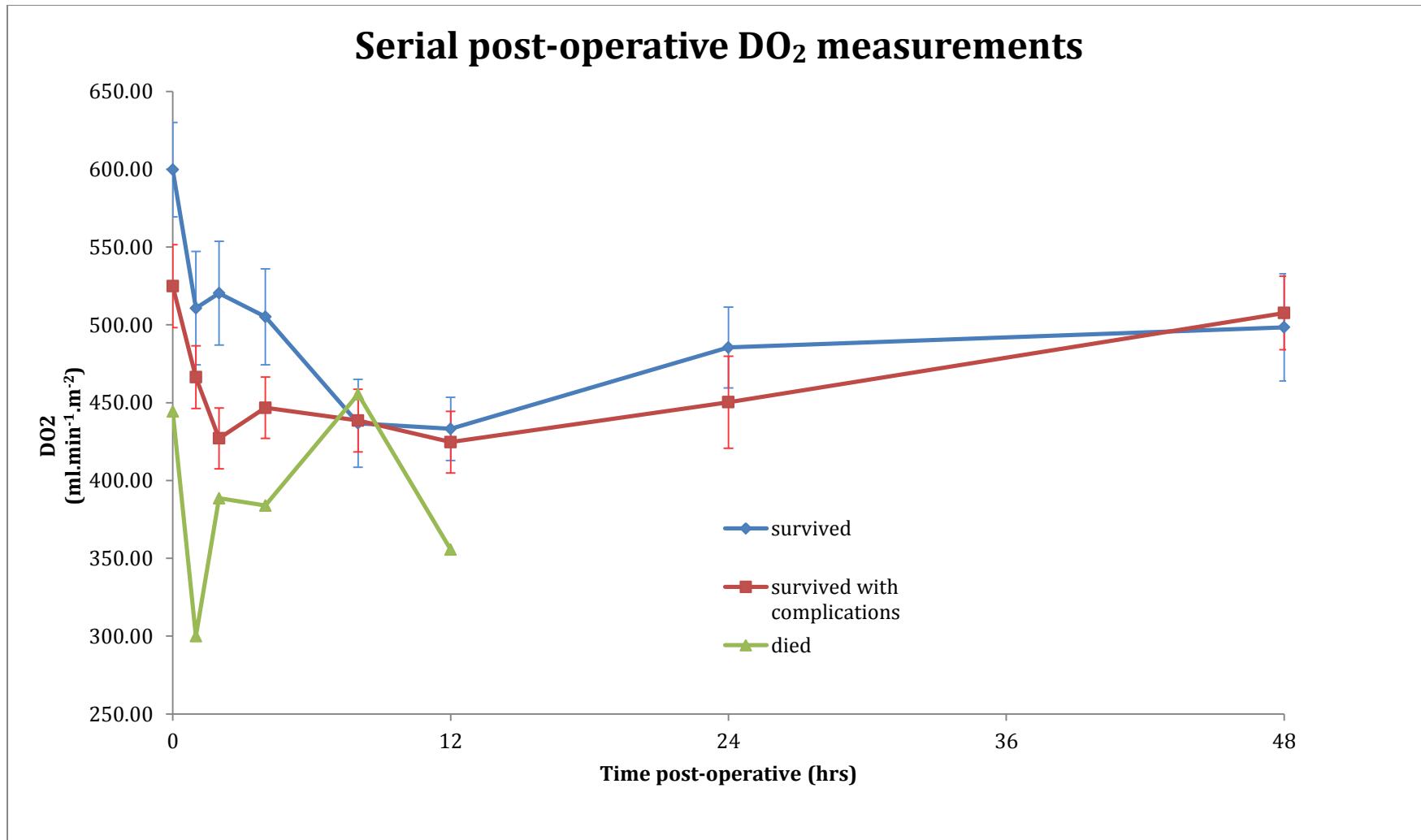


Figure 42 Serial measurements of mean DO₂. Time 0 = pre-operative values. Error bars are SEM Survived n=17, survived with complications n=20, died n=1.

4.3.4 Post-operative oxygen balance

The temporal patterns of cumulative O₂ deficit or excess in the immediate post-operative period for survivors, survivors with complications and the non-survivor are shown in *Table 14* and *Figure 43*. Linear mixed modelling demonstrated that patients developed an oxygen debt in the immediate post-operative period, but that this was subsequently “paid off” and became an O₂ excess, $p = 0.002$. However, there was no statistically significant difference in this pattern between survivors and survivors with complications, $p = 0.731$.

Table 13 shows the mean (*SEM*) of the O₂ deficit at its maximum and the duration of the O₂ deficit for each of the patient groups. The latter represents the time that the net cumulative $\dot{V}O_2$ became positive, indicating that any “oxygen debt” had been repaid.

	Survived	Survived with complications	<i>p</i>	Died
Max O ₂ deficit (L.min ⁻¹ .m ⁻²)	1.04 (0.83)	0.78 (0.38)	0.775	2.15
Time to net cumulative positive $\dot{V}O_2$ (hrs)	13.41 (4.51)	5.79 (2.43)	0.154	4.94

Table 13 Post-operative tissue oxygen deficit

Values are mean (*SEM*). Data was compared with Student’s t-test.

Time	Group			Mixed Model Analysis*	
	Survived	Survived with complications	Died	Effect	<i>p</i> [§]
Net cumulative O ₂ balance (L.min ⁻¹ .m ⁻²)					
1 hour	-0.16 (0.17) (n=17)	-0.33 (0.15) (n=20)	-0.41		
2 hours	-0.56 (0.44) (n=17)	-0.78 (0.39) (n=19)	-1.76		
4 hours	-1.04 (0.83) (n=17)	-0.58 (0.83) (n=19)	-2.15	Group	0.731
8 hours	-0.88 (1.45) (n=17)	1.52 (1.96) (n=19)	7.03		
12 hours	-0.63 (2.20) (n=17)	3.94 (3.04) (n=19)	16.49	Time	0.002
24 hours	3.69 (4.19) (n=17)	12.50 (5.85) (n=19)			
48 hours	16.09 (8.89) (n=13)	40.11 (16.89) (n=13)			

Table 14 Net cumulative oxygen balance patterns by group and results of mixed model analysis

Values are mean (*SEM*). *Analysis compared survived and survived with complications groups only.
[§]*p* values associated with Type III tests of fixed effects.

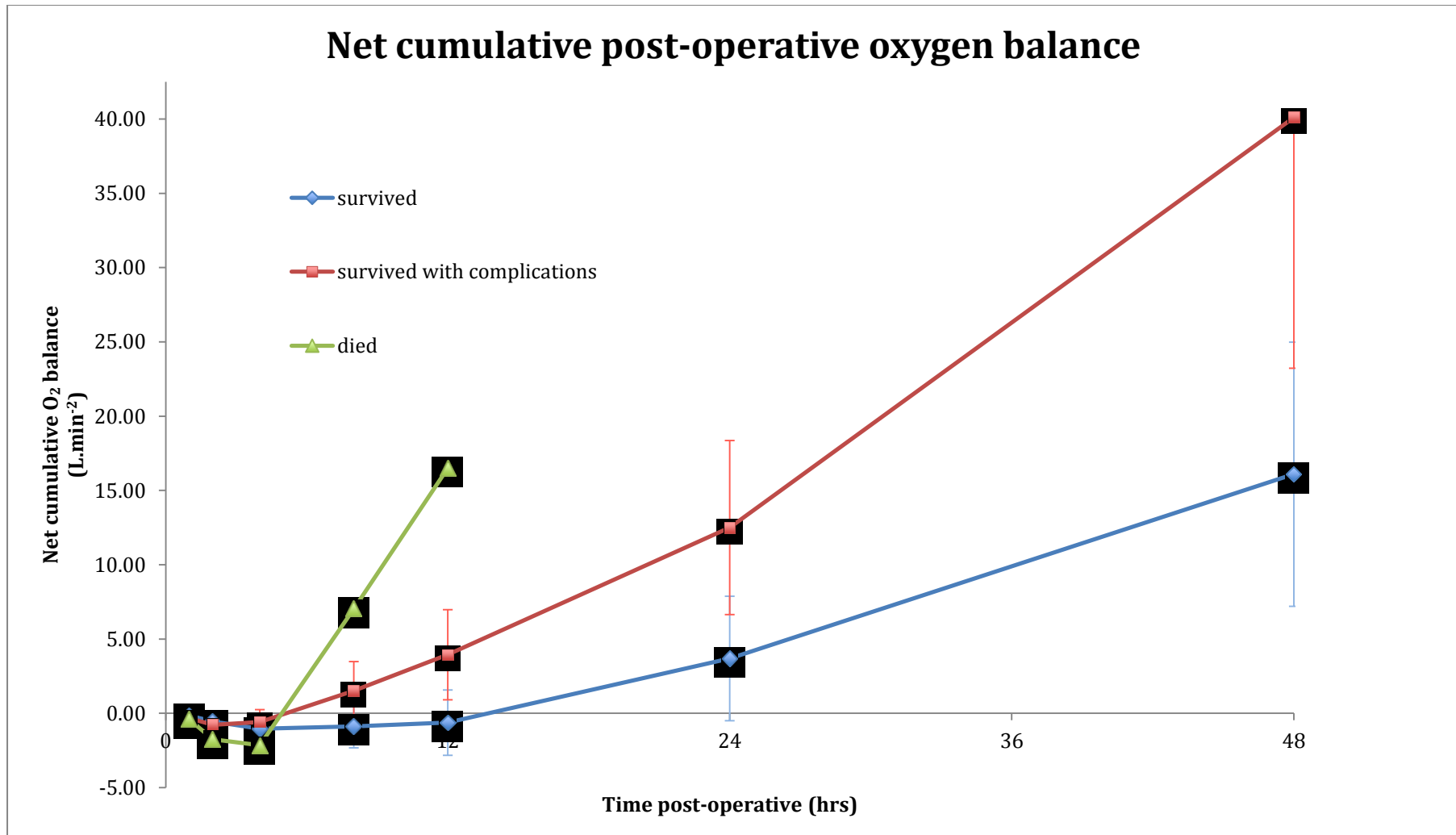


Figure 43 Net cumulative oxygen balance for survivors, survivors with complications and non-survivor. Error bars are SEM

4.3.5 Missing data

Table 15 lists the reasons for any missed readings. There were 20 missed $\dot{V}O_2$ readings and 16 missed DO_2 readings. Only 5 were due to technical reasons (leak from GEM system, n=4, poor SpHb trace, n=1). The most common reading missed was at 48 hours post-operatively (n=11), followed by 1-hour post-operative (n=5), 8-hours (n=2), the remaining time points had one reading missed each. All readings were carried out with an $F_iO_2 = 0.21$, with no instances of patients desaturating <90%. No complications were recorded that could be attributed to the protocol of the study.

Reason for missed reading	Readings affected	Number of readings affected
Leak from GEM system	VO_2	4
Vomiting at time of reading	All readings	4
Significant nausea requiring intervention	All readings	4
Not recorded	All readings	2
Patient withdrawn by clinical team	All readings	2
No investigator	All readings	2
Poor SpHb trace on Pronto-7	Hb.SpO ₂ , DO ₂	1
Delay in patient arriving to recovery	All readings	1
Patient discharged home before reading	All readings	1

Table 15 Reasons for missed readings in feasibility study

4.4 DISCUSSION

It is safe and feasible to use the GEM indirect calorimeter, the esCCO CO monitor and the Masimo Pronto-7 SpHb device to measure $\dot{V}O_2$ and DO_2 pre-operatively and post-operatively in patients undergoing elective colorectal resections. These measurements can be used to calculate estimated post-operative “oxygen debt” in these patients. Although not significantly different in this small feasibility study, there appears to be distinct patterns of $\dot{V}O_2$ and DO_2 after contemporary abdominal surgery in those patients who develop complications, as defined by POMS, or not which would confirm the “ebb and flow” of oxygen previously described [49, 148, 149]. However, the magnitude and direction of change of these O_2 transport variables do not follow those of previous studies resulting in contemporary patterns of net cumulative O_2 debt that differ from those previously described [38].

Patient safety is of paramount importance when any device is used in a novel way. There were no adverse events that could be attributed, either directly or indirectly, to the protocol of the study. Significantly no patients desaturated below 90% during any of the readings. Half (11/22) of missed readings were at the 48-hour time-point which questions the validity of taking readings at this time in future studies, however, this is in the context of 296 possible readings. Technical reasons accounted for 5 missed readings. In conjunction with a low refusal to participate rate (*Figure 40*), these results support the feasibility of the protocol for post-operative measurement of $\dot{V}O_2$ and DO_2 in patients following colorectal surgery.

In seminal papers, that influenced much subsequent research into goal directed therapy and latterly assessment of patients’ pre-operative functional capacity,

Shoemaker *et al.* described an increase in $\dot{V}O_2$ in high-risk patients after major surgery and presented evidence that the inability to meet this demand, was associated with severe post-operative complications and mortality [14, 38]. Using the pulmonary catheter and the reverse Fick equation, they estimated patients' postoperative $\dot{V}O_2$ requirement (using their measured preoperative baseline $\dot{V}O_2$ corrected for temperature) and suggested that oxygen deficit was present when this figure exceeded measured $\dot{V}O_2$. The temporal pattern of post-operative oxygen deficit appeared to differ according to whether patients survive, develop complications or not. Shoemaker used these observations to design an intervention involving manipulation of the cardiovascular system by fluid therapy and drugs to ensure adequate post-operative DO_2 (later called Goal Directed Therapy, GDT), which appeared to dramatically improve clinical outcomes in the setting of high risk surgery [14, 34, 38]. More recently, studies looking at the role of GDT and functional assessment of patients' aerobic fitness suggest that Shoemaker's assumptions may not hold - most less fit patients survive surgery and go home promptly [35] and GDT may not have the impact of previous studies [84, 87, 88, 92, 93]. This is further supported by the current study that appears to show a different pattern of post-operative net cumulative O_2 debt to that previously described. We describe post-operative $\dot{V}O_2$ and DO_2 that is suppressed in the immediate post-operative period, not rising to at or above baseline values until at least 4 hours post-operatively. This questions the central tenet of the GDT paradigm and shows how as yet unidentified mechanisms might contribute to reducing the burden of surgical critical illness [30]. One must consider heart failure as a potential cause of these initial low values given its prevalence in the aging population and is a leading cause of post-operative morbidity and mortality [12]. However, finding this would be

unusual in an entire study population as in the present study group means are presented. It is more likely that rather than a population-based approach to targeting DO_2 to predefined values that a more individualised patient approach is likely to be optimum [81]. In a recent randomised controlled trial of targeted post-operative DO_2 in high-risk surgical patients to their individual pre-operative DO_2 value (POM-O), Ackland *et al.* demonstrated that achievement of preoperative oxygen delivery soon after major surgery is associated with a reduction in early postoperative morbidity, yet this occurred irrespective of additional postoperative haemodynamic manipulation over and above standard of care [30]. It may be that what affects clinical outcomes is care being closely applied and monitored by diligent personnel, rather than monitors and algorithms to target DO_2 *per se* [88].

This study was designed to investigate the feasibility of performing these observations on the target population, and therefore sample size calculations were not performed. Consequently, interpretation of any of our results should be made with caution. The validity and limitations of our techniques to measure post-operative $\dot{V}O_2$ and DO_2 has previously been discussed (see 3.4 *Discussion*). We did not record heart rate (HR) in this study. In retrospect, our failure to record HR is important as an increase in peri-operative HR has been linked to prolonged length of hospital stay after major surgery [156]. A change to the timing of baseline measurements (either in the anaesthetic room immediately pre-operatively, or alternatively at the pre-operative assessment clinic at patient enrolment) could reduce this bias. The post-operative DO_2 pattern of the non-survivor could indicate that there may be a critical threshold

of DO_2 in the immediate post-operative period below which heralds the development of severe morbidity \pm mortality ensues.

We chose as a secondary endpoint the development of post-operative complications as defined by a POMS ≥ 1 on day 5 following surgery. The choice of a categorical measure of post-operative complications may be flawed. The POMS is a binary measure of the presence of complications, which reduced the discriminatory power. It has been well validated in elective major surgery, with good inter-observer agreement and with the advantage that it should capture the presence of morbidity on any given day, which is of sufficient severity to require continued hospital admission [25, 115]. A POMS score performed on Day 5 is likely to be discriminative between patients who are recovering well, and those who are developing complications. However, in rectal surgery, POMS on day 5 may be too early to differentiate between those recovering well and not, as it has been shown that a positive POMS on day 15 after surgery was predictive of an increased mortality risk, whereas positive POMS on day 5 was not [157]. This raises the possibility that any meaningful comparison between the patterns of post-operative $\dot{\text{V}}\text{O}_2$ and DO_2 according to the development of complications or not seen in previous work, the present study and any further work is flawed. Other measures of post-operative complications are equally problematic. The Clavian-Dindo classification system has enjoyed widespread acceptance as a measure [158]. However, this scale fails to discriminate well between serious and relatively minor complications. For example, intestinal ileus can be classified as Grade 2 whether it is treated with pro-kinetic drugs or total parenteral nutrition on the basis that both represent “pharmacological treatment”.

Conclusion

The non-invasive measurement of $\dot{V}O_2$ and DO_2 using the GEM indirect calorimeter, the esCCO CO monitor and the Masimo Pronto-7 SpHb device is safe and feasible in patients after major abdominal surgery. These measurements can be used to calculate estimated post-operative “oxygen debt” in these patients. Although not significantly different in this small study, there appears to be distinct patterns of $\dot{V}O_2$ and DO_2 after contemporary abdominal surgery in those patients who develop complications, as defined by POMS, or not. Contemporary patterns of net cumulative O_2 debt appear to differ from those previously described [38].

Chapter 5

DISCUSSION

This chapter summarises the discussion points arising in Chapters 3 & 4 and attempts to place the contents of this thesis in the context of contemporary peri-operative practice.

5.1 STUDY FINDINGS

Despite the bias and wide limits of agreements the GEM indirect calorimeter, the esCCO CO monitor and the Masimo Pronto-7 SpHb device, techniques demonstrate moderate to good trending ability when compared to currently utilised minimally invasive monitors and have the advantage of being safe, totally non-invasive, reliable and convenient. Therefore, non-invasive techniques could be useful for the bedside monitoring of post-operative $\dot{V}O_2$ and DO_2 patterns of both high-risk and “standard” patients in the critical care setting and on the wards.

It is safe and feasible to use the GEM indirect calorimeter, the esCCO CO monitor and the Masimo Pronto-7 SpHb device to measure $\dot{V}O_2$ and DO_2 pre-operatively and post-operatively in patients undergoing elective colorectal resections. These measurements can be used to calculate estimated post-operative “oxygen debt” in these patients. Although not significantly different in this small study, there appears to be distinct patterns of $\dot{V}O_2$ and DO_2 after contemporary abdominal surgery in those patients who develop complications, as defined by POMS, or not. Contemporary patterns of net cumulative O_2 debt appear to differ from those previously described.

5.2 STUDY IMPLICATIONS

5.2.1 Measuring $\dot{V}O_2$ Post-operatively

There is considerable historical evidence that $\dot{V}O_2$ measured with gas exchange methods is not interchangeable with $\dot{V}O_2$ derived from the reverse Fick equation, and that due to inaccuracies in measurements of CO and the oxygen content of arterial and mixed venous blood, Fick $\dot{V}O_2$ should be used with caution when clinical decisions are based on its interpretation [122-124, 128-133]. Despite this, over the last 3 decades Fick $\dot{V}O_2$ has been the accepted standard in research studies, and clinical practice, due to the cumbersome nature and other technical limitations of the available gas exchange methods [123, 124]. More recently, technological improvements have meant that metabolic carts are more compact and are able to be used at the bedside or incorporated into ventilator circuits, to enable clinicians to measure gas exchange and estimate energy expenditure in patients on general wards or the critical care setting [94, 96, 159].

Our studies confirm this difference between measured and Fick $\dot{V}O_2$. They also demonstrate the acceptability to both patients and clinical staff of the GEM indirect calorimeter in the post-operative setting. Moreover, they show that the GEM is able to track changes in post-operative $\dot{V}O_2$. Furthermore, by decoupling the calculation of $\dot{V}O_2$ from DO_2 (Fick calculations of $\dot{V}O_2$ and DO_2 have the shared variables of CO and C_aO_2), by using independent measurements, this overcomes the possibility of a systematic methodological

error as a consequence of mathematical coupling [144, 146, 147] when supply dependency of O_2 is being investigated [160].

As previous stated, Shoemaker's seminal papers describing the increase in $\dot{V}O_2$ in high-risk patients after major surgery and evidence that the inability to meet this demand, was associated with severe post-operative complications and mortality [14, 38]. He demonstrated differing temporal patterns of post-operative oxygen deficit according survivors, and those who developed complications or not. This developed into the first of many GDT interventions which appeared to dramatically improve clinical outcomes in the setting of high risk surgery [14, 34, 38]. However, more recently, studies looking at the role of GDT and functional assessment of patients' aerobic fitness suggest that Shoemaker's assumptions may not hold [35],[84, 87, 88, 92, 93]. This is further supported by the current study that appears to show a different pattern of post-operative net cumulative O_2 debt to that previously described. To illustrate this the O_2 deficit/excess curves from both studies are compared in *Figure 44*.

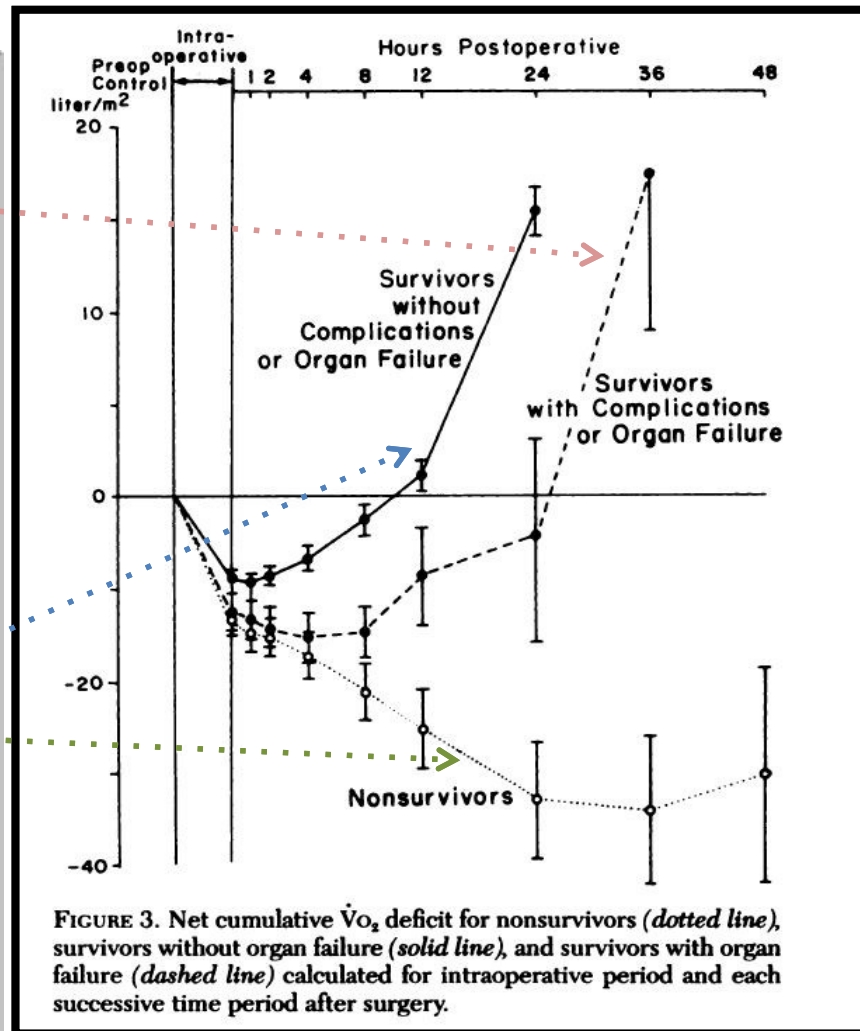
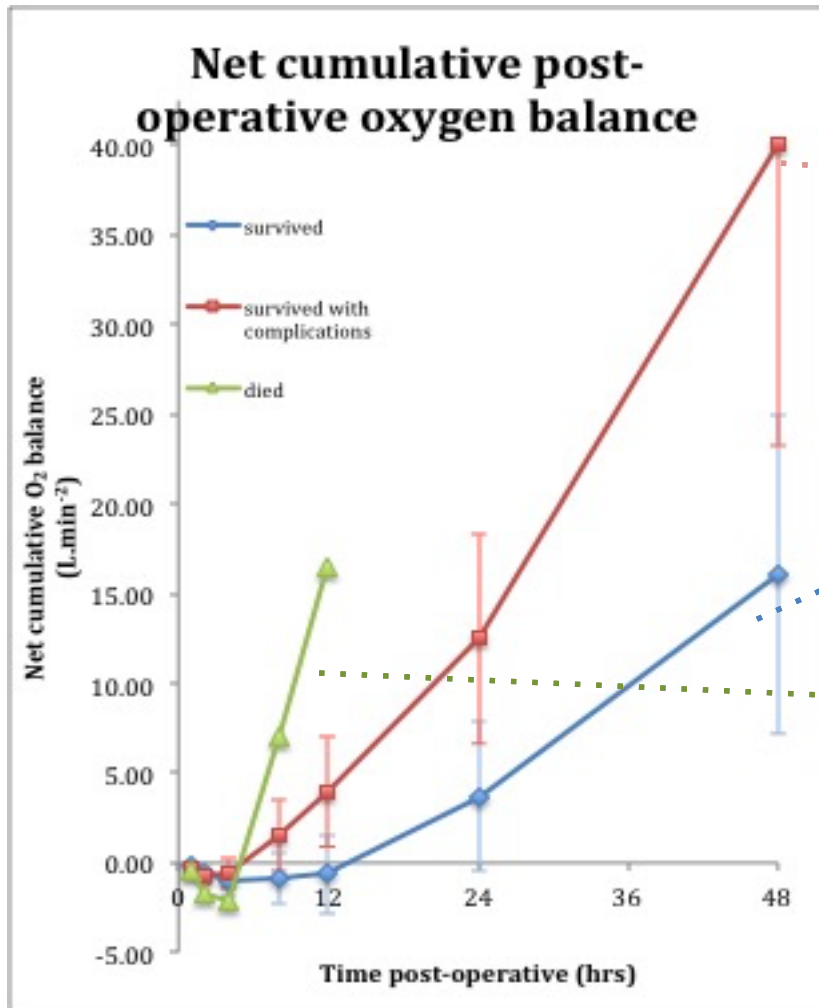


FIGURE 3. Net cumulative $\dot{V}O_2$ deficit for nonsurvivors (dotted line), survivors without organ failure (solid line), and survivors with organ failure (dashed line) calculated for intraoperative period and each successive time period after surgery.

Figure 44 Comparison of Net cumulative O₂ balance graphs, current study compared with Shoemaker et al. (1992) [38].

5.2.1 Measuring DO₂ Post-operatively

DO₂ is the product of CO and C_aO₂. Traditionally these variables have been derived from the PAC. This device has fallen out of favour recently as it has a significant morbidity rate associated with its use and a RCT on the use of the PAC on the survival of high-risk surgical patients showed no benefit in terms of mortality rates [161]. The PAC-man trial [127] was a large pragmatic RCT in the general ICU population and again failed to demonstrate any benefit from PAC use. It did also demonstrate no harm from its use either. In their commentary following the PAC-man trial Reade & Angus [162] recommend that “the clinician weigh carefully the perceived benefits, which may be largely intangible, against the small, but non-zero, risk of harm to the patient.” As a result there has been an expansion in novel CO monitoring devices. We describe the use of one such totally non-invasive CO monitor, the esCCO, in the perioperative setting. Like all such devices the esCCO has inherent limitations and these are discussed in *Chapter 3 & 4*, but primarily the fact that it is in essence a “black-box” that displays CO data from a proprietary algorithm, with an unpublished delay in recording and displaying the data which could adversely affect the comparisons made in this thesis. These concepts are equally true of non-invasive measures of Hb such as the Masimo Pronto-7.

The place of GDT is controversial. GDT may not have the impact of previous studies [84, 87, 88, 92, 93]. There is still a debate of what should be the recommended baseline fluid therapy – of which some answers may be provided by a trial currently still undergoing patient recruitment, RELIEF [163]. This is a randomised controlled trial of restrictive vs. liberal fluid administration in more

than two thousand eight hundred patients undergoing elective major abdominal surgery. Further research will be required to identify patient groups who would most likely to benefit from GDT.

Our results support a hypothesis that it is not the achievement of supra-normal values of DO_2 that is important, rather it is avoiding a critical threshold of DO_2 in the immediate post-operative period that might reduce morbidity and mortality. This might also support the inability of transfusion to improve outcomes in clinical trials – as the increase in DO_2 is not contributing to any increase in VO_2 .

5.3 STUDY LIMITATIONS

The limitations of each study have been discussed fully in the relevant chapters, however, we outline below some of the limitations of our methodology and equipment used. The aim of this thesis was to perform original research to investigate the question “what is the $\dot{V}O_2$ after contemporary major abdominal surgery?” using non-invasive technology, and had two studies. Neither of the two studies had a power calculation performed to inform sample sizes. However, the sample size of the validation study was comparable to previous studies of agreement between methods of CO measurement. The second study was a small feasibility study, and not powered to detect any differences in the groups observed.

5.3.1 Limitations of equipment used

Indirect calorimetry usually requires patients to be in a steady state [128, 129, 143], which may limit its utility in the early post-operative period. We carried out readings with all patients in the supine position with a 30° head-up tilt. No change in their haemodynamic status was evident within 30 minutes of any reading and there was no calorific intake 1 hour prior to any readings. In canopy indirect calorimeters such as the GEM, high gas flows in excess of 40 L.min⁻¹ are used to avoid CO₂ accumulation, resulting in dilution of expiratory gases, and the need to detect small differences in concentrations. Accuracy of O₂ measurement is reduced as F_iO₂ increases due to smaller differences in inspired and expired O₂ fractions. To mitigate against this we carried out all readings on room air (F_iO₂ = 0.21), with no patient de-saturating significantly. Any leaks from the system can also cause inaccuracies of gas collection. We had six readings abandoned due to system leaks, which were identified during GEM calibration, or from unexpectedly low $\dot{V}O_2$ readings.

The GEM is not compatible with ventilators. Thus we were unable to measure post-operative $\dot{V}O_2$ in any mechanically ventilated patients. There are other commercially available calorimeters that can be connected to an anaesthetic circuit [159] that would enable $\dot{V}O_2$ measurements in this group of patients, but these devices are expensive which limits their availability within a public health system for widespread clinical use. In addition clinicians caring for patients in intensive care have the option of invasive measures of DO₂ and $\dot{V}O_2$.

A number of patients refused to participate in either of the studies due to claustrophobia and/or a reluctance to have the GEM hood placed over their heads. In those patients who did participate, 2 readings were abandoned due to patients not wanting to go under the hood due to nausea/vomiting. One patient was withdrawn from the validation study due to acute post-operative confusion.

The Pronto-7 finger probe is sensitive to ambient light and movement and requires adequate blood flow to the finger to enable accurate readings. Only one reading was affected by a poor trace that was not remedial to hand warming or the use of the proprietary opaque finger cover. In one patient with a demyelinating disorder and who was unable to straighten their fingers we were unable to obtain Hb or O₂ saturations at all and therefore unable to calculate non-invasive DO₂.

The esCCO device was very reliable and no abandoned readings were directly attributable to this device, however, some have questioned the clinical utility of the esCCO, with large limits of agreement in comparison studies with thermodilution and transthoracic echocardiography [138-140]. However, like the present study, Ishihara and colleagues demonstrated comparable trending abilities with currently available arterial waveform analysis methods such as the FloTrac/ Vigileo monitor [141].

During the conduct of the validation study we had to change our protocol due to an adverse event with the original invasive CO monitor used – the PiCCOplus

(see *appendix 5*). PiCCOplus utilizes arterial pulse contour analysis following calibration to measure CO and has acceptable agreement and bias in the measurement of cardiac output compared with intermittent thermodilution via a PAC provided a repeat calibration is performed after any major haemodynamic changes [98-100]. We changed to the LiDCOrapid CO monitor, which is uncalibrated and therefore might affect the accuracy of any CO measured invasively and used as our reference method. This is the Achilles Heel of the validation study as the LiDCOrapid does not measure absolute values of CO. This clearly has implications for any conclusions drawn from any comparisons assumed to be accurate to the absolute values of CO. However, the LiDCOrapid is gaining widespread acceptance as a useful CO monitor and has been shown to be useful to assess trending [164].

5.3.2 Post-operative complications

Postoperative mortality is a robust endpoint but was sufficiently uncommon in this patient population to preclude its use as a primary outcome measure. Any choice of a categorical measure of post-operative complications may be flawed. As previously stated in Chapter 4, the POMS is a binary measure of the presence of complications, which reduced the discriminatory power. It has been well validated in elective major surgery, with good inter-observer agreement and with the advantage that it should capture the presence of morbidity on any given day, which is of sufficient severity to require continued hospital admission[25, 115]. A POMS score performed on Day 5 is likely to be discriminative between patients who are recovering well, and those who are developing complications. However, in rectal surgery, POMS on day 5 may be too early to differentiate between those recovering well and not, as it has been shown that a positive POMS on day 15 after surgery was predictive of an increased mortality risk,

whereas positive POMS on day 5 was not [157]. This raises the possibility that any meaningful comparison between the patterns of post-operative $\dot{V}O_2$ and DO_2 according to the development of complications or not seen in previous work, the present study and any further work is flawed.

5.4 CONCLUSIONS AND FUTURE WORK

Much of the pre-operative optimisation work that is currently undertaken is founded on the physiological observations of Shoemaker [14, 38]. Much has changed both surgically and anaesthetically in the ensuing three decades: 2018 is a post-PAC world with an emphasis on non-invasive techniques and enhanced recovery programmes. We have seen improved outcomes in terms of shorter lengths of stay and decreased post-operative morbidity and mortality. $\dot{V}O_2$ patterns after “modern” abdominal surgery are not known.

We have shown that the GEM indirect calorimeter, esCCO monitor and Masimo Pronto-7 SpHb device can reliably measure and track changes in post-operative $\dot{V}O_2$ and DO_2 . Their use is safe and feasible in the post-operative setting, and the pattern of O_2 transport variables appear to differ from that seen historically. Although we demonstrated an ebb and flow in post-operative $\dot{V}O_2$ similar to that seen previously [49], we did not show any significant difference in the temporal patterns of $\dot{V}O_2$, DO_2 or net cumulative O_2 balance. Any further work carried out using these non-invasive techniques to define the relationship between post-operative patterns of $\dot{V}O_2$ and DO_2 and the development of post-operative complications or not would ideally be in an appropriately powered study. The aim would be to determine if there is a difference in post-operative O_2 debt in patients undergoing major abdominal surgery who make an uneventful recovery and those with post-operative morbidity and/or mortality, including any pre-operative risk stratification and mode of surgery (open vs. laparoscopic). Future work might consider a comparison between survivors with and without complications based on base deficit and lactate at the end of surgery and pre-

operative risk stratification with CPET variables e.g. AT. This might help identify which measured variable, either pre-, intra- or post-operative has the greatest discriminatory power to identify those patients who are not recovering well and who would benefit from increased monitoring and ultimately improve individual patients' outcomes. However, the data obtained from the current study does not allow a power calculation to be performed. Further studies could prospectively help identify those patients developing a post-operative O₂ debt as a trigger to alter clinical care (moving a patient to a critical care environment where more invasive monitoring and treatment is possible), and potentially improve outcome.

The pattern of oxygen consumption after contemporary surgery described in these patients supports a hypothesis that GDT based care may not benefit most patients as their DO₂ is well above that required for their $\dot{V}O_2$. It further suggests that a hypothesis describing why fit patients do well after surgery should not be based solely on $\dot{V}O_2$.

REFERENCES

1. Kehlet, H. and M. Mythen, *Why is the surgical high-risk patient still at risk?* Br J Anaesth, 2011. **106**(3): p. 289-91.
2. Khuri, S.F., et al., *Determinants of long-term survival after major surgery and the adverse effect of postoperative complications.* Ann Surg, 2005. **242**(3): p. 326-41; discussion 341-3.
3. Weiser, T.G., et al., *An estimation of the global volume of surgery: a modelling strategy based on available data.* Lancet, 2008. **372**(9633): p. 139-44.
4. Pearse, R.M., et al., *Identification and characterisation of the high-risk surgical population in the United Kingdom.* Crit Care, 2006. **10**(3): p. R81.
5. Grocott, M.P. and R.M. Pearse, *Prognostic studies of perioperative risk: robust methodology is needed.* Br J Anaesth, 2010. **105**(3): p. 243-5.
6. Cheema, F.N., et al., *Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults.* Ann Surg, 2011. **253**(5): p. 867-74.
7. Desborough, J.P., *The stress response to trauma and surgery.* British Journal of Anaesthesia, 2000. **85**(1): p. 109-117.
8. Rhodes, A., et al., *Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study.* Intensive Care Med, 2010. **36**(8): p. 1327-32.
9. Story, D.A., et al., *Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study.* Anaesthesia, 2010. **65**(10): p. 1022-30.
10. NCEPOD, *National Confidential Enquiry Into Patient Outcome and Death - Peri-operative Care: Knowing the Risk* <http://www.ncepod.org.uk/2011poc.html>. Assessed 17/03/2012. , 2011.
11. RCS/DOH, *The Royal College of Surgeons of England and Department of Health. The Higher Risk General Surgical Patient: Towards Improved Care for a Forgotten Group.* <http://www.RoyalCollegeofSurgeonseng.ac.uk/publications/docs/higher-risk-surgical-patient/>. Accessed 17/03/2012. , 2011.
12. Pearse, R.M., et al., *Mortality after surgery in Europe: a 7 day cohort study.* Lancet, 2012. **380**(9847): p. 1059-65.
13. Jhanji, S., et al., *Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust.* Anaesthesia, 2008. **63**(7): p. 695-700.
14. Shoemaker, W.C., *Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients.* CHEST Journal, 1988. **94**(6): p. 1176.
15. Shoemaker, W.C., et al., *Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients.* Chest, 1988. **94**(6): p. 1176-86.
16. Boyd, O., R.M. Grounds, and E.D. Bennett, *A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on*

- mortality in high-risk surgical patients. *JAMA*, 1993. **270**(22): p. 2699-707.
17. Sinclair, R.C.F., et al., *Does patient reported exercise capacity correlate with anaerobic threshold?* *Anaesthesia*, 2009. **64**: p. 462.
 18. Struthers, R., et al., *Assessing fitness for surgery: a comparison of questionnaire, incremental shuttle walk, and cardiopulmonary exercise testing in general surgical patients.* *Br J Anaesth*, 2008. **101**(6): p. 774-80.
 19. Wijesundera, D.N., et al., *Association of echocardiography before major elective non-cardiac surgery with postoperative survival and length of hospital stay: population based cohort study.* *BMJ*, 2011. **342**: p. d3695.
 20. Wolters, U., et al., *ASA classification and perioperative variables as predictors of postoperative outcome.* *Br J Anaesth*, 1996. **77**(2): p. 217-22.
 21. Wolters, U., et al., *Risk factors, complications, and outcome in surgery: a multivariate analysis.* *Eur J Surg*, 1997. **163**(8): p. 563-8.
 22. Boyd, O. and N. Jackson, *How is risk defined in high-risk surgical patient management?* *Crit Care*, 2005. **9**(4): p. 390-6.
 23. Lee, T.H., et al., *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.* *Circulation*, 1999. **100**(10): p. 1043-9.
 24. Boersma, E., et al., *Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee cardiac risk index.* *Am J Med*, 2005. **118**(10): p. 1134-41.
 25. Grocott, M.P., et al., *The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery.* *J Clin Epidemiol*, 2007. **60**(9): p. 919-28.
 26. Copeland, G.P., D. Jones, and M. Walters, *POSSUM: a scoring system for surgical audit.* *Br J Surg*, 1991. **78**(3): p. 355-60.
 27. Whiteley, M.S., et al., *An evaluation of the POSSUM surgical scoring system.* *Br J Surg*, 1996. **83**(6): p. 812-5.
 28. Tekkis, P.P., et al., *Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM).* *Br J Surg*, 2004. **91**(9): p. 1174-82.
 29. Edwards, M., J. Whittle, and G.L. Ackland, *Biomarkers to guide perioperative management.* *Postgrad Med J*, 2011. **87**(1030): p. 542-9.
 30. Ackland, G.L., et al., *Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial.* *Lancet Respir Med*, 2015. **3**(1): p. 33-41.
 31. Older, P., et al., *Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing.* *Chest*, 1993. **104**(3): p. 701-4.
 32. Zikria, B.A., et al., *Alterations in ventilatory function and breathing patterns following surgical trauma.* *Ann Surg*, 1974. **179**(1): p. 1-7.
 33. Older, P., A. Hall, and R. Hader, *Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly.* *Chest*, 1999. **116**(2): p. 355-62.

34. Wilson, J., et al., *Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery*. BMJ, 1999. **318**(7191): p. 1099-103.
35. Snowden, C.P., et al., *Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery*. Ann Surg, 2010. **251**(3): p. 535-41.
36. Wilson, R.J., et al., *Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery*. Br J Anaesth, 2010. **105**(3): p. 297-303.
37. Bland, R.D., et al., *Hemodynamic and oxygen transport patterns in surviving and nonsurviving postoperative patients*. Crit Care Med, 1985. **13**(2): p. 85-90.
38. Shoemaker, W.C., P.L. Appel, and H.B. Kram, *Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients*. CHEST Journal, 1992. **102**(1): p. 208.
39. Lugo, G., et al., *Relationship between oxygen consumption and oxygen delivery during anesthesia in high-risk surgical patients*. Crit Care Med, 1993. **21**(1): p. 64-9.
40. Huddart, S., et al., *Preoperative cardiopulmonary exercise testing in England - a national survey*. Perioper Med (Lond), 2013. **2**(1): p. 4.
41. Older, P. and A. Hall, *Clinical review: how to identify high-risk surgical patients*. Crit Care, 2004. **8**(5): p. 369-72.
42. Wilson, R.J., et al., *Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery*. British Journal of Anaesthesia, 2010. **105**(3): p. 297-303.
43. Silverman, M.N. and P.A. Deuster, *Biological mechanisms underlying the role of physical fitness in health and resilience*. Interface Focus, 2014. **4**(5): p. 20140040.
44. West, M.A., et al., *Validation of preoperative cardiopulmonary exercise testing-derived variables to predict in-hospital morbidity after major colorectal surgery*. Br J Surg, 2016. **103**(6): p. 744-752.
45. Snowden, C.P., et al., *Cardiorespiratory fitness predicts mortality and hospital length of stay after major elective surgery in older people*. Ann Surg, 2013. **257**(6): p. 999-1004.
46. Lai, C.W., et al., *Patients' inability to perform a preoperative cardiopulmonary exercise test or demonstrate an anaerobic threshold is associated with inferior outcomes after major colorectal surgery*. Br J Anaesth, 2013. **111**(4): p. 607-11.
47. Carlisle, J., et al., *Factors associated with survival after resection of colorectal adenocarcinoma in 314 patients*. Br J Anaesth, 2012. **108**(3): p. 430-5.
48. Swart, M. and J.B. Carlisle, *Case-controlled study of critical care or surgical ward care after elective open colorectal surgery*. British Journal of Surgery, 2012. **99**(2): p. 295-9.
49. Cuthbertson, D.P., *Observations on the disturbance of metabolism produced by injury to the limbs*. Q J Med, 1932. **1**: p. 233-46.
50. Moor, D., G. Aggarwal, and N. Quiney, *Systemic response to surgery*. Surgery, 2017. **35**(4): p. 220-223.
51. Dabrowska, A.M. and R. Slotwinski, *The immune response to surgery and infection*. Cent Eur J Immunol, 2014. **39**(4): p. 532-7.

52. Scott, M.J. and T.E. Miller, *Pathophysiology of major surgery and the role of enhanced recovery pathways and the anesthesiologist to improve outcomes*. *Anesthesiol Clin*, 2015. **33**(1): p. 79-91.
53. Kehlet, H., *Multimodal approach to control postoperative pathophysiology and rehabilitation*. *Br J Anaesth*, 1997. **78**(5): p. 606-17.
54. Varadhan, K.K., et al., *The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials*. *Clin Nutr*, 2010. **29**(4): p. 434-40.
55. Adamina, M., et al., *Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery*. *Surgery*, 2011. **149**(6): p. 830-40.
56. Nicholson, A., et al., *Systematic review and meta-analysis of enhanced recovery programmes in surgical patients*. *Br J Surg*, 2014. **101**(3): p. 172-88.
57. Slater, M., *Olympics cycling: Marginal gains underpin Team GB dominance*, in *BBC Sport*. 2012.
58. Ljungqvist, O., M. Scott, and K.C. Fearon, *Enhanced Recovery After Surgery: A Review*. *JAMA Surg*, 2017. **152**(3): p. 292-298.
59. Gustafsson, U.O., et al., *Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery*. *Arch Surg*, 2011. **146**(5): p. 571-7.
60. Gustafsson, U.O., et al., *Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study*. *World J Surg*, 2016. **40**(7): p. 1741-7.
61. Kehlet, H. and T. Mogensen, *Hospital stay of 2 days after open sigmoidectomy with a multimodal rehabilitation programme*. *Br J Surg*, 1999. **86**(2): p. 227-30.
62. Delaney, C.P., et al., *'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery*. *Br J Surg*, 2001. **88**(11): p. 1533-8.
63. Levy, B.F., et al., *23-hour-stay laparoscopic colectomy*. *Dis Colon Rectum*, 2009. **52**(7): p. 1239-43.
64. Bundgaard-Nielsen, M., N.H. Secher, and H. Kehlet, *'Liberal' vs. 'restrictive' perioperative fluid therapy--a critical assessment of the evidence*. *Acta Anaesthesiol Scand*, 2009. **53**(7): p. 843-51.
65. Rahbari, N.N., et al., *Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery*. *Br J Surg*, 2009. **96**(4): p. 331-41.
66. Corcoran, T., et al., *Perioperative fluid management strategies in major surgery: a stratified meta-analysis*. *Anesth Analg*, 2012. **114**(3): p. 640-51.
67. Myles, P., et al., *Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial*. *BMJ Open*, 2017. **7**(3): p. e015358.
68. Varadhan, K.K. and D.N. Lobo, *A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right*. *Proc Nutr Soc*, 2010. **69**(4): p. 488-98.

69. Boland, M.R., et al., *Perioperative fluid restriction in major abdominal surgery: systematic review and meta-analysis of randomized, clinical trials*. World J Surg, 2013. **37**(6): p. 1193-202.
70. Mythen, M.G. and A.R. Webb, *Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost*. Intensive Care Med, 1994. **20**(2): p. 99-104.
71. Giglio, M.T., et al., *Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials*. Br J Anaesth, 2009. **103**(5): p. 637-46.
72. Wolff, C.B., *Normal cardiac output, oxygen delivery and oxygen extraction*. Advances in Experimental Medicine & Biology, 2007. **599**: p. 169-82.
73. Sanders, G., et al., *Randomized clinical trial of intravenous fluid replacement during bowel preparation for surgery*. Br J Surg, 2001. **88**(10): p. 1363-5.
74. Holte, K. and H. Kehlet, *Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery*. J Am Coll Surg, 2006. **202**(6): p. 971-89.
75. Chappell, D., et al., *A rational approach to perioperative fluid management*. Anesthesiology, 2008. **109**(4): p. 723-40.
76. Bellamy, M.C., *Wet, dry or something else?* Br J Anaesth, 2006. **97**(6): p. 755-7.
77. Gan, T.J., et al., *Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery*. Anesthesiology, 2002. **97**(4): p. 820-6.
78. Abbas, S.M. and A.G. Hill, *Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery*. Anaesthesia, 2008. **63**(1): p. 44-51.
79. Wakeling, H.G., et al., *Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery*. Br J Anaesth, 2005. **95**(5): p. 634-42.
80. Noblett, S.E., et al., *Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection*. BRITISH JOURNAL OF SURGERY, 2006. **93**(9): p. 1069-1076.
81. Grocott, M.P., et al., *Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery*. Cochrane Database Syst Rev, 2012. **11**: p. CD004082.
82. Srinivasa, S., et al., *Oesophageal Doppler-guided fluid administration in colorectal surgery: critical appraisal of published clinical trials*. Acta Anaesthesiol Scand, 2011. **55**(1): p. 4-13.
83. NICE, *Medical technologies guidance MTG3: CardioQ-ODM oesophageal doppler monitor*. 2011.
84. Senagore, A.J., et al., *Fluid management for laparoscopic colectomy: a prospective, randomized assessment of goal-directed administration of balanced salt solution or hetastarch coupled with an enhanced recovery program*. Dis Colon Rectum, 2009. **52**(12): p. 1935-40.
85. Brandstrup, B., et al., *Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance?* Br J Anaesth, 2012. **109**(2): p. 191-9.

86. Pearse, R.M., et al., *Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review*. JAMA, 2014. **311**(21): p. 2181-90.
87. Challand, C., et al., *Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery*. British Journal of Anaesthesia, 2012. **108**(1): p. 53-62.
88. Lai, C.W., et al., *Randomized controlled trial of stroke volume optimization during elective major abdominal surgery in patients stratified by aerobic fitness*. Br J Anaesth, 2015. **115**(4): p. 578-89.
89. Srinivasa, S., et al., *Systematic review and meta-analysis of oesophageal Doppler-guided fluid management in colorectal surgery*. Br J Surg, 2013. **100**(13): p. 1701-8.
90. Gomez-Izquierdo, J.C., et al., *Meta-analysis of the effect of goal-directed therapy on bowel function after abdominal surgery*. Br J Surg, 2015. **102**(6): p. 577-89.
91. Rollins, K.E. and D.N. Lobo, *Intraoperative Goal-directed Fluid Therapy in Elective Major Abdominal Surgery: A Meta-analysis of Randomized Controlled Trials*. Ann Surg, 2016. **263**(3): p. 465-76.
92. Davies, S.J., D. Yates, and R.J. Wilson, *Dopexamine has no additional benefit in high-risk patients receiving goal-directed fluid therapy undergoing major abdominal surgery*. Anesth Analg, 2011. **112**(1): p. 130-8.
93. Royds, M.T., et al., *Proceedings of the Anaesthetic Research Society Meeting * Aberdeen Exhibition Centre, Aberdeen, 21-22 June 2012*. British Journal of Anaesthesia, 2012. **109**(4): p. 655P-668P.
94. Nicholson, M.J., et al., *The performance of a variable-flow indirect calorimeter*. Physiological Measurement, 1996. **17**(1): p. 43-55.
95. Kennedy, S., et al., *Comparison of the GEM and the ECAL indirect calorimeters against the Deltatrac for measures of RMR and diet-induced thermogenesis*. Journal of nutritional science, 2014. **3**.
96. Walsh, T.S., *Recent advances in gas exchange measurement in intensive care patients*. British Journal of Anaesthesia, 2003. **91**(1): p. 120-31.
97. Earlybird. *Earlybird diabetes study*. [cited 2018 15 August 2018]; Available from: <https://medicine.exeter.ac.uk/research/healthresearch/earlybird/>.
98. Goedje, O., et al., *Continuous cardiac output by femoral arterial thermodilution calibrated pulse contour analysis: comparison with pulmonary arterial thermodilution*. Crit Care Med, 1999. **27**(11): p. 2407-12.
99. Jonas, M., J. Fennell, and C.S. Brudney, *Haemodynamic optimisation of the surgical patient revisited*. Anaesthesia International, 2008. **2**(1): p. 1-5
100. Godje, O., et al., *Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability*. Crit Care Med, 2002. **30**(1): p. 52-8.

101. Costa, M.G., et al., *Continuous and intermittent cardiac output measurement in hyperdynamic conditions: pulmonary artery catheter vs. lithium dilution technique*. Intensive Care Medicine, 2008. **34**(2): p. 257-63.
102. Costa, M.G., et al., *Uncalibrated continuous cardiac output measurement in liver transplant patients: LiDCOrapid system versus pulmonary artery catheter*. Journal of Cardiothoracic & Vascular Anesthesia, 2014. **28**(3): p. 540-6.
103. Reinhart, K., et al., *Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand*. Chest, 1989. **95**(6): p. 1216-21.
104. Yamada, T., et al., *Multicenter study verifying a method of noninvasive continuous cardiac output measurement using pulse wave transit time: a comparison with intermittent bolus thermodilution cardiac output*. Anesth Analg, 2012. **115**(1): p. 82-7.
105. Masimo. *Masimo rainbow Pulse CO-Oximetry*. 2016 [28/04/2016]; Available from: <http://www.masimo.co.uk/Rainbow/about.htm>.
106. Shah, N., E.A. Osea, and G.J. Martinez, *Accuracy of noninvasive hemoglobin and invasive point-of-care hemoglobin testing compared with a laboratory analyzer*. International journal of laboratory hematology, 2014. **36**(1): p. 56.
107. Joseph, B., et al., *Transforming hemoglobin measurement in trauma patients: noninvasive spot check hemoglobin*. Journal of the American College of Surgeons, 2015. **220**(1): p. 93.
108. Checketts, M.R., et al., *Recommendations for standards of monitoring during anaesthesia and recovery 2015 : Association of Anaesthetists of Great Britain and Ireland*. Anaesthesia, 2016. **71**(1): p. 85-93.
109. Bland, J.M. and D.G. Altman, *Agreement between methods of measurement with multiple observations per individual*. J Biopharm Stat, 2007. **17**(4): p. 571-82.
110. Bland, J.M. and D.G. Altman, *Statistical methods for assessing agreement between two methods of clinical measurement*. Lancet, 1986. **1**(8476): p. 307-10.
111. Critchley, L.A. and J.A. Critchley, *A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques*. J Clin Monit Comput, 1999. **15**(2): p. 85-91.
112. Critchley, L.A., A. Lee, and A.M. Ho, *A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output*. Anesth Analg, 2010. **111**(5): p. 1180-92.
113. Critchley, L.A., X.X. Yang, and A. Lee, *Assessment of trending ability of cardiac output monitors by polar plot methodology*. J Cardiothorac Vasc Anesth, 2011. **25**(3): p. 536-46.
114. Peyton, P.J. and S.W. Chong, *Minimally invasive measurement of cardiac output during surgery and critical care: a meta-analysis of accuracy and precision*. Anesthesiology, 2010. **113**(5): p. 1220-35.
115. Bennett-Guerrero, E., et al., *The use of a postoperative morbidity survey to evaluate patients with prolonged hospitalization after routine, moderate-risk, elective surgery*. Anesth Analg, 1999. **89**(2): p. 514-9.

116. Campbell, M.J.P., *Statistics at square two : understanding modern statistical applications in medicine*. 2nd ed. ed. 2006, Oxford: Blackwell.
117. Campbell, I.T., et al., *A comparison of the effects of intermittent and continuous nasogastric feeding on the oxygen consumption and nitrogen balance of patients after major head and neck surgery*. American Journal of Clinical Nutrition, 1983. **38**(6): p. 870-8.
118. Diggle, P., *Analysis of longitudinal data*. 2nd ed. / Peter J. Diggle ...[et al.] ed. 2002, Oxford: Oxford University Press.
119. Finnerty, C.C., et al., *The surgically induced stress response*. JPEN J Parenter Enteral Nutr, 2013. **37**(5 Suppl): p. 21S-9S.
120. Rivers, E., et al., *Early goal-directed therapy in the treatment of severe sepsis and septic shock*. N Engl J Med, 2001. **345**(19): p. 1368-77.
121. Shoemaker, W.C., et al., *Physiologic patterns in surviving and nonsurviving shock patients. Use of sequential cardiorespiratory variables in defining criteria for therapeutic goals and early warning of death*. Arch Surg, 1973. **106**(5): p. 630-6.
122. Stock, M.C. and M.E. Ryan, *Oxygen consumption calculated from the Fick equation has limited utility*. Crit Care Med, 1996. **24**(1): p. 86-90.
123. Levinson, M.R., et al., *Indirect calorimetry in the mechanically ventilated patient*. Crit Care Med, 1987. **15**(2): p. 144-7.
124. Takala, J., et al., *Measurement of gas exchange in intensive care: laboratory and clinical validation of a new device*. Crit Care Med, 1989. **17**(10): p. 1041-7.
125. Koo, K.K., et al., *Pulmonary artery catheters: evolving rates and reasons for use*. Crit Care Med, 2011. **39**(7): p. 1613-8.
126. Balk, E., et al., in *Evaluation of the Evidence on Benefits and Harms of Pulmonary Artery Catheter Use in Critical Care Settings*. 2008: Rockville (MD).
127. Harvey, S., et al., *Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial*. Lancet, 2005. **366**(9484): p. 472-7.
128. Oudemans-van Straaten, H.M., et al., *Oxygen consumption after cardiopulmonary bypass--implications of different measuring methods*. Intensive Care Med, 1993. **19**(2): p. 105-10.
129. Walsh, T.S., P. Hopton, and A. Lee, *A comparison between the Fick method and indirect calorimetry for determining oxygen consumption in patients with fulminant hepatic failure*. Crit Care Med, 1998. **26**(7): p. 1200-7.
130. Thrush, D.N., *Spirometric versus Fick-derived oxygen consumption: which method is better?* Crit Care Med, 1996. **24**(1): p. 91-5.
131. Hofland, J., R. Tenbrinck, and W. Erdmann, *Comparison of closed-circuit and Fick-derived oxygen consumption during anaesthesia for liver transplantation in patients*. Adv Exp Med Biol, 2003. **540**: p. 305-11.
132. Smithies, M.N., et al., *Comparison of oxygen consumption measurements: indirect calorimetry versus the reversed Fick method*. Crit Care Med, 1991. **19**(11): p. 1401-6.

133. Jolliet, P., et al., *Relationship between pulmonary oxygen consumption, lung inflammation, and calculated venous admixture in patients with acute lung injury*. Intensive Care Med, 1996. **22**(4): p. 277-85.
134. Myburgh, J.A., R.K. Webb, and L.I. Worthley, *Ventilation/perfusion indices do not correlate with the difference between oxygen consumption measured by the Fick principle and metabolic monitoring systems in critically ill patients*. Crit Care Med, 1992. **20**(4): p. 479-82.
135. Cobean, R.A., et al., *Nutritional assessment using a pulmonary artery catheter*. J Trauma, 1992. **33**(3): p. 452-6.
136. Williams, R.R. and C.R. Fuenning, *Circulatory indirect calorimetry in the critically ill*. JPEN J Parenter Enteral Nutr, 1991. **15**(5): p. 509-12.
137. Pestana, D. and A. Garcia-de-Lorenzo, *Calculated versus measured oxygen consumption during aortic surgery: reliability of the Fick method*. Anesth Analg, 1994. **78**(2): p. 253-6.
138. Sinha, A.C., et al., *Comparison between continuous non-invasive estimated cardiac output by pulse wave transit time and thermodilution method*. Annals of Cardiac Anaesthesia, 2014. **17**(4): p. 273-7.
139. Ball, T.R., et al., *Accuracy of noninvasive estimated continuous cardiac output (esCCO) compared to thermodilution cardiac output: a pilot study in cardiac patients*. Journal of Cardiothoracic & Vascular Anesthesia, 2013. **27**(6): p. 1128-32.
140. Fischer, M.O., et al., *The diagnostic accuracy of estimated continuous cardiac output compared with transthoracic echocardiography*. Canadian Journal of Anaesthesia, 2014. **61**(1): p. 19-26.
141. Ishihara, H., et al., *The ability of a new continuous cardiac output monitor to measure trends in cardiac output following implementation of a patient information calibration and an automated exclusion algorithm*. J Clin Monit Comput, 2012. **26**(6): p. 465-71.
142. Colquhoun, D.A., et al., *Ability of the Masimo pulse CO-Oximeter to detect changes in hemoglobin*. Journal of Clinical Monitoring & Computing, 2012. **26**(2): p. 69-73.
143. Brandi, L.S., et al., *Effects of ventilator resetting on indirect calorimetry measurement in the critically ill surgical patient*. Critical Care Medicine, 1999. **27**(3): p. 531-9.
144. Walsh, T.S. and A. Lee, *Mathematical coupling in medical research: lessons from studies of oxygen kinetics*. Br J Anaesth, 1998. **81**(2): p. 118-20.
145. Alhashemi, J.A., M. Cecconi, and C.K. Hofer, *Cardiac output monitoring: an integrative perspective*. Critical care (London, England), 2011. **15**(2): p. 214.
146. Stratton, H.H., P.J. Feustel, and J.C. Newell, *Regression of calculated variables in the presence of shared measurement error*. J Appl Physiol (1985), 1987. **62**(5): p. 2083-93.
147. Archie, J.P., Jr., *Mathematic coupling of data: a common source of error*. Ann Surg, 1981. **193**(3): p. 296-303.
148. Cournard, A., et al., *Studies in the circulation in clinical shock*. Surgery, 1943. **13**.
149. Clowes, G.H.A. and L.R.M. Del Guercio, *Circulatory response to trauma of surgical operations*. Metabolism, 1960. **9**.

150. Shoemaker, W.C., P.L. Appel, and H.B. Kram, *Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery*. Crit Care Med, 1993. **21**(7): p. 977-90.
151. Yu, M., et al., *Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study*. Crit Care Med, 1993. **21**(6): p. 830-8.
152. Davies, S.J., et al., *Comparison of stroke volume and fluid responsiveness measurements in commonly used technologies for goal-directed therapy*. Journal of Clinical Anesthesia, 2013. **25**(6): p. 466-74.
153. Hayes, M.A., et al., *Elevation of systemic oxygen delivery in the treatment of critically ill patients*. N Engl J Med, 1994. **330**(24): p. 1717-22.
154. Gattinoni, L., et al., *A trial of goal-oriented hemodynamic therapy in critically ill patients*. SvO₂ Collaborative Group. N Engl J Med, 1995. **333**(16): p. 1025-32.
155. Eddleston, J., D. Goldhill, and J. Morris, *Levels of Critical care for adult patients*. 2009, The Intensive Care Society: London.
156. Whittle, J., et al., *Sympathetic autonomic dysfunction and impaired cardiovascular performance in higher risk surgical patients: implications for perioperative sympatholysis*. Open Heart, 2015. **2**(1): p. e000268.
157. Moonesinghe, S.R., et al., *Survival after postoperative morbidity: a longitudinal observational cohort study*. Br J Anaesth, 2014. **113**(6): p. 977-84.
158. Dindo, D., N. Demartines, and P.A. Clavien, *Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey*. Ann Surg, 2004. **240**(2): p. 205-13.
159. Black, C., M.P.W. Grocott, and M. Singer, *Metabolic monitoring in the intensive care unit: a comparison of the Medgraphics Ultima, Deltatrac II, and Douglas bag collection methods*. British Journal of Anaesthesia, 2014.
160. Leach, R.M. and D.F. Treacher, *The pulmonary physician and critical care*. 6. *Oxygen transport: the relation between oxygen delivery and consumption*. Thorax, 1992. **47**(11): p. 971-8.
161. Sandham, J.D., et al., *A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients*. N Engl J Med, 2003. **348**(1): p. 5-14.
162. Reade, M.C. and D.C. Angus, *PAC-Man: game over for the pulmonary artery catheter?* Crit Care, 2006. **10**(1): p. 303.
163. RELIEF, *REstrictive versus LIBeral Fluid Therapy in Major Abdominal Surgery*. <http://www.relief.org.au/>, 2015: p. Assessed on 25/01/15.
164. Hadian, M., et al., *Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters*. Crit Care, 2010. **14**(6): p. R212.

APPENDIX 1 Validation study patient information sheet

Patient Information Sheet

A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Your participation in this study is entirely voluntary.

Thank you for reading this.

What is the purpose of the study?

Major surgery can put a significant strain on the heart and lungs and may mean a long hospital stay. Some patients may have complications after major surgery. It is difficult to predict which patients this will happen to. In the past research confirmed that the body consumes more oxygen after surgery. Many patients went to an intensive care unit (ITU) and had invasive monitoring lines inserted into them to guide their treatment.

Since this research was carried out there have been many advances in how we care for our patients before, during and after surgery. Fewer patients now have the “lines” and go to ITU than before but results are better. Patients with problems with their hearts and lungs, who might have done badly in the past, now do well. It may be that in 2013 surgery puts less stress on the body and we don’t see the increased

need for oxygen seen before, but as we are putting fewer monitoring lines in patients we can't measure this easily.

Our hospital has previously researched measuring oxygen requirements in children. They were asked to breath normally while their heads were in a large "goldfish bowl", but we aren't sure how well this technique will work in patients after major abdominal surgery. Likewise we have new technology which will allow us to estimate how well the oxygen is being delivered to the body by attaching the patient to normal monitors rather than using lines that go into the body. They stay outside the body and do not involve needles: they are attached either by sticky pads or a probe that comfortably fits on a finger or a cuff around the upper arm. They are not uncomfortable and they do not expose you to any risk.

A key step before we can routinely employ these technologies is to see how well they agree with established methods. However, we can only do this in patients who are routinely looked after with the invasive monitoring lines in ITU after surgery.

Why have I been chosen?

You have agreed to have a planned operation following discussions with your surgeon. As a normal part of the anaesthetic during your type of operation all patients have monitoring lines inserted. For approximately 24 hours after your surgery, you will also normally be looked after in ITU.

For this study we need 20 patients in Derriford Hospital to take part and you are invited to be one.

Do I have to take part?

No. It is entirely your decision as to whether you take part or not. Even if you do, you are free to withdraw at any time and without giving a reason and the standard of your on-going care will not be any less as a consequence. If you decide not to take part your usual healthcare will not be affected in any way

If you do decide to take part you will be asked to sign a consent form. You will be given a signed copy of the consent form for your own records.

What will happen to me if I take part?

Taking part in the study will neither delay nor speed up your surgery. All care provided and procedures carried out before, during and after your operation will be the same whether or not you take part in this study with the exception of below:

1. On six occasions in the first 24 hours after your operation, your oxygen consumption will be measured using the GEM Hood (see picture). This is placed over your head and will be in place for around 10 minutes for each measurement. The hood is connected to a machine that measures how much oxygen you use whilst you are wearing it. You will have had a chance to see this at your pre-assessment and/or Cardiopulmonary Exercise Test (CPET) appointment.
2. Whilst you are wearing the hood you will have some additional continuous monitoring: Two simple probes attached to two of your fingers, a set of leads attached to your chest by sticky pads and a cuff attached around your upper arm.
3. Another monitor (LiDCO Rapid) is attached to the line that you will already have in place in your artery. Using this line the LiDCO Rapid can give a great deal of information about the ability of the heart to pump efficiently. Samples of blood will be taken from the lines **in your arteries and veins** at the beginning and end of the measurement period to measure the oxygen and haemoglobin levels in your blood.

What are the possible advantages and disadvantages of taking part?

The care you receive before, during and after your planned surgery will not be affected by taking part in this study. Patients having your type of surgery will always have a monitoring line placed in an artery in order to monitor blood pressure. This is

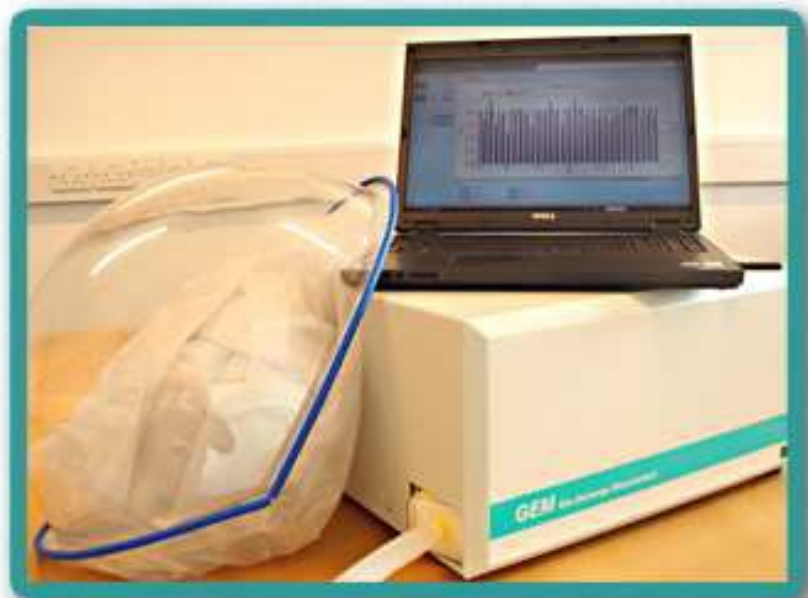
usually placed in the artery at the wrist, but occasionally other arteries are used. The lines are specifically designed for use at these sites and we use an ultrasound scanner to identify the vessel to be used and verify that it is suitable.

We fully expect some people might not like wearing the GEM hood after their operation. You will have had an opportunity to see it and try it on at your pre-assessment appointment and hopefully this will help you decide whether you wish to take part in this study. However, you are free to withdraw from the study at any time.

This study may help us to understand your condition better and help us to select the best treatment for people like you in the future.

Will my taking part in this study be kept confidential?

All the information collected about you during the course of the research will be kept for 5 years after the study finishes and is strictly confidential. Any published report of the research will not identify you.



The GEM Hood.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will promptly do their best to answer your questions. We do not want you to worry.

Should you have reason to complain about the way you have been treated at any stage during the study you can access the NHS patient advisory liaison service (PALS) who will be able to advise and help you:

Patient Advice & Liaison Service	Monday to Friday 9.00 am to
4.00 pm	
Patient Services Office	Telephone: 0845 155 8123 / 01752
439884 Level 7	E-mail:
plh-tr.PALS@nhs.net	
Derriford Hospital	
Plymouth	
PL6 8DH	

Harm – Legal Bits

In the unlikely event you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action against Plymouth Hospitals NHS Trust. The normal National Health Service complaints mechanisms are still available to you.

Who is organising and funding the research?

The study is being undertaken as part of an MD research degree by Mr A Kimble (Surgical Research Registrar) at Plymouth University. Plymouth Hospitals NHS Trust (PHNT) has helped organize the study. Mr A Kimble, Dr G Minto and Dr R Struthers (Consultant Anaesthetists) are the principal investigators, in conjunction with Professor R Sneyd (Consultant Anaesthetist), and Mr K Hosie (Consultant Surgeon). All are employees of the PHNT.

We have a grant from the National Institute of Academic Anaesthesia to fund the study.

What will happen to the results of this study?

The results will be collected and analysed by the researchers. The data and any conclusions made may be presented at national academic meetings or published in a medical journal. If you wish to receive a summary of the results when the study is completed, please inform a member of the research team. This can be done at the time of signing the consent form or at any time via the contact details given below.

Who has reviewed the study?

The Plymouth & Cornwall Research Ethics Committee has given approval for this study. This is an ethical review body who act independently of the NHS but whose approval process runs concurrently with that of the Trust Research & Development Department.

GP Notification

Unless you specifically tell us not to, your GP will be sent a letter informing them of your participation in this study.

What we need from you

We would like you to take time to read and understand this information and then decide whether or not you would like to take part in the study. If you agree, then we will need to ask you to sign a consent form to confirm this in writing. We will not need you to do anything more after this.

Thank you for taking the time to read this information sheet.

Should you have any queries about this study you may contact Mr Adam Kimble (Surgical Research Registrar) through the main hospital switchboard on 0845 1558155 (bleep 89958), through Mr Hosie's Secretary on 01752 763964 or via email a.kimble@nhs.net

Thank you very much for your co-operation with this study.

You will be given a copy of this sheet and a consent form to keep.

APPENDIX 2 Validation study consent form

CONSENT FORM

A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.

Cornwall & Plymouth REC Reference: 13/SW/0177

R&D Reference: 13/P/083, UKCRN ID: 15072

Mr A Kimble, Dr G Minto, Dr R Struthers, Prof R Sneyd, & Mr KB Hosie

Study ID Number

Hospital number

Please initial the box if you agree:

- | | | |
|-----------|---|---|
| 1. | I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information and received satisfactory answers to my questions. | <input style="width: 40px; height: 20px;" type="checkbox"/> |
| 2. | I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. | <input style="width: 40px; height: 20px;" type="checkbox"/> |
| 3. | I am willing to allow the researchers and individuals from regulatory authorities access to my medical records but understand that only information directly related to the study will be extracted and that strict confidentiality will be maintained. | <input style="width: 40px; height: 20px;" type="checkbox"/> |
| 4. | I agree to take part in the above study. | <input style="width: 40px; height: 20px;" type="checkbox"/> |
| 5. | I agree to allow my GP and Surgeon to be informed of my participation in this study | <input style="width: 40px; height: 20px;" type="checkbox"/> |

.....

Name of Patient/Witness

.....

Signature

.....

Date

.....

Name of person Authorized
to take consent

.....

Signature

.....

Date

A witness should sign above if the patient is unable to sign but has indicated their consent. 1 form to patient, 1 for the researcher and 1 to be kept in the hospital medical notes

APPENDIX 3 CO₂ST patient information sheet

Patient Information Sheet

**The Cost in Oxygen of Surgical Trauma (CO₂ST) -
A feasibility study of the non-invasive measurement of oxygen
delivery and consumption after elective major abdominal
surgery.**

You are being invited to take part in a research study. Before you decide whether or not you wish to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Please ask us if there is anything that is not clear or if you would like more information. Your participation in this study is entirely voluntary.

Thank you for reading this.

What is the purpose of the study?

Major surgery can put a significant strain on the heart and lungs and may mean a long hospital stay. Some patients may have complications after major surgery, but it is difficult to predict which patients this will happen to.

In the past research confirmed that the body uses more oxygen after surgery. Many patients went to an intensive care unit (ITU) and closely monitored as part of their treatment. However, since this research was carried out there have been many advances in how we care for our patients before, during and after surgery. Fewer patients go to ITU than before, and yet patients with problems with their hearts and lungs, who might have done badly in the past, now do well. It may be that in 2014, surgery puts less stress on the body and we don't see the increased need for oxygen

seen before, but because fewer people are admitted to ITU we can't measure this easily.

We have previously researched measuring oxygen requirements non-invasively in patients after surgery. They were asked to breath normally while their heads were in a large "goldfish bowl" (The GEM Hood – see picture), and had some sticky pads placed on their chest, a monitor that fitted comfortably on a finger and a blood pressure cuff around the upper arm. They are not uncomfortable and do not expose you to any risk.

From this research we know these technologies work and are well tolerated by patients after surgery. The purpose of the present study is to use these techniques to see if there is indeed an increase in the need for oxygen after major abdominal surgery in the 21st century.

Why have I been chosen?

Following discussions with your surgeon, you have agreed to have a planned operation involving your abdomen. For this study we need 40 patients in Derriford Hospital to take part and you are invited to be one.

Do I have to take part?

No. It is entirely your decision as to whether you take part or not. Even if you do, you are free to withdraw at any time and without giving a reason and the standard of your on-going care will not be any less as a consequence. If you decide not to take part your usual healthcare will not be affected in any way.

If you do decide to take part you will be asked to sign a consent form. You will be given a signed copy of the consent form for your own records.

What will happen to me if I take part?

Taking part in the study will neither delay nor speed up your surgery. All care provided and procedures carried out before, during and after your operation will be the same whether or not you take part in this study with the exception of below:

1. On the morning of your surgery before you go to the operating theatre, and on 8 occasions in the 48 hours after your operation, the amount of oxygen you are using will be measured with the GEM Hood (see picture). This is placed over your head and will be in place for around 10 minutes for each measurement. The hood is connected to a machine that measures how much oxygen you use whilst you are wearing it. You will have had a chance to see this at your pre-assessment and/or Cardiopulmonary Exercise Test (CPET) appointment.
2. Whilst you are wearing the hood you will have some additional monitoring: Two simple probes attached to two of your fingers, a set of leads attached to your chest by sticky pads and a cuff attached around your upper arm.
3. Your medical notes will be examined on the 5th day after your operation to ascertain if you have had any problems during your recovery from surgery.

What are the possible advantages and disadvantages of taking part?

The care you receive before, during and after your planned surgery will not be affected by taking part in this study.

We fully expect some people might not like wearing the GEM hood after their operation. You will have had an opportunity to see it and try it on at your pre-assessment appointment and hopefully this will help you decide whether you wish to take part in this study. However, you are free to withdraw from the study at any time.

This study may help us to understand your condition better and help us to select the best treatment for people like you in the future.

Will my taking part in this study be kept confidential?

All the information collected about you during the course of the research will be kept for 5 years after the study finishes and is strictly confidential. Any published report of the research will not identify you.



The GEM Hood.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will promptly do their best to answer your questions. We do not want you to worry.

Should you have reason to complain about the way you have been treated at any stage during the study you can access the NHS patient advisory liaison service (PALS) who will be able to advise and help you:

Patient Advice & Liaison Service

Monday to Friday 9.00 am to 4.00 pm

Patient Services Office
439884

Telephone: 0845 155 8123 / 01752

Level 7

E-mail: plh-tr.PALS@nhs.net

Plymouth

PL6 8DH

In the unlikely event you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action against Plymouth Hospitals NHS Trust. The normal National Health Service complaints mechanisms are still available to you.

Who is organising and funding the research?

The study is being undertaken as part of a Medical Doctorate (MD) research degree by Mr A Kimble (Surgical Research Registrar) at Plymouth University. Plymouth Hospitals NHS Trust (PHNT) has helped organize the study. Mr A Kimble, Dr G Minto and Dr R Struthers (Consultant Anaesthetists) are the principal investigators, in conjunction with Professor R Sneyd (Consultant Anaesthetist), and Mr K Hosie (Consultant Surgeon). All are employees of the PHNT.

We have grants from the charity Bowel Cancer West and the Plymouth Hospitals Charitable Fund to help fund the study.

What will happen to the results of this study?

The results will be collected and analysed by the researchers. The data and any conclusions made may be presented at national academic meetings or published in a medical journal. If you wish to receive a summary of the results when the study is completed, please inform a member of the research team. This can be done at the time of signing the consent form or at any time via the contact details given below.

Who has reviewed the study?

The Plymouth & Cornwall Research Ethics Committee has given approval for this study. This is an ethical review body who act independently of the NHS but whose approval process runs concurrently with that of the Trust Research & Development Department.

GP Notification

Unless you specifically tell us not to, your GP will be sent a letter informing them of your participation in this study.

What we need from you

We would like you to take time to read and understand this information and then decide whether or not you would like to take part in the study. If you agree, then we will need to ask you to sign a consent form to confirm this in writing. We will not need you to do anything more after this.

Thank you for taking the time to read this information sheet.

Should you have any queries about this study you may contact Mr Adam Kimble (Surgical Research Registrar) through the main hospital switchboard on 0845 1558155 (bleep 89958), through Mr Hosie's Secretary on 01752 763964 or via email a.kimble@nhs.net

Thank you very much for your co-operation with this study.

APPENDIX 4 CO₂ST consent form

CONSENT FORM

The Cost in Oxygen of Surgical Trauma (CO₂ST) -

A feasibility study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.

Cornwall & Plymouth REC Reference: 14/SW/1109

R&D Reference: 14/P/123

ClinicalTrials.gov Identifier: NCT02238561

Investigators: Mr A Kimble, Dr G Minto, Dr R Struthers, Prof R Sneyd, & Mr
KB Hosie

Study ID Number

Hospital number

Please initial the boxes below if you agree:

1. I confirm that I have read and understand the information sheet (version 1.1, 3rd Nov 2014) for the above study. I have had the opportunity to consider the information and received satisfactory answers to my questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I am willing to allow the researchers and individuals from the study sponsors and regulatory authorities access to my medical records but understand that only information directly related to the study will be extracted and that strict confidentiality will be maintained.

4. I agree to take part in the above study.

5. I agree to allow my GP and Surgeon to be informed of my participation in this study.

.....
Name of Patient/Witness Signature Date

.....
Name of person Authorized Signature Date
to take consent

A witness should sign above if the patient is unable to sign but has indicated their consent. 1 form to patient, 1 for the researcher and 1 to be kept in the hospital medical notes

APPENDIX 5 Adverse event report Validation Study

During the early stages of **A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.** NRES Committee South West - Cornwall & Plymouth: 13/SW/0177, NIHR CRN 15072, there were two adverse events. The first event led to a change in the protocol to measuring the diameter of the brachial artery prior to insertion of the PiCCO arterial line. Following a second adverse event, that was felt to be related to the PiCCO arterial line, the study protocol was changed to use the LiDCOrapid as the source of CO measurement. The following documents relate to the reporting and outcomes of these adverse events with the MHRA, Pulsion (Munich, Germany, the manufacturer of PiCCO), and the local ethics committee.

Documents included are:

1. Report of Serious adverse event (DF19)
2. Detailed report of Serious adverse event (DF19)
3. Report of serious adverse event (DF28)
4. Detailed report of serious adverse event (DF29)
5. MHRA incident report
6. Summary of Pulsion incident report

REPORT OF SERIOUS ADVERSE EVENT (SAE)

1. Details of Chief Investigator

Name:	Adam Kimble
Address:	Colorectal Unit, Level 7, Derriford Hospital Plymouth Devon PL6 8DH
Telephone:	01752 439004
Email:	a.kimble@nhs.net
Fax:	

2. Details of study

Full title of study:	A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.
Name of main REC:	Cornwall & Plymouth REC
Main REC reference number:	13/SW/0177
Research sponsor:	Plymouth Hospitals NHS Trust Research and Development Department
Sponsor's reference for this report: (if applicable)	

3. Type of event

Please categorise this event, ticking all appropriate options:

Death <input type="checkbox"/>	Life threatening <input type="checkbox"/>	Hospitalisation or prolongation of existing hospitalization <input type="checkbox"/>
Persistent or significant disability or incapacity <input type="checkbox"/>	Congenital anomaly or birth defect <input type="checkbox"/>	Other <input checked="" type="checkbox"/>

4. Circumstances of event

Date of SAE:	27/11/2013
Location:	Penrose Ward, Derriford Hospital
Describe the circumstances of the event: <i>(Attach copy of detailed report if necessary)</i>	At 21:30 patient DF19 (SC) suddenly displayed signs of a right brachial artery occlusion which was deemed related to the arterial line that was placed in the brachial artery. The patient was reviewed by the vascular consultant on call and a brachial embolectomy performed under local anaesthetic with resultant restoration of blood flow to the right hand. (see attached full report)
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	The PiCCO monitor as used in the protocol for minimally invasive cardiac output monitoring requires either a brachial or femoral arterial line as per the manufacturers guidelines. In this case , the patient's brachial artery was narrower than usual due to an anatomical anomaly. We will add to the protocol that the investigator will ultrasound scan the brachial arteries prior to line insertion to ensure they are of adequate size for line insertion.

5. Declaration

Signature of Chief Investigator:	Adam Kimble
Print name:	Adam Kimble
Date of submission:	28/11/2013

REPORT OF SERIOUS ADVERSE EVENT: DF19

A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.

PHNT R&D ref: 13/P/083

Cornwall & Plymouth REC Ref: 13/SW/0177

The following events took place on 27 November 2013 and relate to patient [REDACTED] hereafter identified as study number DF19.

DF19 underwent an open resection of a colorectal liver metastasis on 27/11/2013 after being consented into the study per-operatively. As part of the study protocol DF19 had a PiCCO arterial line inserted into her right brachial artery by the anaesthetist Dr G Minto (Co-investigator). Manufacturers instructions require that the brachial artery be used, and the device is specifically designed for this purpose. Placement was difficult, requiring more than one pass of the equipment, however once placed the arterial line was used without any problems throughout the operation. Post-operatively DF19 was woken up and extubated and moved to Penrose high dependency unit as per local policy. All research equipment was set up as per protocol by the CI Adam Kimble.

Prior to starting any measurements the nurse looking after DF19 took a sample of blood from the arterial line for analysis utilising standard precautions. Following this at approximately 19:00 hrs it was noted that the arterial trace suggested that the arterial line had become blocked, which is not uncommon. Various manoeuvres were tried to unblock the line including flushing with saline, aspirating the line and withdrawing the line by 0.5cm under aseptic conditions (carried out by the ITU/HDU doctor). Withdrawing the line was successful in establishing a normal arterial line trace on the monitor and enabling free flushing and aspiration of the line.

Protocol then proceeded as usual. However (as recorded on the CRF) a thermodilution procedure was attempted (to calibrate the PiCCO monitor as per manufacturers guidelines and protocol). 15mls of cold normal saline is injected into a central venous line and the temperature change is sensed at the arterial line tip. On this occasion no temperature change was sensed and it was thought that this was due to a problem with the injection site sensor (situated on the central line in the neck). 2 further unsuccessful attempts were made at thermodilution – Dr Minto was called to assist with calibration of the equipment & arrived at approx 21:15.

After reviewing all equipment Dr Minto agreed that the problem was probably due to the injection sensor which was exchanged for a new one. At 21:30 DF19 complained of sudden tingling of her right hand. Assessment showed a cooler hand (compare to the left), with no brachial, radial or ulnar pulses palpable. An occlusion of the right brachial artery was suspected and the arterial line removed. Further assessment with a handheld Doppler (a device that detects blood flow with sound waves) confirmed low blood flow in the right forearm and the on call vascular consultant, Mr Ioannis Vlachakis, was contacted at 2155.

Mr Vlachakis attended DF19 and agreed that there were signs of an acute brachial artery occlusion and suggested a brachial embolectomy be performed under local anaesthetic. DF19 consented to this. At surgery a brachial artery thrombus (blood clot) was identified and removed with resultant restoration of blood flow to the right hand. The vascular surgeon commented that the patient had an anatomical variant: a high bifurcation of the brachial artery, such that the calibre of the vessel at the elbow (site of placement) was narrower than is usual. This is a reasonably common anatomical variant. Dr Minto has inserted more than 2000 arterial lines in clinical practice (although most are done in the radial artery according to manufacturer guidelines of different systems) and not seen this complication before.

Post-operative assessment of the right hand did not demonstrate any obvious problems with any of the blood vessels, nerves or muscles and DF19's symptoms had all resolved. The clinical condition of the circulation has returned to normal with no sequelae.

The PiCCO arterial line was placed according to manufacturers guidelines, but due to a relatively common anatomical variant, caused temporary injury requiring a procedure. This anatomical variant can be excluded by targeted ultrasound examination prior to insertion (to confirm that the artery is large enough to safely admit the arterial catheter, and an alternative insertion site (femoral) is available). The investigating team will amend the protocol such that confirmation on ultrasound of an adequate calibre brachial artery is required prior to use of the brachial artery.

REPORT OF SERIOUS ADVERSE EVENT (SAE)

1. Details of Chief Investigator

Name:	Adam Kimble
Address:	Colorectal Unit, Level 7, Derriford Hospital Plymouth Devon PL6 8DH
Telephone:	01752 439004
Email:	a.kimble@nhs.net
Fax:	

2. Details of study

Full title of study:	A validation study of the non-invasive measurement of oxygen delivery and consumption after elective major abdominal surgery.
Name of main REC:	Cornwall & Plymouth REC
Main REC reference number:	13/SW/0177
Research sponsor:	Plymouth Hospitals NHS Trust Research and Development Department
Sponsor's reference for this report: (if applicable)	

3. Type of event

Please categorise this event, ticking all appropriate options:

Death <input type="checkbox"/>	Life threatening <input type="checkbox"/>	Hospitalisation or prolongation of existing hospitalization <input type="checkbox"/>
Persistent or significant disability or incapacity <input type="checkbox"/>	Congenital anomaly or birth defect <input type="checkbox"/>	Other <input checked="" type="checkbox"/>

4. Circumstances of event

Date of SAE:	06/01/2014
Location:	Penrose Ward, Derriford Hospital
Describe the circumstances of the event: <i>(Attach copy of detailed report if necessary)</i>	At 17:30 patient DF28 (GM) complained of an ache in his left arm. The left arm was cooler than the right but all pulses were present. Given a previous SAE relating to brachial artery catheters requiring an embolectomy, to prevent a further SAE the brachial artery catheter was removed. (Please see detailed report attached)
What is your assessment of the implications, if any, for the safety of study participants and how will these be addressed?	<p>The PiCCO monitor as used in the protocol for minimally invasive cardiac output monitoring requires either a brachial or femoral arterial line as per the manufacturer's guidelines. In addition, pre-insertion scanning to ensure the artery is of adequate size (>3mm – in this case 3.7mm) is undertaken. We have now had two adverse events related to use of the system according to manufacturer's guidelines.</p> <p>We propose action as follows:</p> <ol style="list-style-type: none"> 1. notification of MHRA (or equivalent national safety body) about the cluster 2. notify the manufacturer again 3. for this study we have been using PICCO to measure cardiac output as it is a well validated system for doing so – however at PHNT cardiac output is much more commonly measured, using an alternative system, the LiDCO Rapid. This is effectively a software application which re-analyses standard monitoring signals. It is within acceptable limits of comparison with gold standard measurement of cardiac output, though not as well validated as the PiCCO.

5. Declaration

Signature of Chief Investigator:	Adam Kimble
Print name:	Adam Kimble
Date of submission:	07/01/2014



Adverse Incident Report

About you

Your name	Gary Minto
Position/Occupation	Consultant Anaesthetist
Organisation	Plymouth Hospitals NHS Trust
Your address	Derriford Hospital Plymouth PL68DH
Your telephone number	017524392065
Your email address	gary.minto@nhs.net
Email Copy To	collinson@nhs.net a.kimble@nhs.net
Local reference number	DF19 and DF28
Consultant in charge	Bowles
Type of device	General Report Form / All other devices
Incident Number	2014/001/007/401/006

Device & Incident details

Type of injury	Minor
Type of device	PICCO brachial artery catheter
Model	PVPK2014L16-NF
Manufacturer name	Pulsion Medical UK Limited
Manufacturer phone number	0845 4811647
Catalogue number	
Serial number	
Lot or batch number	447013
Date of manufacture	
Expiry date	30 Jul 2014
Quantity defective	
Current location of device	
Has the manufacturer / supplier been contacted?	Yes
Is the device CE Marked?	Yes
Date of incident	27 Nov 2013

Details of incident / nature of device defect

2 incidents (referred to as 1 and 2 below)

1. a brachial artery thrombus in relation to use of brachial artery catheter (licenced indication)
2. decreased blood flow in relation to use of a brachial artery catheter in a different patient on 6.1.14

Details of injury (to patient, carer or healthcare professional):

1. decreased perfusion to right hand with complaint of numbness in hand
2. complaint of discomfort in upper arm (adjacent to catheter insertion site) - cooler hand (left) on that side

Action taken (includes any action by patient, carer or healthcare professional, or by the manufacturer or supplier)

1. embolectomy under local anaesthetic , restoration of perfusion with no longterm consequences
2. removal of catheter - circulation restored

Attachments

PULSION Medical Systems SE • Hans-Riedl-Str. 21 • D-85622 Feldkirchen, Germany

MHRA Adverse Incident Center
151 Buckingham Palace Road
Victoria
London, SW1W 9SZ
United Kingdom

Direct number: +49 89-459914-201 Fax: +49 89-459914-208 E-Mail: kammerzell@pulsion.com Date: 31 January 2014

MHRA incident report Ref. 2014/001/007/401/006

Dear Sir or Madam,

Please find our response to your letter from January 10th 2014 regarding the incident report.

Part 1

A. Device details representing the last 3 years:

Is the device CE marked under any of the Medical Device Directives	Yes	Identify of the Notified Body	CE 0124 – Dekra
Date first sold in UK	30.06.2009		
No. of devices in UK	8669	No. of similar incidents in UK	0
No. of devices in EU	49101	No. of similar incidents in EU	1, reported to BfArM in October 2013
No. of devices worldwide	57678	No. of similar incidents worldwide	0
Date of manufacture	05.02.2013	Date the problem or adverse incident occurred or was detected	07.01.2014

The available clinical investigations show that catheterisation of the brachial artery is associated with a risk of 1/3000 or even higher [reference 1, 2]. Our data from reported complains is far below this ratio.

PULSION Medical Systems SE • Postal address: Hans-Riedl-Str. 21 • D-85622 Feldkirchen, Germany
Shipping address: Hans-Riedl-Str. 17 • D-85622 Feldkirchen, Germany • Phone. +49-(0)89-45 99 14-0 • Fax. +49-(0)89-45 99 14-18
Board of Directors: Dr. Burkhard Wittek (Chairman) • CEO: Patricio Lacalle
Amtsgericht München • HRB 192563 • USt-IdNr. (German Tax Number) DE204234444
UniCredit Bank AG, Bank Code 700 202 70, Account Nr. 1 5187 967, BIC (SWIFT): HYVEDEMMXXX, IBAN: DE78 7002 0270 00151 87967
Münchener Bank eG, Bank Code 701 900 00, Account Nr. 400 41 67, BIC (SWIFT): GENODEF1M01, IBAN: DE08 7019 0000 0004 0041 67
info@pulsion.com • www.PULSION.com

B. Investigation of the cause of the incident:

- Manufacturing records didn't reveal any abnormalities. The documents are available upon request
- The involved product wasn't returned. Inspection of the product from the same batch did not reveal any abnormalities. Please see the attached report of Technical Root Cause Investigation
- Concerning the factors contributing to the cause of the incident we conclude that:
 - i. Poor design could be excluded as published studies report a much higher rate of similar complications with other products
 - ii. Non-conformity is highly improbable. No records of non-conformity of the involved batch were found. Inspection of the product from the same batch did not reveal any abnormalities. Please see the attached report of Technical Root Cause Investigation
 - iii. Inappropriate use. According to the reporter the device was used in accordance with the intended use of the device
 - iv. The instructions for use (IFU) have several indications about the risk of thrombosis and embolism. The IFU indicates precisely how control of the perfusion should be performed when catheter is placed (IFU is attached).
- Several causes can be considered as the root cause of the event:
 - i. Abnormality of patient's vessels. As stated in the complaint report the physician *"concluded that the thrombus was formed due to a vascular abnormality in the patient (having narrower arteries than normal) that compounded the clot formation with the PiCCO catheter in the brachial artery"*
 - ii. The critical condition of the patient in the ICU could cause a change in the coagulation status and generate an increased tendency to develop thrombus in the vessels
 - iii. Low frequency in the control of the distal perfusion of the arm could be the cause for the first incident. As described in the IFU *"adequacy of perfusion can be monitored using clinical inspection, surface temperature measurement, or by applying a pulse oximetry sensor to a digit downstream of the puncture site, in order to continuously ensure pulsatile flow"*.

In the case of the second incident adequate perfusion control was effective in preventing a thrombosis. The catheter was removed and the circulation was restored without any further measures.
 - iv. Issues related to the technical skills of the physician who has placed the catheter including precision of the puncture site, force of the use of the introducer, use of the

PULSION Medical Systems SE • Postal address: Hans-Riedl-Str. 21 • D-85622 Feldkirchen, Germany
Shipping address: Hans-Riedl-Str. 17 • D-85622 Feldkirchen, Germany • Phone: +49-(0)89-45 99 14-0 • Fax: +49-(0)89-45 99 14-18
Board of Directors: Dr. Burkhard Wittek (Chairman) • CEO: Patricio Lacalle
Amtsgericht München • HRB 192563 • USt-IdNr. (German Tax Number) DE204234444
UniCredit Bank AG, Bank Code 700 202 70, Account Nr. 1 5187 967, BIC (SWIFT): HYVEDE33XXX, IBAN: DE78 7002 0270 00151 87967
Münchener Bank eG, Bank Code 701 900 00, Account Nr. 400 41 67, BIC (SWIFT): GENODEF1M01, IBAN: DE08 7019 0000 0004 0041 67
info@pulsion.com • www.PULSION.com

dilatator etc. However, according to the complaint reports on file no information related to poor technical skills of the doctor is available.

- v. Administration of vasopressors and inotropic agents is reported as a possible cause of thrombosis [see reference 1]. However, the use of these agents is common in the Operating Room (OR) and ICU.

C. Risk assessment:

- The final outcome of the patients was reported as follows:
Patient 1: embolectomy under local anaesthetic, restoration of perfusion with no long-term consequences
Patient 2: removal of catheter - circulation restored, no long-term consequences.
- As described in the Clinical Evaluation and reported in clinical studies there is always a patient risk associated with the puncture of the artery in general. The specific risk for the brachial artery is reported to be 1/3000 punctures and higher [see reference 2]. However, our records show that the risk associated with the PULSION product is much lower than reported (see also the table in part 1).
- The PULSION PiCCO catheter is intended for use in critically ill patients in ICU and OR. These patients suffer from severe illness and require advanced haemodynamic monitoring which is associated with certain known risks. The complication risk including infection, organ failure and death of critically ill patients is reported to be between 30 – 50 % depending on patient's history and condition. The use of advanced monitoring including the PiCCO technology provides very valuable information and has been shown to be beneficial for preventing complications. As stated in the clinical evaluation document "*risk-benefit profile justifies its use*" of the catheter for thermodilution measurement.

Part 2

According to our record a similar event accrued in one hospital in Stuttgart. We reported it as required to the authority in Germany (BfArM case number 6507/13). The results of the investigation did not reveal any abnormality / non-conformity of the product. No further cases were reported in the previous 3 years.

Part 3

No corrective / preventative actions including field safety correction actions were initiated due to these events.

Sincerely



Sergej Kammerzell
Safety Officer

Attachments:

1. Technical report_Root Cause Investigation 14-0011
2. In-vitro compatibility tests 1-4
3. Technical drawing
4. IFU
5. References:

[1] Cousins at al. AANA Journal 72:267-271

[2] Barazal et al. Anaesthesiology 73:38-45, 1990

APPENDIX 6 GEM manufacturer's annual service and calibration, and monthly alcohol burn data

GEM Nutrition Limited

t. 01925 607000
f. 01925 607398
m. 07801 586208
gem.nutrition@btinternet.com
Adam Kimble
Colorectal Research Fellow
Derriford Hospital

Daresbury Innovation Centre
Keckwick Lane
Daresbury
Cheshire
WA4 4FS

Service Report 2013

Plymouth GEM

Visit on: 28 August

Reason for Visit: Check overall GEM system is functioning after
storage/move Annual Service and Calibration
Operator training

Observations:

1. Initial Inspection all OK

Comments – Original Laptop not available so loaded software on XP
Laptop
All works, except calibration progress windows not visible

Corrective Action:

1. N/A

In addition: Replaced fan filter
Replaced Nafion

Calibration

Alcohol Burn:

Expected	Actual	Error %
0.667	0.681	+2.1
0.667	0.701	+5.1
0.667	0.664	-0.45

Flow Calibration:

Expected	Actual	Error %
0.0	0.0	0
14.2	13.94	-1.8
20.0	19.3	-3.5
39.6	38.4	-3.0
59.6	57.6	-3.4
Max	74.0	-3.1

Service and Calibration carried out by:

Austen Bradley

28 August 2013

Monthly alcohol burns:

Date	Actual	Error %
21/10/13	0.661	-0.9
	0.659	-1.2
	0.687	+3.0
06/01/14	0.669	+0.3
	0.692	+3.7
	0.652	-2.2
06/02/14	0.651	-2.4
	0.678	+1.6
	0.665	-0.3
06/03/14	0.677	+1.5
	0.649	-2.7
	0.667	+0.0
09/04/14	0.662	-0.7
	0.673	+0.9
	0.673	+0.9
12/05/14	0.679	+1.8
	0.689	+3.3
	0.653	-2.1
10/06/14	0.651	-2.4
	0.684	+2.5
	0.696	+4.3
28/11/14	0.670	+0.4
	0.650	-2.5
	0.695	+4.2
13/01/15	0.674	+1.0
	0.642	-3.7
	0.688	+3.1
10/02/15	0.664	-0.4
	0.684	+2.5
	0.674	+1.0