Development of a standardised forearm exercise model to predict surgical outcome

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DECLARATION

I Mark Andrew Hamilton confirm the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated below and in the thesis.

Chapter 1 (nil)

Chapter 2 and Chapter 3

Assistance with blood gas analysis by Mr Jim Pate

Chapter 4 (nil)

Chapter 5

Assistance with cardiopulmonary exercise testing and analysis by Mr Jim Pate and Miss Helen Luery

Chapter 6

Surgical outcome data collection by Miss Claire Matejowsky

Chapter 7 (nil)

List of Abbreviations

SO_2	Saturation of oxygen
PO_2	Partial pressure of oxygen
PCO_2	Partial pressure of carbon dioxide
ACS	American College of Surgeons
APACHE	Acute Physiology and Chronic Health Evaluation
ASA	American Society of Anesthesiologists
ASA-PS	American Society of Anesthesiologists (ASA) Physical Status Classification
AT	Anaerobic Threshold
ATP	Adenosine Triphosphate
BUPA	British United Provident Association
CI	Cardiac Index
CONSORT	Consolidated Standards of Reporting Trials
CO	Cardiac Output
CPET	Cardiopulmonary Exercise Testing
CYC	Cyclical
DO_2i	Oxygen Delivery Index
DSE	Dobutamine Stress echocardiography
FEV_1	Forced Expiratory Volume in 1 second
GDP	Gross Domestic Product

GI	Gastrointestinal
HDU	High Dependency Unit
HLOS	Hospital Length of Stay
ICU	Intensive Care Unit
ISO	Isometric
MVC	Maximal Voluntary Contraction
NADH	Nicotinamide Adenine Dinucleotide
NCEPOD	National Confidential Enquiry into Perioperative Death
NIRS	Near infrared spectroscopy
NSQIP	National Surgical Quality Improvement Program
OE ratio	Observed to expected ratio
POMS	Postoperative Morbidity Survey
POSSUM	Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity
P-POSSUM	Portsmouth version of the POSSUM
RCRI	Revised Cardiac Risk Index or Lee Cardiac Risk Index
SRS	Surgical Risk Score
VA	US Department of Veterans Affairs
V_E	Ventilatory Equivalents
VO_2	Oxygen consumption
VO_2 peak	Maximal Oxygen Consumption
WHO	World Health Organisation

Abstract

The prediction and measurement of surgical outcome is difficult. Current methods of perioperative risk prediction do not perform particularly well on an individual basis with guidelines suggesting a stepwise approach to perioperative risk assessment. Part of this stepwise approach is an assessment of functional capacity. Cardiopulmonary exercise testing has a body of evidence to support its use as a measurement of functional capacity and predictor of perioperative risk. In addition grip strength as assessed by handgrip dynamometry has been shown to be predictive of surgical outcome.

This thesis examines the development and testing of a standardised forearm handgrip exercise model to predict mortality and morbidity in orthopaedic surgical patients.

This thesis investigates the development of two standardised forearm handgrip exercise models, one using an intermittent (cyclical) exercise protocol and the other using a static (isometric) protocol. Having established reliable methods of using each as a preoperative test, the metabolic output i.e. the measurable venous products of metabolism; lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation were compared. The comparison showed that the isometric exercise model was the stronger stimulus for anaerobic respiration. Each exercise model was also compared to an anaerobic threshold as measured by cardiopulmonary exercise testing in the same individuals. The isometric model showed a consistent and statistically significant relationship with the anaerobic threshold as measured by cardiopulmonary exercise testing but not the cyclical model.

Finally the isometric forearm exercise model was prospectively tested in a pilot study of 21 orthopaedic patients undergoing joint replacement surgery for its ability to predict surgical outcome.

The maximal voluntary contraction from handgrip dynamometry was predictive of complications and length of stay and although not statistically significant there was a clear trend for those with fewer complications and shorter lengths of hospital stay to produce more lactate during isometric forearm exercise testing.

SUMMARY OF THE AIMS AND OBJECTIVES OF THE THESIS

All the work contained within this thesis was conducted at the Middlesex Hospital, London UK between December 2004 and December 2005.

Main aims & Objectives

1) To review the literature on the prediction of surgical outcome.
2) To highlight from the literature review the role of exercise and functional testing in predicting surgical outcome.
3) To develop a bedside exercise test that could be used to predict surgical outcome.
4) To construct and prove the validity and practicality of a forearm exercise model in healthy volunteers.
5) To compare the relationship between this forearm exercise test and established models of assessing whole body functional capacity currently used to predict surgical outcome such as cardiopulmonary exercise testing.
6) To identify a suitable test endpoints from the forearm exercise test that could be used to predict surgical outcome.
7) To undertake a prospective study on the ability of the chosen forearm exercise model to predict surgical outcome in an elective orthopaedic population requiring primary joint replacements.

ETHICS

The program of study was originally submitted to The Joint UCL/UCLH Committees on the Ethics of Human Research (Committee A) on the 6th October 2004.

REC reference number: 04/Q0505/96

Further information was supplied as requested to the committee on the 8th December 2004.

Full permission for the study was granted by Dr Raymond MacAllister as Chair of the committee on the 21st December 2004.

An application to the same committee was considered and approved on the 1st April 2005, for a minor amendment to the program related to studying orthopaedic patients.

All power calculations are shown in the methods sections of the relevant chapters.

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Table of Contents

Table of Tables

Table of Figures

Chapter 1: The prediction of surgical outcome and a focused review of the literature for handgrip dynamometry and cardiopulmonary exercise testing

1.0 Introduction

This chapter will briefly discuss the principles of measuring and defining surgical outcome and the importance of risk adjusting data.

I will then discuss current methodology used to predict surgical outcome.

I will finish the chapter by focusing on functional exercise testing with a specific focus on cardiopulmonary exercise testing and handgrip dynamometry.

Currently there is no perfect method of predicting surgical outcome. Methods of prediction to date have often been based on large retrospective populations of patients and do not allow for the prediction of an individual's risk but that of the population in which they sit.

The terms surgical outcome and perioperative outcome are often used interchangeably but do not necessarily mean the same thing. Many surgical procedures for example a hip replacement have a technical outcome of success in terms of restoration of functional capacity or correct alignment of hip prosthesis and femoral shaft. The patient may however have suffered a number of postoperative events or complications such as a wound infection that delayed or made their recovery process prolonged or traumatic and are termed morbid

events. This thesis will aim to look at the possibility of predicting surgical outcome with regards to morbidity and mortality and not the technical success of surgery itself.

Surgical outcome in this thesis will therefore refer specifically to morbidity (complications) and mortality (death) associated with a surgical event unless otherwise stated.

1.1 MEASURING AND DEFINING SURGICAL OUTCOME

As mentioned above surgical outcome means different things to different people. For the patient it often means curing of a disease, returning to physical activity or a job. For the surgeon it may be the technical success of an operation, the operative time taken or the rate of post-operative infection. For the manager it may be the number of drugs needed or bed days occupied, the quantity of equipment used during the operation or the cost the specified treatment. What they all have in common however is the desire to objectively describe the measure they are interested in and in many cases be able to predict and modify that measurement.

The healthcare burden of surgery is enormous, with recent estimates of major surgical operations undertaken worldwide in excess of 234 million [1]

Recently calls for increased clinical safety and accountability following high profile healthcare scandals, the drive to give patients a choice between different healthcare providers, and the linkage of funding to measured results have driven the outcomes reporting agenda forward. Cardiac surgery has led in the reporting of outcomes following surgery [2-4], and other surgical specialties are now following [2]. But these initiatives are limited by the lack of validated instruments for describing the variety of outcomes occurring to individual patients. The measures currently used to assess outcome following surgery have significant limitations.

Mortality is the most commonly cited variable but the low event rate following elective surgery limits its applicability as a general outcome measure. Length of

hospital stay is known to be affected by medical and non-medical factors and therefore functions as a hybrid measure of process and outcome [3-6]. Recording of perioperative morbidity has hitherto been limited: a recent systematic review of the measurement and monitoring of surgical adverse events found inconsistency in the quality of reporting of postoperative adverse events limiting accurate comparison of rates over time and between institutions [7]. A reliable and valid index of short-term post-operative morbidity would be of enormous value in quality of care, prognostic and effectiveness research.

The Post-Operative Morbidity Survey (POMS) is the only published prospective method for describing short-term morbidity following major surgery [8]. The POMS (see Table 1.1) contains 18 items that address nine domains of post-operative morbidity. For each domain either presence or absence of morbidity is recorded on the basis of objective criteria. POMS is starting to be used in outcomes research [9] and in effectiveness research [10].

Table 1.1 The Post Operative Morbidity Survey

Morbidity type	**Criteria**
Pulmonary	Has the patient developed a new requirement for oxygen or respiratory support?
Infectious	Currently on antibiotics and/or has had a temperature of >38°C in the last 24 hours.
Renal	Presence of oliguria < 500ml/24hours, increased serum creatinine (>30% from pre operative level); urinary catheter in situ.
Gastrointestinal	Unable to tolerate an enteral diet for any reason including nausea, vomiting and abdominal distension.
Cardiovascular	Diagnostic tests or therapy within the last 24 hours for any of the following: new MI or ischaemia, hypotension (requiring fluid therapy >200ml/hr or pharmacological therapy, atrial or ventricular arrhythmias, cardiogenic pulmonary oedema, thrombotic event (requiring anticoagulation).
Neurological	New focal neurological deficit, confusion, delirium or coma.
Haematological	Requirement for any of the following within the last 24 hrs: 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 post-operative pain significant enough to require parenteral opioids or regional analgesia.

1.2 Methods used to predict surgical outcome

There are three major methods currently used to predict surgical outcome: 1) Preoperative risk scores, 2) Functional capacity assessment and 3) Adjunctive clinical investigations. Most if not all can be used in a step wise assessment of patients prior to surgery as recommended by recent international guidelines [11, 12].

1.2.1 Pre- operative risk scores

There are a number of pre and postoperative risk scores and variables that have been used to predict morbidity and or mortality in both emergency and elective surgery and these are shown in Table 1.2. I will describe and review the most commonly used of these scores in this thesis.

Table 1.2 Currently available risk scores and variables used in elective and emergency surgery showing information source required and prediction for morbidity and mortality

	Information Source		Prediction		
Risk Score / Variable	**Preoperative**	**Postoperative**	**Morbidity**	**Mortality**	**Discussed in Thesis**
Age	*		*	*	YES
American Society of Anesthesiologists Physical Status Classification (ASA-PS) [13]	*		*	*	YES
Boersma [14]	*			*	YES
Boey Score [15]	*			*	NO
Charlson comorbidity index [16]	*			*	YES
Cleveland Colorectal Model [17]	*	*		*	NO
Detsky [18]	*		*		YES
Donati Score [19]	*		*		NO
Fitness Score [20]	*	*		*	NO
Glasgow Aneurysm Score [21]	*			*	NO
Goldman [22]	*		*	*	YES
Hardman Index [23]	*			*	NO
Lee [24]	*		*	*	YES
National Surgical Quality Improvement Program (NSQIP) [25]	*	*	*	*	YES
Physiological and Operative Severity for the Enumeration of Mortality and [26, 27]	*	*	*	*	YES
Reiss Index [28]	*	*		*	NO
Sickness Assessment [29]	*			*	NO
Surgical Risk Score (SRS) [30]	*	*		*	YES
VA Pneumonia Prediction Index [31]	*		*		YES
VA respiratory Failure Score [32]	*		*		YES
Veltkamp Score [33]	*		*		NO

1.2.1.1 American Society of Anesthesiologists (ASA)

The American Society of Anesthesiologists (ASA) physical status classification (ASA-PS) was originally developed in 1941[13] by the American Society of Anesthetists and later revised in 1963[34] to a form close to that used today (see Table 1.3). It was designed to provide a simple and concise summary of a patient's global preoperative health status and consists of six different subjectively differentiated categories, with an ASA grade of VI being reserved for brain dead patients, awaiting organ harvesting. There have been modifiers added to the score such as "G" for gravid [35], and "E" for emergency in an attempt to reduce the inconsistency of the score [36], but it's most widespread use remains as a five point grading classification from ASA 1 – V.

It was never intended or expected to be a good predictor of surgical outcome on an individual basis, but was expected to provide a description of "anaesthetic risk", that could be clearly communicated and provide a uniform system for statistical and epidemiological purposes. It lacks the sensitivity and specificity to predict on individual patients, not least because it does not take into account the severity of the surgical procedure itself and doe not quantify surgical risk. Many authors have however used it and minor modifications of it to predict outcome from surgery, as described in the following paragraphs.

Table 1.3 American Society of Anesthesiologists Physical Status Score 2010[37]

ASA Grade	Criterion
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation***
VI	A declared brain-dead patient whose organs are being removed for donor purposes

There is however a clear evidence of it's effectiveness in being able to predict a broad range of surgical outcomes from mortality to perioperative complications and length of stay in a diverse group of patients from those with cirrhosis through to trauma [38-49].

1.2.1.2 Surgical Risk Score

In 2002 the American Society of Anesthesiologists Physical Status Classification was combined with an urgency of surgery score from the National confidential Enquiry into Patient Outcome and Death (NCEPOD) categories and a measure of surgical severity using the British United Provident Association (BUPA) operative severity scores [30] (see Table 1.4)

Table 1.4 Surgical Risk Score (Sutton 2002)

CEPOD	Criteria	Score
Elective	Routine booked non-urgent case, e.g. varicose veins or hernia 1	1
Scheduled	Booked admission, e.g. cancer of the colon or AAA 2	2
Urgent	Cases requiring treatment within 24±48 h of admission,	3
Emergency	Cases requiring immediate treatment, e.g. ruptured AAA 4	4
BUPA		
Minor	Removal of sebaceous cyst, skin lesions, oesophagogastric duodenoscopy	1
Intermediate	Unilateral varicose veins, unilateral hernia repair, colonoscopy 2	2
Major	Appendicectomy, open cholecystectomy 3	3
Major plus	Gastrectomy, any colectomy, laparoscopic cholecystectomy 4	4
Complex major	Carotid endarterectomy, AAA repair, limb salvage, anterior resection, oesophagectomy	5
ASA		
I	No systemic disease 1	1
II	Mild systemic disease 2	2
III	Systemic disease affecting activity 3	3
IV	Serious disease but not moribund 4	4
V	Moribund, not expected to survive 5	5

The resultant score comes from a simple summing of each scored category. For patients undergoing high risk surgery the receiver operating curves were not significantly different to either Physiological and Operative Severity for the Enumeration of Mortality and Morbidity (POSSUM) or Portsmouth-Physiological and Operative Severity for the Enumeration of Mortality and Morbidity (P-POSSUM) for predicting mortality [50]. For patients undergoing lower risk surgery

the SRS score was significantly predictive for mortality and unlike POSSUM did not appear to over predict mortality for low risk procedures [30].

1.2.1.3 Physiological and Operative Severity for the Enumeration of Mortality and Morbidity (POSSUM)

In 1991 a Urology Surgeon named Graham Copeland described a scoring system for surgical audit that he called the Physiological and Operative Severity for the Enumeration of Mortality and Morbidity and used the abbreviated acronym (POSSUM) to label his system [26].

The system uses an 18 component scoring system comprised of 12 variables from a preoperative physiological assessment and 6 variables from the operative severity assessment (See Tables 1.5 & 1.6). Originally 48 physiological variables and 12 perioperative variables were scrutinised by multivariate analysis for their ability to predict morbidity and mortality rates up to 30 days post surgery. Those 18 variables with the highest predictive ability were then included in the final score as described above.

The percentage risk of either mortality or morbidity is calculated by categorising the variables on an exponential scale and then putting the summed product of the two component scores into a logistic regression equation. Mortality and morbidity are calculated from two different equations and both produced significant equations for mortality and morbidity prediction [26].

Copeland's original study also produced a prospective validation cohort, which was analysed for observed versus expected rates of mortality and morbidity. The observed rates did not differ significantly from the expected rates derived from the calculations [26].

Many studies have confirmed the utility of POSSUM in predicting postoperative mortality and or morbidity [50-55]. There are however some criticism of POSSUM in that it may significantly overestimate risk for those with a predicated risk of death of less than 10% [56]. Other studies have also shown it and some of it's derivative systems to significantly overestimate perioperative risk [57-66]. This may be because of the inherent use of logistic regression equations in that if all the Variables in POSSUM are normal i.e summed to 12, then there is still a calculated risk of death of 1.08% [56].

In 1998 David Prytherch reworked Copeland's POSSUM scoring system and published the Portsmouth-POSSUM (P-POSSUM) [27]. He used the same variables as Copeland but modified the regression equation using a large local dataset. His new system in a limited number of studies appears to calculate risk better than the original POSSUM score [27, 50, 61, 66-68], but still has a propensity to significantly overestimate risk [59, 64, 68-71] and in some cases even underestimate risk [50, 72-74]. He did not however produce a score for morbidity at the time of publication.

Many surgical specialities have now developed surgical specific POSSUM risk models, which have the obvious advantage of introducing data specific to the surgery being undertaken and allowing for better calibration and have been shown to be better at risk prediction than the original POSSUM. There are scores available for vascular [52] , colorectal (Cr-POSSUM) [59, 72, 74-77], oesophageal [69, 78, 79] and orthopaedic surgery [80], but again there is evidence to suggest they may not be precise enough for accurate risk prediction [59, 79, 81-83].

POSSUM was originally intended as a tool for audit and surgical comparison and caution must be exercised in predicating individual risk, given the various imprecisions in its measurement.

Table 1.5 Physiological scoring table for POSSUM score, scored at the time of surgery (Copeland 1991)

	Score			
	1	**2**	**4**	**8**
Age (years)	≤60	61-70	≥71	
Cardiac signs Chest radiograph	No failure	Diuretic, digoxin, antianginal or hypertensive therapy	Peripheral oedema; warfarin therapy, Borderline cardiomegaly	Raised jugular venous pressure Cardiomegaly
Respiratory history Chest radiograph	No dyspnoea	Dyspnoea on exertion Mild COAD	Limiting dyspnoea (one flight) Moderate COAD	Dyspnoea at rest (rate >30/min) Fibrosis or consolidation
Blood pressure (systolic) (mmHg)	110-130	100-109, 131-170	≥171, 90-99	≤89
Pulse (beats/min)	50-80	81-100, 40-49	101-120	≥121, ≤39
Glasgow coma score	15	12-14	9-11	≤8
Haemoglobin (g/100 ml)	13-16	11.5-12'9 16.1-17.0	10.0-11.4 17.1-18.0	≤9.9, ≥18.1
White cell count (x 10'*/1)	4-10	10.1-20 , 3.1-4	≥20.1, ≤3	
Urea (mmol/l)	≤7.5	7.6-10	10.1-15	≥15.1
Potassium (mmol/l)	3.5-5	3.2-3.4, 5.1-5.3	2.9-3.1, 5.4-5.9	≤2.8, ≥6
Sodium (mmol/l)	≥136	131-135	126-130	≤125
Electro-cardiogram	Normal		Atrial fibrillation (rate 6-90)	Any other abnormal rhythm or >5 ectopics/min Q waves or ST/T wave

COAD=chronic obstructive airways disease

Table 1.6 Operative severity score for POSSUM score, scored after surgical procedure (Copeland 1991).

	Score			
	1	**2**	**4**	**8**
Operative severity*	Minor	Moderate	Major	Major +
Multiple procedures	1		2	>2
Total blood loss (ml)	≤ 100	101-500	501-999	≥1000
Peritoneal soiling	None	Minor (serous fluid)	Local pus	Free bowel content, pus or blood
Presence of malignancy	None	Primary only	Nodal metastases	Distant metastases
Mode of surgery	Elective		Emergency resuscitation of >2 h possible, Operation <24 h after admission	Emergency (immediate surgery <2 h needed)

1.2.1.4 Charlson comorbidity index

The Charlson index was originally developed and validated in 1987 as a weighted index method for classifying comorbid conditions which may affect the risk of dying in longitudinal medical studies [84]. It was modified and evaluated seven years later to incorporate age in a small group of 226 hypertensive and diabetic patients undergoing elective surgery, who were followed up for 5 years from hospital discharge [16]. The study confirmed it's ability to be a valid predictor of death in patients undergoing elective surgery [16]. Subsequent studies using the original Charlson index and the age-comorbidity index have shown inconsistent results in predicting mortality, which has limited its incorporation into clinical practice. The both appear to be able to reasonably predict long term (5 year) survival in diabetics [85] undergoing elective surgery and for patients

having lung resections for carcinoma [86-88], yet they perform less well for those with urological carcinoma [89-91].

As an index like many others it was designed to predict the outcome of populations and not that of individuals.

1.2.1.5 Cardiac risk and non-cardiac surgery

There has been a steady evolution of risk scores to predict adverse cardiovascular outcomes since the original work by Goldman et al in 1977 [22]. Each has seen an improvement on its predecessor in its predictive ability.

1.2.1.5.1 Goldman

The Goldman index is a 9-point multifactorial index combining clinical examination, investigations and surgical severity with a disproportionate score assigned to each variable within in it, (see Table 1.7). It soon found widespread use due to it's simplicity and proved to be more predictive than the ASA score for predicating perioperative cardiovascular morbidity [92], but less good at predicting mortality [47]. The combination of the ASA score with Goldman's index did however improve the prediction of mortality [93].

Table 1.7 The Goldman cardiac risk index (abbreviated 1977)

Clinical Variable	Score
Third heart sound	11
Elevated jugular venous pressure	11
Myocardial infarction within 6 months	10
ECG: premature atrial contractions or non-sinus rhythm	7
ECG: >5 premature ventricular contractions/minute	7
Age > 70 years	5
Emergency procedure	4
Intra-thoracic, intra-abdominal or thoracic surgery	3
Poor general status, metabolic or bed ridden	3

There are a number of problems with the Goldman index that centre around the subjective nature of the clinical variables. For instance there is considerable intraobserver variability in recognition of a raised jugular venous pressure and the presence of a third heart sound, both of which are integral components of the index. The same is true for components such as “poor general status”, which have a strongly subjective nature to their categorisation and thus on the overall index score. The subjective nature of these observations are not unique to the Goldman index and affect almost all of the scores described in this thesis. Although unlikely to be the sole cause of their inability to consistently predict risk, subjectivity of assessment almost certainly plays an important part.

1.2.1.5.2 Detsky

In 1986 Detsky modified the Goldman index by using a Bayesian statistical approach, but using the same clinical variables and presented the risk index in the form of a simple nomogram [18]. It did not prove to be any more superior to the ASA score or the Goldman index in predicting perioperative cardiovascular complications [94].

1.2.1.5.3 Lee (Revised cardiac Risk Index)

Twenty-two years after Goldman described his index, Lee introduced the revised cardiac risk index [24]. The original paper describes the derivation and subsequent validation cohorts and uses a simple six point scoring system to apportion cardiac risk in non-cardiac surgery, (see Table 1.8). It combines data from the patient's preoperative comorbid state and type of surgery undertaken. It is probably the most widely used risk scoring system in current clinical practice and remains the best validated of the current scoring systems. It is used by the most recent American College of Cardiology / American Heart Association guidelines on perioperative cardiac risk as the basis for a clinical evaluation system to determine who is likely to benefit from preoperative testing and intervention [11]. It was originally designed to predict any of five complications, myocardial infraction, pulmonary embolism, ventricular fibrillation, cardiac arrest and complete heart block. In a recent systematic review by Ford et al it's ability to discriminate between those at high and low risk of cardiac events after non-cardiac surgery was confirmed [95]. In the same review however, the authors also highlight the fact that it did not perform as well in predicting cardiac events in vascular surgery or in predicating death, with

many studies being heterogeneous clinically and statistically and of low methodological quality [95].

Table 1.8 a) The Lee index (Lee 1999) and b) Points scoring and risk of perioperative complications

a)

Clinical variable	Score
High risk surgery	1
Coronary heart disease	1
Congestive heart failure	1
Cerebrovascular disease	1
Diabetes mellitus on insulin	1
Serum creatininie >2 mg/dl	1

b)

Points	Class	Risk	Complications
0	I	Very low	0.4 %
1	II	Low	0.9 %
2	III	Moderate	6.6 %
3	IV	High	>11 %

1.2.1.5.4 Boersma

The latest adaptation of the revised cardiac risk index (Lee index) is by Boersma et al, who broadened the surgical categories to 4, introduced variables for open vs. laparoscopic surgery, elective vs. emergency surgery and added 6 age categories [14]. The main strength for this scoring system is that it is derived from 9 years of retrospective surgical outcome data from non-cardiac surgery operations containing 108,593 patients and performed better than the original Lee index in predicting cardiovascular mortality [14]. It has not however been prospectively tested in a surgical population outside of the Netherlands.

1.2.2 Age

Age is a fundamental component of many of the scoring systems described in this chapter, but is rarely used alone for prediction of surgical outcome. Age alone has been shown to be a poor predictor of mortality, morbidity and length of stay in multivariate analysis [96]. For any given age however, an individual has a statistical chance of dying (see Figure 1.1 and Table 1.9) that has lessened in the last 25 years as both male and female life expectancy have increased, with male life expectancy having risen to 77.2 years.

As the population ages the number of comorbidities rises per individual and any individual of the same age but with differing degrees of comorbidity will have a different life expectancy. For example if we take two 71 years old male patients, a) has diabetes mellitus, ischaemic heart disease and renal failure and b) has no demonstrable comorbidity, it is b) that has a significantly higher chance of dying at anytime point irrespective of surgery. So age will always have a

powerful effect on any risk score that incorporates it, but it may be nothing more than a surrogate marker of comorbidity.

Recently perioperative risk calculators have been proposed in the guidelines on perioperative assessment by AAGBI which build on the statistical chance of dying and incorporate surgical severity and patient comorbidity [97]. They are yet to be tested in large prospective studies however, but age is always likely to remain a core component of any risk prediction model.

Figure 1.1 Rise in average life expectancy at birth for males and females 1980 – 2006 (http://www.statistics.gov.uk/cci/nugget.asp?id=168)

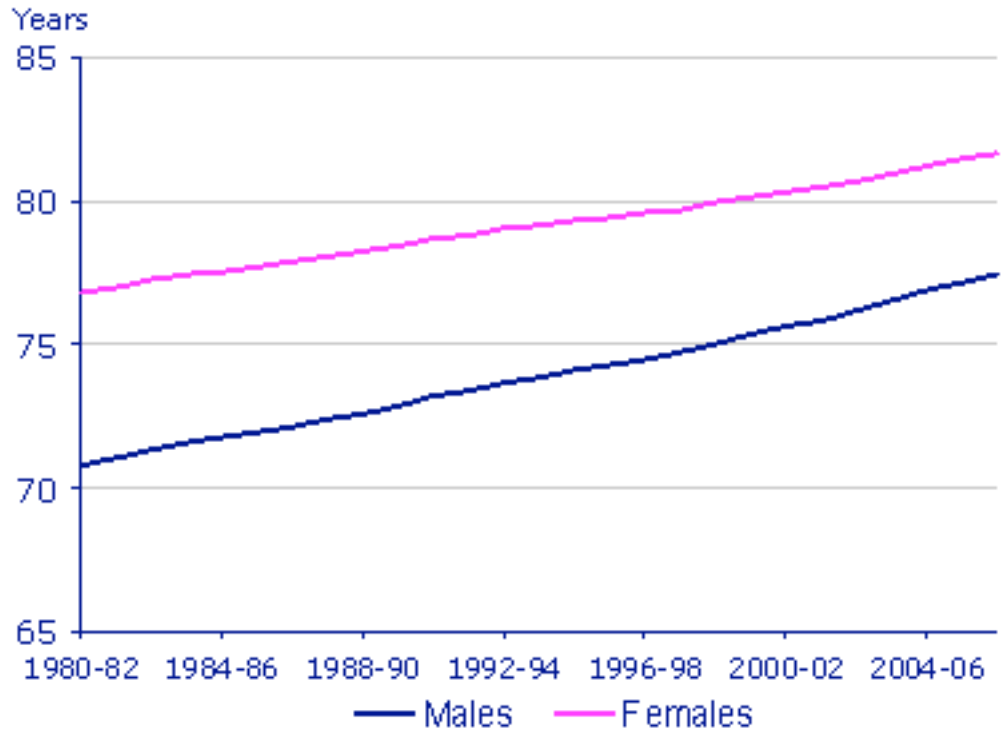


Table 1.9 Average life expectancy for each decade of life - 2006-2008

	Average period expectation of life at given age	
Age	**Males**	**Females**
0	77.40	81.63
10	67.93	72.09
20	58.12	62.20
30	48.52	52.37
40	39.05	42.65
50	29.85	33.21
60	21.29	24.26
70	13.77	16.05
80	7.79	9.18
90	3.98	4.48
100	1.95	2.17

Adapted from Interim Life Tables, United Kingdom 2006-2008 (www.statisitcs.gov.uk -accessed Auhst 17th 2010)

1.2.3 National Surgical Quality Improvement Program (NSQIP)

The Veterans Affairs (VA) hospitals in the United States have been mandated by law to report surgical outcome since 1986. As part of this program between 1991 and 1993 they prospectively collected data on over 117,000 major surgical procedures and from this data constructed 30 day mortality and morbidity risk adjustment models for 9 surgical specialities [25]. Eight of these surgical specialities are reviewed annually using logistic regression analysis to create and enhance existing models for each speciality, with upwards of 23 individual components related to preoperative morbidity and surgical care [4].

The system is used predominantly for national audit comparison and epidemiological research, but has been translated into non-VA hospitals [98] and the private sector successfully [99]. The size, complexity and broad coverage of surgical specialities and hospitals put the NSQIP model in a unique position and have led to some fascinating insights into the long term outcome from surgery. In 2005 Khuri et al using the NSQIP database reported on the long term outcome of over 105,000 patients undergoing surgery [100]. What they found was that the occurrence of a postoperative complication within 30 days of surgery was more important in predicting the long term survival of surgical patients than any preoperative patient risk or intraoperative factor [100]. Hamel et al using the same dataset looked at surgical outcome in an elderly population of over 590,000 patients, finding the NSQIP mortality risk model to perform well on patients over 80, but postoperative complications in those over 80 were associated with a high 30 day mortality [101].

It is most likely that models built on large local datasets of patients represent the direction of travel for perioperative risk calculators and have significantly enhanced traditional scoring systems such as the revised cardiac risk index [14].

It is somewhat disappointing that the United Kingdom with a centralised and government funded healthcare system such as the NHS has nothing like this for comparison. Much of the data available in the UK is from hospital episode statics data that is independently risk adjusted by agencies such as Dr Foster and fed back to hospitals and healthcare agencies, but does not have the complexity or intent of systems such as NSQIP to help us better understand perioperative risk assessment and modification.

1.2.4 Functional exercise testing

The objective assessment of exercise capacity is a core component of most preoperative consultations and an integral component of many more sophisticated risk assessment programs. Deriving an assessment of exercise capacity however from subjective patient based questionnaires or from formal exercise testing is possible and desirable. These will be described below.

Table 1.10 Summary table of functional exercise testing

Evidence	Test	Cost
+	Stair Climbing	Cheap
+	Subjective exercise questionnaires	Cheap
++	Cardiopulmonary exercise testing	Expensive
+	Shuttle testing	Moderate

1.2.4.1 Stair climbing

The four most recent studies to prospectively evaluate stair climbing for patients undergoing thoracic surgery, all suggest that an inability to climb 2 flights of stairs is a good predictor of increased perioperative mortality [102-105]. The most recent and largest of which, however suggests it may not be a good

discriminator of morbidity [104]. In a small study of high risk patients by Reilly et al the inability to climb 2 flights of stairs was associated with a positive predictive value of 82% for post-operative complications [106]. Many/all of the studies evaluating stair climbing to date have included thoracic surgery patients. Pulmonary function has an obvious and crucial role in recovery from thoracic surgery, with the FEV_1 being the best predictor of survival after lung resection surgery [107]. If one excludes thoracic surgery patients, it is clear stair climbing is not a good discriminator for perioperative mortality and does not induce a sufficient enough stress response [107, 108]. There are in addition many problems of standardising stair climbing with respect to stair height, speed of assent and the inability of claudicating patient to perform such exercise. A standardisation of these would possibly improve the test significantly.

1.2.4.2 Subjective exercise questionnaires and assessment

Although most preoperative questioning by anaesthetists will involve an enquiry as to the patients reported exercise tolerance it is rarely standardised and simply reported as good, adequate or poor.

Reilly et al showed the merit in this in 1999 by looking at symptom limited exercise capacity as reported by the patient and found it to be a reasonable predictor of in hospital risk [106].

Partially in an attempt to standardise the subjective assessment of exercise and correlate it to exercise capacity Htalky et al developed a 12 item scale that correlated with peak oxygen uptake. Their original cohort consisted of 50 patients from which they developed the index and called it the Duke Activity Status Index (DASI), (See Table 1.11)[109] They used an empirical equation to

then estimate peak oxygen uptake (Estimated peak oxygen uptake = (0.43 * (DASI)) + 9.6) from the sum of the values for all 12 items [109].

Table 1.11 Self administered, 12 point Duke Activity Status Index (Hlatky et al 1989)

Item	Activity	Yes	No
1	Can you take care of yourself (eating dressing bathing or using the toilet)?	2.75	0
2	Can you walk indoors such as around your house?	1.75	0
3	Can you walk a block or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.5	0
5	Can you run a short distance?	8	0
6	Can you do light work around the house like dusting or washing dishes?	2.7	0
7	Can you do moderate work around the house like vacuuming sweeping floors or carrying in groceries?	3.5	0
8	Can you do heavy work around the house like scrubbing floors or lifting and moving heavy furniture?	8	0
9	Can you do yard work like raking leaves weeding or pushing a power mower?	4.5	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities like golf bowling dancing doubles tennis or throwing a baseball or football?	6	0
12	Can you participate in strenuous sports like swimming singles tennis football basketball or skiing?	7.5	0

The scores are based on the estimated metabolic equivalent for that particular activity (1 MET = 3.5 mls/Kg/min), which is the resting oxygen consumption of a 70 Kg male at rest. Despite being widely used it has been show to be less predictive of outcome compared to simples scores e.g. the ASA score [110]. For this reason it is more commonly used as part of a broader assessment of patients such as in the American College of Cardiology/American Heart Association guidelines on perioperative cardiac risk prevention [11], where in the absence of formal exercise testing it is a useful surrogate.

1.2.4.3 Cardiopulmonary exercise testing

The epidemiological evidence that physical activity confers sustained health benefits, not only by reducing the event rate of cardiovascular disease but also in he prevention of certain types of cancer and reduction in type 2 diabetes continues to grow [111]. There is conflicting evidence with regards to the intensity of exercise undertaken. Vigorous regular exercise has clear benefit as does moderate levels of regular activity such as walking, which may be more appropriate as the population ages and the ability to undertake vigorous exercise is diminished and more sedentary forms of exercise are undertaken [112].What is also clear is that a sedentary lifestyle has a strong predisposing influence on cardiovascular and metabolic diseases e.g. obesity, coronary artery disease, stroke and hypertension and mortality [113].

Cardiologists have used treadmill exercise testing to detect coronary artery disease for many years, by looking for inducible ischaemia through incremental levels of exercise (such as the Bruce protocol), with a reasonable degree of sensitivity and specificity [114]. Even in populations with high levels of coronary artery disease such as vascular patents, using the same technology and techniques to identify coronary ischaemia and then relate them to perioperative outcome was initially unsatisfactory, when compared to conventional nuclear imaging techniques [115]. What was clear from early attempts however was that it was consistently possible to associate poor patient outcome with poor exercise performance, but many of the studies failed to reach statistical significance and were small studies [116-119]. For instance the study by Bonow et al looked at 45 patients with symptomatic aortic regurgitation and found exercise capacity to be a poor predictor of postoperative mortality and imprecise in assessing preoperative left ventricular dysfunction, but useful in predicting long term

survival after the operation [116]. In a slightly larger study of 200 patients over 40 undergoing major elective non-cardiac surgery Carliner et al were unable to demonstrate that exercise testing added substantially to the preoperative risk assessment with the only statistically significant predicator in multivariate analysis being the preoperative ECG [117].

The 1980's also saw the emergence of cardiopulmonary exercise testing which soon established itself as a well validated and repeatable measure of exercise capacity [120]. In essence cardiopulmonary exercise testing consists of continuous expired and inspired gas analysis at the mouth, pulse oximetry, non-invasive blood pressure measurement and recording of a continuous electrocardiogram whilst progressing through an incremental (ramped) exercise protocol on a bicycle ergometer or treadmill. Full details of measurement possibilities and analysis techniques are available in Chapter 5, but the two measurements of relevance to perioperative risk estimation are the maximum oxygen consumption (VO_2 peak) and the anaerobic threshold (AT).

Anaerobic threshold is a submaximal and objective marker of aerobic capacity and is reached significantly earlier in exercise than VO_2 peak and as such is relatively independent of patient motivation. It is reached when the contribution from anaerobic respiration becomes significant and oxygen supply to the muscles cannot meet its demands. There are tables for VO_2 peak that are based on age, height and gender to which values from cardiopulmonary exercise testing can be compared and is a very reproducible marker of cardiorespiratory fitness [121, 122].

It wasn't until 1993 that the first of two studies by Pauls Older's group in Australia confirmed the correlation between exercise capacity and perioperative outcome [123]. In a study of 187 elderly patients undergoing major surgery they

showed that an anaerobic threshold of <11 mls/Kg /min was associated with a mortality of 18% compared with the overall study mortality of 7.5% and a mortality rate of 0.8% for those with an anaerobic threshold of > 11 mls/Kg/min [123]. Furthermore for those with an At < 11 mls/Kg/min and preoperative ischaemia during testing the mortality increased to 42%, but preoperative ischaemia with a high anaerobic threshold i.e. > 11 mls/Kg/min had a mortality rate closer to 4% [123].

In 1999 a second study by the same group additionally reported on a series of 448 patients > 60 years of age undergoing major intrabdominal surgery in whom they used cardiopulmonary exercise testing to stratify care to an ICU, HDU or ward level postoperatively based on evidence of myocardial ischaemia and anaerobic threshold during cardiopulmonary exercise testing and the expected oxygen demand of the surgical procedure being undertaken [124]. Again they found that an anaerobic threshold <11 mls/Kg/min was predictive of poor outcome, but equally important was that in those patients deemed fit for surgery and ward based care there were no deaths, compared to a study mortality of 3.9% [124].

In all eleven studies have looked at the utility of cardiopulmonary exercise testing to predict perioperative risk [123-133] of which the most recent systematic review includes nine studies [134]. Two studies have looked at it's utility in abdominal aortic aneurysm repair [125, 131] the first of which by Nugent et al used VO_2 peak in 30 patients and found no association with postoperative complications in the 12 months of study follow up, but a trend towards more complications in those with a VO_2 peak < 20/mls/Kg/min [131]. Carlsile et al however found a stronger association in 130 patients with anaerobic threshold, VO_2 peak and the Ventilatory equivalent for oxygen (V_E/ VO_2) for survival, with

V_E/ VO_2 being the strongest predictor of 30 day and mid term survival [125] . The addition of the revised cardiac risk index to the cardiopulmonary exercise testing variables further enhanced the predictive ability of testing [125].

Only one study has looked at 59 hepatic transplantation patients and grouped them retrospectively into survivors and non-survivors [126]. They conclude that survivors were significantly more likely to have a VO_2 peak < 60% of predicted and a VO_2 – anaerobic threshold of <50% of predicted [126].

Four studies have looked at upper gastrointestinal surgery patients [127-130]. The first paper by Nagamatsu et al in 1994 in 52 patients found significantly more cardiopulmonary complications in the group with low VO_2 max and anaerobic threshold [130]. In their second paper in 2001 of 91 patients they retrospectively grouped patients with moderately advance oesophageal cancer into two groups according to the presence or absence of cardiopulmonary complications after oesophagectomy [129]. They confirmed the finding of lower VO_2 max values in those with complications but were unable to find the same association with anaerobic threshold [129]. The study by Forshaw et al showed similar results in 78 patients undergoing oesophagectomy, with significantly lower VO_2 peak values in those with complications and although significant, relatively poor receiver operating characteristics curves of 0.63 (95% CI o.50 – 0.76) and 0.62 (95% CI 0.49 – 0.75) for VO_2 peak and anaerobic threshold respectively [127]. The last upper GI study is by McCullogh et al in 109 bariatric patients undergoing laparoscopic bypass surgery [128]. They used a slightly different approach by grouping patients into tertiles based on their VO_2 peak and found a significant difference in complications for those with a VO_2 peak of < 15.8 mls/Kg/min and for those with a VO_2 peak > 15.8 mls/Kg/min of 16.6% and 2.8% respectively [128]. In addition despite recording anaerobic threshold it was not analysed as a

postoperative indicator but hospital length of stay and 30 day readmission rates were highest in those in the lower tertile for VO_2 peak [128].

Of the four studies looking at major elective surgery [123, 124, 132, 133], the two by Older et al have been described above [123, 124]. The two studies by Wilson et al and Snowden et al are not only the largest (847 and 171 patients respectively) of the described studies but looked at mortality and complications respectively and used slightly differing thresholds for anaerobic threshold, (<10.9 mls/Kg/min vs. 10.1 mls/Kg/min) [132, 133]. The largest study by Wilson et al of 847 patients were analysed retrospectively for clinical risk factors and cardiopulmonary exercise testing data to determine their relationship with all cause mortality after surgery. They found a clinical history of ischaemic heart disease, and anaerobic threshold <10.9 mls/Kg/min and a V_E/ VO_2 of >34 to be predictive of hospital and 90 day mortality, with anaerobic threshold having the highest risk ratio (RR) of 6.8 (95% CI 1.6 – 29.5) [133]. Of interest is the elevation in the RR to 10.0 (95% CI 1.7 – 61) for those with no documented history of ischaemic heart disease [133]. Snowden and colleagues performed a prospective study on 171 patients using a algorithm based activity assessment, the Veterans Activity Questionnaire index (VASI), and cardiopulmonary exercise testing to look at complications on day 7 using the Post operative Morbidity Survery [132]. In addition to the VASI being predictive of outcome they too found anaerobic threshold to be predictive of outcome with those having ≥ 1 complication having lower a lower anaerobic threshold (9.1 vs. 11.9 mls/Kg/min, P=0.001), that was accurate with an area under the curve of 0.85, a sensitivity of 88% and a specificity of 79% at an optimum anaerobic threshold of 10.1 mls/Kg/min [132]. They conclude by stating “preoperative anaerobic threshold significantly improved outcome prediction when compared to the use of VASI alone” [132]

It is clear from the studies described here that both VO_2 peak, V_E/ VO_2 and anaerobic threshold are reproducible, accurate and capable of predicting perioperative mortality and morbidity. Furthermore CPET may have the ability to individualise risk prediction.

There is however a continued debate as to the exact physiological basis of anaerobic threshold [135], mainly because there is accruing evidence to suggest that hypoxia may not be the driving force for lactate production and that anaerobic threshold may be nothing more than a marker of exercise capacity. This theme will be examined in more detail later on in this chapter under metabolic performance on pages 62-69.

The balance of evidence from the most recent systematic review suggests that VO_2 peak and anaerobic threshold are useful markers to predict surgical outcome, with the evidence slightly favouring VO_2 peak [134]. Despite the fact that cardiopulmonary exercise testing has been used as a tool to predict surgical outcome and stratify surgical care for over 35 years, there have only been 2,308 patients studied and published in peer reviewed clinical trials worldwide with nearly 1,000 of those published as recently as 2010 [132, 133]. This is in stark contrast to the fact that in 2009 over 10,000 cardiopulmonary exercise tests were estimated to have been done preoperatively in the UK alone as part of a preoperative assessment [136]. There has always been a strong biological plausibility to cardiopulmonary exercise testing and it has been adopted widely throughout the UK despite a relatively light body of evidence to support it. Furthermore there is some disagreement and debate within the cardiopulmonary exercise testing fraternity as to which is the best marker of exercise capacity to use for preoperative testing with oxygen pulse, ventilatory equivalents, anaerobic threshold and VO_2 peak all having protagonists and

detractors. One also needs to remember that not everybody can do an exercise test such as those with severe musculoskeletal pain or claudication. There are a number of prospective randomised clinical trials ongoing that will undoubtedly add to our understanding, but there is still a considerable setup and running cost to cardiopulmonary exercise testing coupled with its infancy and relatively small evidence base that has to borne in mind when evaluating it as a preoperative test.

No currently published study has looked exclusively at cardiopulmonary exercise testing in orthopaedic patients to predict perioperative risk.

1.2.4.4 Shuttle testing

Shuttle walk testing has been validated shown to be an extremely reproducible test [137, 138]. It requires patients to move on flat ground between two fixed points in a fixed amount of time that decreases as the test progresses. The more times the points are reached the greater the distance walked and the higher the assessment value. It is however more of a screening test for patients unlikely to need further investigation, with patients achieving in excess of 400m needing little or none and patients achieving less than 250m being referred on for further testing [137, 138].

1.2.5 Other Investigations

This section will focus on echocardiography and clinical guidelines.

1.2.5.1 Echocardiography and Clinical Investigations

No non-invasive or invasive clinical investigation is capable of predicting outcome alone. For the main part they are used as adjunctive tests in step wise assessment of perioperative risk as seen in the American College of Cardiology

/ American Heart Association guidelines on prevention of perioperative cardiac risk [11]. Poldermans et al showed a highly significant reduction in mortality by instigating perioperative beta blockade for patients undergoing non-cardiac surgery, determined at risk by a positive Dobutamine Stress echocardiography (DSE) [139]. As a test DSE has a high negative predictive value, but modest positive predictive value. Myocardial perfusion scintigraphy however has a high sensitivity but poor specificity and was found in a recent meta-analysis in vascular patients to be the less good test [140].

The majority of adjunctive testing is however aimed at identifying occult coronary artery disease or stratifying known ischaemic and valvular heart disease. The main controversy in using these tests to predict perioperative risk is that they simply identify a treatable cardiac condition that may not improve perioperative risk if dealt with preoperatively. For instance the recent coronary artery revascularisation before major vascular surgery study, reports no benefit in stable coronary artery disease if prophylactically revascularised prior to surgery [141]. Of note were the exclusion of patients with left main stem disease and unstable angina. With percutaneous coronary artery intervention comes the added complexity of the stents used i.e. bare metal or drug eluting and the optimum timing of surgery and stopping of antiplatelet agents designed to stop in stent thrombosis. The most recent European guidelines provide some guidance on the timing of surgery after such events with elective surgery being postponed for up to a year minimum for patients with new drug eluting stents [12], which further complicates the perioperative risk evaluation.

1.2.5.2 Handgrip dynamometry

The use of handgrip dynamometry to assess grip strength is not new and It has found widespread use in the fields of sport and exercise medicine.

There are a wide variety of tests available to measure and analyse muscle strength and of these tests handgrip dynamometry is not only the simplest to apply, but also the most widely studied. Handgrip exercise also primarily affects only two flexor muscles, the flexor digitorum profuns and the flexor digitorum superficialis muscles. Consequent to this there is a large dataset available which describes the normal range of handgrip strength in normal and abnormal populations, enabling deviations from these to be objectively calculated. Handgrip strength has been shown to be a valid surrogate of overall muscular strength and is commonly used for this purpose [142, 143].

In addition low handgrip strength has repeatedly been shown to be associated with disability, mortality, cognitive decline and adverse surgical outcomes [144]. The most common use for handgrip dynamometry is as a test of strength and muscular function but there are studies that describe it's use as an exercise therapy for instance the use of isometric exercise using handgrip dynamometry has also shown benefit in reducing systolic and diastolic blood pressure [145]

The most often studied groups are the elderly and surgical populations and in these it is grip strength that is most commonly cited as the predominant test value.

1.2.5.2.1 Normal values

The range of normal values for handgrip dynamometry is well-established [146-150]. Males have a higher average grip strength than females (mean (± SD) for 30-34 year olds, 55 (7.1)N vs. 33.8 (5.9)N) [151], which declines with age (mean

(± SD) for 70 – 74 year olds, 41.7 (8.9)N vs. 26.4 (6.8)N [151]. It is most probable that grip strength is stronger in the dominant hand than the non-dominant, but this may not be true for left handed people with some studies suggesting the non-dominant hand to be up to 22.6% stronger [152].

The following section will describe the association of grip strength studies with clinically important outcomes.

1.2.5.2.2 Grip strength

Grip strength is the most commonly used test endpoint of handgrip dynamometry.

1.2.5.2.2.1 Postoperative outcomes

There are eighteen studies that directly relate handgrip strength to perioperative outcomes in the literature, (see Table 1.12) [153-169]. The most common perioperative outcome predicted by limited grip strength is postoperative complications. The finding is not universal however with some authors finding no relationship between low grip strength and postoperative complications [154-156]. There are a number of clear advantages to using such a simple technology when compared to cardiopulmonary exercise testing in that a bicycle ergometer and metabolic cart are not needed, the result is on the whole very objective and can be performed by those bed bound such as with fractured neck of femur patients or patients undergoing emergency surgery.

Most recently Beloosesky et al looked retrospectively at 105 patients who had been operated on for a fractured neck of femur and found a reasonable correlation between handgrip strength 1 week postoperatively and functional

recovery at 6 months [153]. Three other studies have also looked at fractured neck of femur patients who represent a particularly frail group with common nutritional and mobility deficiencies [157, 167, 169]. The largest of which in 205 female post neck of femur fracture patients only showed a moderate correlation with functional outcome compared to Beloosesky [169]. Visser et al report a similar story by following up 90 women for 1 year and showing that the group that lost almost 29% of their grip strength had a poorer functional recovery [167]. Only one study was performed on coronary artery bypass patients and failed to show any benefit in predicting length of stay or compilations [155].

Of the two studies in liver transplant patients, handgrip testing was done as part of a nutritional assessment preoperatively [158, 164]. The study by Figueiredo in 53 patients did not demonstrate any correlation with complications, but did show lower grip strength to be significantly associated with a longer ICU stay [158]. In the slightly larger study by Le Cornu in 82 patients there was a significant association with major perioperative complications, sepsis and length of stay for those with a grip strength <85% of normals [164]. The remaining studies can be divided into four categories: Abdominal surgery (n=4), Major surgery (n=4), Vascular surgery (n=1) and Maxillofacial surgery (n=1). The studies by Brenner and Dannhauser in major and abdominal surgery respectively did not show any correlation between handgrip strength and perioperative outcome [154, 156]. In addition to doing preoperative handgrip strength testing Griffith et al also tested on days 1,3,5 and 7 postoperatively in 61 vascular patients. Grip strength per se was not predicative of mortality for the six patients that died, but the decrease in grip strength from the first to the 7th day was predictive for the seven patients who developed complications [159]. The one maxillofacial study found a value of preoperative grip strength <85% of controls to be highly predictive of

postoperative complications (48% vs 18%, P=0.004) [160]. Mahalakshmi used four predictive parameters to predict perioperative complications in 100 abdominal surgery patients and found maximal grip strength to be better than serum albumin but worse than clinical nutritional scoring in predicting complications [165]. Kidjian in a similar group of 102 abdominal surgery patients in whom 87% developed complications found handgrip strength to be the most sensitive test in predicting complications compared to standard biochemical nutritional variables [163]. Similarly Kalfarentzos found handgrip dynamometry to be more sensitive (77.78 vs 66.6%), more specific (86.11% vs 65.28%) and have a higher positive predictive value (58.33% vs 32.4%) for predicting postoperative mortality and morbidity than their standard prognostic nutritional index, with dynamometry being 100% sensitive for mortality [163]. Hunt used grip strength as part of a preoperative nutritional status indicator in a group of 205 surgical patients with a complications rate of 14% and found it to be the most sensitive single parameter in predicting postoperative complications [161]. Webb et al derived control data from 247 healthy volunteers and found a grip strength of less than 85% to be the best cut off value for predicting postoperative complications with a sensitivity of 74% [168]. Finally Schroeder et al found a weak but significant (r^2=0.352, P=0.01) correlation between grip strength and postoperative fatigue in 84 patients undergoing surgery [166].

What the vast majority of these studies have in common is that they were done as part of or instead of a nutritional assessment, reflecting the fact that elderly surgical patients often represent a potentially frail malnourished group at high risk of perioperative complications and death. It is entirely possible that publication bias may have altered the balance of this review with only 3 of the

studies reporting negative results, but there is a strong biological plausibility to strength and recovery and likely represents a true result.

As alluded to earlier in this thesis the concept of handgrip dynamometry to predict surgical outcome is very appealing for a number of reasons. Firstly there is a vast wealth of literature from which to draw normal values for populations for comparison. Secondly the technique is both repeatable and easy to standardise with most available equipment being easy to calibrate and most equipment being eminently portable. Thirdly the result of a maximal voluntary contraction or an average of three attempts provides a relatively succinct endpoint for the test that is easily quantifiable. Fourthly the cost of equipment is very cheap, as are the running costs and the interpretation of the test does not need such advanced training as that needed to interpret a cardiopulmonary exercise test. Fifthly the forearm lends itself very well to scientific study with the majority of exercise being done by 2 muscles, the fact that it has predominantly one artery to supply it and the ability to sample venous effluent from exercising muscle from the antecubetal fossa where most of the deep veins drain and it's accessibility. Lastly unlike whole body exercise such as running or cycling, exercise by the forearm muscle does not rely so heavily on large increase in cardiac output by the heart and lungs and is thus relatively independent from the cardiopulmonary system, allowing relatively moribund patients to perform the test.

Table 1.12 Perioperative handgrip exercise studies used to predict postoperative outcome

Study	Year	Number of patients	Type of surgery	Conclusions & test	Predicated	Significant
Beloosekyet al	2010	105	Fractured neck of femur	Lower grip strength 1 week post hip fracture	Motor function at 6 months	yes
Brenner et al	1989	249	Major surgery	Lower preoperative grip strength	Increased frequency of complications	no
Cook et al	2001	200	Coronary heart bypass surgery	Maximum grip strength	Complications, LOS	no
Dannhauser et al	1995	52	Abdominal surgery	Preoperative grip strength	Part of prognostic model	no
Davies et al	1984	76	Female Hip fractures	Grip strength < 15 Kg	Complications	yes
Figueirdo et al	2000	53	Liver Transplant	Lower preoperative grip strength	ICU LOS	yes
Grffith et al	1989	61	Vascular Surgery	Reduced preoperative grip strength	Complications	yes
Guo et al	1996	127	Oral and maxillofacial cancer	Preoperative grip strength<85% of controls	Complications	yes
Hunt et al	1985	205	Surgery	Preoperative grip strength<85% of normal	Complications	yes
Kalfarentzous	1989	95	Gastrointestinal cancer	Preoperative grip strength<85% of normal	Mortality, morbidity	yes
Klidjian et al	1980	102	Abdominal surgery	Preoperative grip strength<85% of normal	Complications	yes
Le Cornu et al	2000	82	Liver Transplant	Preoperative grip strength<85% of normal	LOS, Complications, Sepsis	yes
Mahalakshmi et al	2004	100	Abdominal surgery	Strength =<85% control mean	Complications, LOS	yes
Schroeder et al	1993	84	Major surgery	Lower preoperative grip strength	Postoperative fatigue	yes
Visser et al	2000	90	Female hip fractures	Loss of grip strength	Poor mobility recovery	yes
Webb et al	1989	90	Major surgery	Preoperative grip strength<85% of normal	Complications, LOS	yes
Wehern et al	2005	205	Female fractured neck of femur	Lower Grip strength	Functional outcome	yes

1.2.5.2.2..2 Mortality

Low levels of physical inactivity lead to low muscle mass and associated low muscle strength. In a longitudinal study of 1071 men over a 25 year period Metter et al showed a clear link between grip strength and mortality [170]. They found that a low and declining muscle strength was associated with mortality but was independent of muscle mass or physical activity [170]. Furthermore for those <60 years old it was the rate of loss of strength that proved most predictive, whereas in those > 60 years old strength itself was more important.

Recently Ling et al published a series of 555 Dutch subjects who were followed up over 9.5 years in a subset analysis of the Leiden 85-plus study. Four hundred and forty four (80%) of these patients died during this time, with an elevation of all cause risk for mortality in those in the lowest tertile at 85 years of age ([HR] 1.35) and those in the lowest two tertiles at 89 years of age ([HR] 2.04) [171].

1.2.5.2.2.3 Cognitive decline

In a 7 year follow up study of 2160 Mexican Americans, Alfaro-Acha et al showed an association between those subjects in the lowest quartile for handgrip strength and their decline in cognitive function over time [172]. With those in the upper quartile having relatively well preserved cognitive function over the course of the study [172].

1.2.5.2.2.4 Causality

There is unlikely to be a causal link between grip strength and outcome, moreover grip strength reflects function or the nutritional state of the patient. However in a large scale study of 919 moderately and severely disabled women Rantanen et al suggest that handgrip strength is a powerful predicator of all cause mortality and an indicator of overall muscle strength, but “may predict mortality through mechanisms other than those leading from disease to muscle impairment” [173].

1.3 Metabolic performance and exercise physiology relevant to this thesis

The release of muscle metabolites during exercise evokes potent cardiovascular reflexes to increase blood pressure and vasoconstrictor responses to counteract local vasodilatation, increasing sympathetic discharge to active and in active muscle [174]. Furthermore there is evidence that these responses may be attenuated or modified by exercise training [175]. Intensive handgrip exercise does not however significantly challenge the cardiorespiratory system in healthy individuals.

Muscles cells and their mitochondria derive oxygen from the arterial system through the dissociation of oxygen from haemoglobin and diffusion across the capillaries to the cell [176]. Under conditions of intense exercise such as a 100m sprint the cellular demand for oxygen outstrips its capacity for delivery resulting in hydrogen ions release through adenosine triphosphate (ATP) hydrolysis, which are not effectively buffered by mitochondrial ATP production. The result is a net transport out of the cell via the lactate/H^+ transporter and the H^+/Na^+ exchanger and diffusion into the blood [177, 178]. It is however difficult to study the cellular process directly, but studies with intramuscular catheters have given us some insights [179], as have nuclear magnetic resonance scanning [180, 181].

The traditional concept of lactic acidosis occurring when the supply of oxygen to the tissue does not meet it's demands, may not be entirely correct [182]. Glycolysis is the metabolic pathway by which glucose is

converted into glucose and pyruvate. The energy release during this process is converted into high energy compounds such as ATP and reducing compounds such as nicotinamide adenine dinucleotide (NADH). Under aerobic (oxygen dependent) conditions this is a highly effective pathway liberating 34 moles of ATP via further aerobic reactions utilising pyruvate and $NAD^{+,}$ but under anaerobic conditions (oxygen independent) only two molecules of pyruvate are produced and two molecules of ATP. The net result of anaerobic respiration is a greater flux of substrate through the pathway, which can quickly exhaust available substrate and is therefore limited in its longevity. Under aerobic conditions oxygen acts as the final electron acceptor in the respiratory chain. There are four main steps to the process: 1) The pyruvate formed from the glycolysis of glucose is converted into acetyl-CoA and CO_2 within the mitochondria, 2) The acetyl CoA enters the enters the Krebs Cycle or the citric acid cycle where it is fully oxidised to carbon dioxide and water with net NADH production, 3) The NADH is oxidised to NAD^+ by the electron transport chain, creating a hydrogen ion gradient across the inner membrane of the mitochondria and 4) The proton gradient drives oxidative phosphorylation to produce ATP. Under anaerobic conditions it is much simpler with the pyruvate produced from glucose acting as the main oxidiser and in the process being converted to lactate. This results in the oxidation of NADH back to NAD^+ (see Figure 1.2)

Figure 1.2 The conversion of pyruvate to lactate.

$$\text{Pyruvate} + \text{NADH} + H^+ \rightarrow \text{Lactate} + NAD^+$$

NADH = Nicotinamide adenine dinucleotide

The acidosis that occurs in exercise and is associated with lactate is predominantly derived from the cleavage of ATP to release hydrogen ions. Under anaerobic conditions it is anaerobic metabolism that produces most ATP as it is capable of producing it at a high rate and hence the associated acidosis as the buffering systems of the cell are overwhelmed. This has theoretical physiological advantage in that it encourages oxyhaemoglobin to dissociate and release oxygen from he blood to tissues.

There is continued controversy however, about the role that a lack of oxygen plays in the stimulus to produce first pyruvate and then lactate, with increasing evidence to suggest that oxygen availability is only one of several factors that may cause an increase in muscle and blood lactate during exercise [183-185]. The normal range for lactate in venous blood is 0.5 – 2.2 mmol/L [186, 187], with lactate being produced at rest by glycolysis in the presence or absence of oxygen [188]. Exercise physiologists have long since used the concept of a “lactate threshold” to evaluate athletes and help design training programs, but its definition is not clearly defined and is often used interchangeably with anaerobic threshold which may be technically incorrect, although they both represent a spectrum of

metabolic change. Connett best described the lactate threshold as “The point during exercise of increasing intensity at which blood lactate begins to accumulate above resting levels, where lactate clearance is no longer able to keep up with lactate production” [184]. During low intensity exercise lactate levels do not become elevated and remain close to normal levels, but rise quickly as the intensity of exercise increases, commonly showing a sharp upward inflection point [189, 190]. The accumulation of lactate however simply reflects the ratio of production to clearance at that particular point in time and does not tell us anything about the availability or non-availability of oxygen, hence using the terms anaerobic or aerobic threshold may be misleading. As the concentration of blood lactate rises above 4 mmol/L there is an accumulation of lactate referred to as the onset of blood lactate accumulation, which is often used in preference to the lactate threshold as it can be hard to identify with certainty [191, 192]. The best indicator of performance however is probably the maximal lactate state when the rate of lactate clearance equals the rate of lactate production [193, 194]. Lactate threshold is commonly expressed as a percentage of maximal oxygen consumption (VO_2 peak/max) with elite athletes having lactate thresholds at 70-80% of VO_2 peak/max and untrained individuals operating closer to the 50-60% mark [195, 196]. Even if two people have the same VO_2 peak/max it does not necessarily mean they will have the same lactate threshold, and the one with a higher lactate threshold will generally perform better in endurance type exercise [196]. It is possible to improve an individuals lactate threshold through training. For instance Costill et al showed a peak lactate level of

approximately 12 mmol/L could be reduced to approximately 6 mmol/L in 200m swimmers with a dedicated training program over 25 weeks [197] but there is debate as to whether this is through decreased production [198] or through increased clearance of lactate [199].

As shown above the generation of lactate allows for the continued processing of carbohydrates into ATP through glycolysis and although traditionally though of as a waste product of metabolism it is a functional part of the energy supply chain. There is clear evidence that lactate is passed from cell to cell as two carbon fragments to allow for processing in different cells and organs via the lactate shuttle as described by Brooks in 1984 [200]. Lactate that is not oxidised in the muscle diffuses into the blood where it is transported to the liver in a process known as the Cori cycle, where it can be converted back into pyruvate in the presence of oxygen, which can then recreate glucose through gluconeogenesis. Furthermore Lactate is the preferred source of fuel for the brain, heart and most slow twitch muscle fibres [201-203].

Peak levels of lactate can reach over 30 mmol/L, but more commonly 20-25 mmol/L is normal [204], with peak levels occurring in the blood up to 5 minutes after the cessation of exercise [186]. Of considerable interest is the fact that trained individuals are not only capable of generating higher levels of lactate at the point of failure, but can perform similar levels of work with lower levels of lactate than untrained individuals [205].

Although overly simplistic the effects of exercise training are essentially twofold. Firstly there is an improvement in VO_2 peak and although this is largely genetically determined an untrained individual can improve their

VO_2 peak by as much as 20% [188, 206]. Much of this increase comes from improvements in cardiorespiratory performance with enhanced gas exchange and blood flow through the lungs, increased cardiac output and enhanced blood flow to skeletal muscle, organs and tissues hence improving oxygen delivery. Secondly there are peripheral adaptations at the muscular and cellular level resulting in better exercise efficiency and fuel utilisation. As described above the lactate threshold may rise or the point at which lactate begins to acumulate can certainly be improved [207, 208]. These peripheral adaptations are however complex and not completely understood. At a musculoskeletal level there is an increase in the size and density of mitochondria, an increase in oxidative enzyme activity, increases in myoglobin concentrations and increased capillaries in muscle. There also appears to be a change in the metabolic characteristics of muscle fibres with endurance training. Elite endurance athletes have a high proportion of type I muscle fibres which have a high mitochondrial density and enzyme capacity allowing most energy production to be derived from aerobic metabolism [209, 210]. Whilst training does not appear to change the muscle type (i.e. Type II to type I), it does make them metabolically more efficient [211, 212]. The culmination of these changes mean that the body is better able to produce energy via aerobic metabolism and to utilise and tolerate better the end products of anaerobic metabolism.

The exercise physiology of patients with comorbidities may not be so straightforward but does appear to be in keeping with the mechanisms described above. Studies in patients with chronic heart failure have

shown that low level exercise can improve exercise tolerance, not through improvements in central cardiac performance i.e. cardiac output and stroke volume but mainly through peripheral adaptations, with an increase in mitochondrial density and thus an improvement in oxidative capacity [213]. This is an important observation and is in keeping with other studies that suggest improvements in functional capacity with training are primarily dependent on peripheral changes [214, 215].

It is clear in healthy individuals that training improves central cardiac performance and thus the ability to deliver and utilise oxygen in exercising tissues as well as raising an individual's tolerance to academia, lactate accumulation and possibly their ability to utilise lactate more effectively. Fitter patients may also benefit from these advantages when undergoing surgery, but the picture is less straightforward. The balance of evidence suggests that artificially raising an individual's oxygen delivery by manipulation of central haemodynamics with fluids and positive inotropes to levels around 600 mls/min/m^2 decreases both mortality and morbidity in moderate and high risk surgical patients [216]. Whilst others have shown that it is the rate of lactate clearance that predicts survival and not the raising of oxygen delivery itself [217]. Indeed high levels of lactate and the inability to clear them have long been seen as bad prognostic markers in the critically ill, with lactate simply reflecting early energy failure and an imbalance between supply and demand [218]. Peripheral adaptations of the oxidative system have not been consistently proven with the artificial manipulation of central haemodynamics in perioperative care and it is likely the benefit from such short therapy, (1 –

12 hours) is through the prevention of organ under perfusion, but this remains a very controversial area.

Cardiopulmonary exercise testing is capable of identifying the anaerobic threshold of an individual at submaximal exercise and is strongly reliant on both the central cardiorespiratory performance i.e. oxygen delivery, as well as the peripheral cellular performance of that individual i.e. mitochondrial density and efficiency. The identification of the anaerobic threshold by cardiopulmonary exercise testing has been shown to be predicative of surgical outcome. Short-term intense exercise in the forearm is however likely to be much more reliant on the peripheral cellular performance than it is on the central cardiorespiratory performance. It is plausible therefore that identification of the anaerobic threshold or a surrogate thereof of a small muscle group in the forearm in a forearm exercise model may be equally predictive of surgical outcome as that identified by cardiopulmonary exercise testing, accepting the fact that it is more reliant on peripheral cellular performance.

1.3.1 Rhythmic isometric exercise (Cyclical)

Rhythmic or cyclical exercise implies a repetitive cycle of muscle contraction and release. Exercise can be both isometric and rhythmic. The forearm has been a popular organ to study due to its simplicity of access and it's supply from one predominant artery. Despite this, exact values of oxygen, acid base and lactate for exercising muscle are not always reported.

Soller et al looked at the influence of increasing maximal voluntary contraction on intramuscular and venous values of oxygen and acid base status of exercising muscle [179]. They used rhythmic isometric handgrip exercise at increasing levels of MVC with a 2s on and 1 second off pattern. They were able to demonstrate that intramuscular oxygen had reached close to 0 Kpa with maximal voluntary contractions of 30% and 45%, although it was clearly possible to demonstrate changes in both venous and intramuscular values from 15% of maximal voluntary contraction [179]. Interestingly they observed an approximately 50% reduction in venous PO_2 which began to plateau out as exercise continued but found intramuscular PO_2 continued to drop to near zero levels [179]. They also observed reduction in pH and elevations on PCO_2 as exercise progressed and that as the exercise intensity increased the separation between intramuscular and venous values increased, with intramuscular levels continuing to rise at a faster rate [179].

Sogol et al used increasing transmural pressure to mimic ischaemic conditions or a mismatch in the oxygen supply/demand balance using three different models of exercise that varied in maximal voluntary contraction, contraction patterns per minute and the pressure applied to the exterior of the forearm in a sealed tank to assess the effects of training on pressor responses [175]. They showed a positive effect of training by having to increase the level of transmural pressure applied to produce a similar but attenuated metabolic response including lactate and pH changes. They were not however able to demonstrate changes in venous oxygenation change with training [175].

There is an increase in blood flow following muscle contraction during the relaxation phase as local metabolites cause vasodilatation and for intermittent isometric exercise it is most likely that muscle oxygenation is maintained as oxygenated blood is returned to the exercising muscles [219].

1.3.2 Static isometric exercise (Isometric)

There are far fewer studies that report static handgrip exercise with concomitant measurement of muscle metabolites. Cui et al used lactate as a surrogate marker of cellular metabolites when trying to deduce the effect of muscle metabolites on mechanorecptor mediated muscle sympathetic activity. They used a static isometric exercise regime at 30% of MVC until fatigue, by sampling lactate from the antecubital vein they were able to show a significant increase in lactate above basal levels with venous lactate levels of 2- 3 mmol/L [220].

In an effort to understand the contribution of aging to metaboreceptor induced sympathetic response to hypoxia, Houssiere et al were able to demonstrate significant changes from baseline for lactate by using a regime of 30% MVC for 3 minutes, but do not report mean and standard deviations for the quantity of lactate released [221].

During isometric exercise there is a consequent rise in intramuscular pressure and a reduction in blood flow in the microcirculation because of vessel compression [222]. The compression leads to a rapid ejection of blood from these vessels and in turn restricts the arterial flow of blood to the exercising muscle [219]. Sustained isometric exercise (>30% maximal

voluntary contraction) is always accompanied by an increase in intramuscular pressure and consequently causes substantial and sustained ischaemia to the exercising muscle [223-225]. These observations suggest that sustained isometric exercise should create favourable conditions to stimulate anaerobic metabolism in the exercising forearm muscles and produce a proportionate metabolic response. The study by Katayama et al go some way to confirming this hypothesis [226]. They used a sustained and intermittent model of isometric exercise to look at the effects of hypoxia on muscle deoxygenation. They found as hypothesised that hypoxic conditions had no discernable effect on the sustained isometric model but did on the intermittent isometric model with respect to muscle deoxygentation, suggesting that sustained isometric forearm exercise produces more hypoxic conditions [226].

Both an intermittent and sustained isometric forearm exercise model will be taken forward as candidate models for forearm exercise to predict surgical outcome and will be the main theme of this thesis.

I would hypothesise that the isometric forearm exercise model is likely to produce a model with a greater stimulus to anaerobic metabolism and give a stronger and clearer signal. The cyclical model however may be more tolerable due to partial replenishment of the blood supply in the relaxation phase of it's cycling resulting in more work being done over time with the potential to produce a larger metabolic signal, which may be more useful in a patient population.

There is to my knowledge no study that has looked at the metabolic output i.e. the measurable venous products of metabolism; forearm

lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) of a standardised handgrip exercise model to predict surgical outcome.

Throughout this thesis the term metabolic output will refer to the measureable markers of anaerobic metabolism in venous blood i.e.; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) as measured by near infrared spectroscopy.

1.4 Hypothesis

Cells that are deprived of oxygen have to utilise anaerobic respiration to produce energy rich compounds capable of sustaining cellular function. Exercise above an individual's anaerobic threshold results in proportionally more anaerobic respiration and the production of end products of metabolism such as lactate, Hydrogen ions and CO_2.

There is a reasonable body of evidence to suggest that assessing an individuals anaerobic threshold through cardiopulmonary exercise testing may help in predicting surgical outcome and stratifying perioperative care and that handgrip dynamometry has been shown to be capable of predicting surgical outcome through grip strength determination.

This thesis will set out to explore a number of hypotheses:

1) There is a fundamental difference in the metabolic output i.e the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) between a rhythmic isometric (Cyclical) handgrip exercise model and a static isometric (Isometric) handgrip exercise model.

2) The metabolic output from exercising forearm muscle i.e the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) or cumulative markers thereof of a standardised handgrip exercise model will have a direct relationship to the anaerobic threshold in the same individual as measured by cardiopulmonary exercise testing.

3) The metabolic output from exercising forearm muscle i.e. the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) or cumulative markers thereof of a standardised handgrip exercise model will be able to identify those patients at risk of a poor surgical outcome and thereby allow it to be used as a preoperative test instead of cardiopulmonary exercise testing, or for those patients unable to perform a cardiopulmonary exercise test.

1.5 Plan of investigation

This thesis will firstly examine the practicality and metabolic response of two different standardised forearm exercise models to look at the impact of different exercise regimes (cyclical and isometric) on muscle and cellular function in healthy volunteers (Chapters 2,3 & 4).

The performance of each standardised forearm exercise model will then be benchmarked against formal cardiopulmonary exercise testing in the same group of healthy volunteers to identify a candidate standardised forearm exercise model and test endpoint (Chapter 5).

The standardised forearm exercise model will be prospectively trailed in a pilot cohort of orthopaedic patients undergoing joint replacement for its ability to predict postoperative outcome (Chapter 6).

Chapter 2: THE DEVELOPMENT OF A CYCLICAL HANDGRIP EXERCISE MODEL

2.0 INTRODUCTION

Exercising muscle uses oxygen to produce high-energy compounds such as ATP that help sustain muscular activity. Oxygen delivery to the exercising muscle is crucial in bringing enough oxygen to sustain aerobic respiration and the efficient production of large quantities of ATP for each molecule of glucose used. Most often physical performance is limited by the amount of oxygen that can be delivered per unit time, otherwise the muscles rely on inefficient anaerobic respiration to supply energy. This process cannot continue indefinitely and there is a large variation in the population in their ability to sustain aerobic respiration. Elite endurance athletes most commonly have high anaerobic thresholds which can be improved with training [196].

A forearm model has been used before to look at the expression of cytokines and muscle metabolism during exercise and is a useful model because it is easily accessible, amenable to blood sampling and simple to quantify work done or a force applied to it.

There are two principle methods of exercising the muscles of the forearm. The first is a sustained contraction, so called “Isometric exercise” and the second is cyclical or “repetitive isometric”. Each has a number of strengths and weaknesses as a model as outlined in Chapter 1.

The forearm model was chosen to explore further the relationship between oxygen utilisation, tissue oxygenation and metabolism in the exercising muscle. In Chapter 5 a comparison is made between isolated muscular exercise and whole body exercise with regards to oxygen utilisation.

This chapter will look at the development of a forearm exercise model based on a cyclical pattern of isometric work and rest and examine it's effect on local markers of aerobic and anaerobic metabolism.

2.1 Effects of venous occlusion

Effect of venous occlusion for cannulation on venous blood gas variables

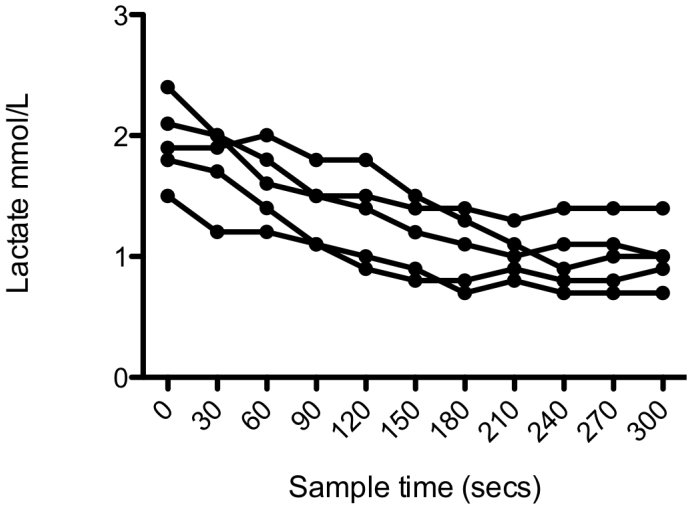
It is most probable that the venous occlusion required for cannulation of the antecubital fossa will have an effect on the metabolism of the forearm muscle secondary to venous blood stagnation and oxygen utilisation. 5 healthy volunteers were studied to determine the time required for venous blood gas variables to return to normal values after 60 seconds of venous occlusion. A tourniquet was applied to the upper arm to achieve venous occlusion during which a 20G cannula was inserted into the antecubital fossa of the same arm, to which a 3-way tap was connected. The tourniquet was released after a total of 60 seconds. Uncuffed sequential venous sampling was undertaken at 30-second intervals for 5 minutes thereafter via the cannula and analysed on a Radiometer series 700 for pH, PCO_2, PO_2, SO_2 and lactate. The dead space of the cannula was discarded prior to each sample being drawn and flushed with 5 mls of 0.9% saline after each sample was drawn.

2.1.1 Results

For the majority of subjects there was a return to steady state of the blood gas variables by 180 seconds. All of the subjects had returned to steady state (Less than 5% variability) by 210 seconds (see Figure 2.1).

To ensure the effects of venous occlusion did not influence the results, based on the observations in the healthy volunteers a period of 5 minutes was set between venous cannulation and the drawing of samples for baseline data.

Figure 2.1 Graph of forearm lactate decline to a steady state after venous cuffing for cannulation. Each line represents a single subject, with samples taken at 30 second intervals.



2.2 MATERIALS AND METHODS

2.2.1 Subjects

Healthy adult individuals were recruited by local advertisement. All subjects gave written informed consent to the study as had been previously agreed by the local research ethics committee of University College London Hospitals. All subjects were screened as healthy by questionnaire and medical examination by the study investigator prior to participating in the study.

2.2.2 Equipment

2.2.2.1 Near Infrared spectroscopy measurement of tissue oxygenation.

Near infrared spectroscopy (NIRS) uses fibre-optic light in the near infrared light spectrum to measure the percentage of oxygen saturation in haemoglobin and associated chromophores based on spectrophotmetric principles [227]. NIRS has been used successfully for many years to measure tissue oxygenation in human and animal muscle under static and exercising conditions with variable degrees of accuracy depending on methods used, site of measurement and size of probe used (a surrogate of tissue penetration)[225-239]. A new generation of NIRS machine was used to monitor tissue oxygenation saturation (STO_2), because of an increase in it's accuracy due to algorithm development [227]. The NIRS machine uses single depth attenuation measurements at 680, 720, 760 and 800 mm and uses second derivative spectroscopy to reduce light scattering effects. It differs predominantly from previous methods by

using a wide 40 mm wavelength gap to improve sensitivity to oxyhaemoglobin [227]. NIRS measures arterial and venous oxyhaemoglobin at the microcirculatory level and is a reflection of both oxygen delivery and oxygen consumption [240, 241]. The light emitted from a probe attached to the surface of the skin is reflected back from the tissues that underlie it to give an average of absorbance which is recorded by the machine to give an indication of the ration of oxygenated and deoxygenated blood.

Near infrared spectroscopy was used to measure tissue oxygen saturation in the exercising forearm muscle using an Inspectra™ Tissue spectrometer model 325. The Inspectra™ was attached to a computer running Inspectra™ software version 2.0 via an Inspectra™ Optolink™ RS232 Optical converter. This provided real time acquisition of data at 3-second intervals, which was stored on the computer for later analysis. Prior to each experiment the Inspectra™ was calibrated using the Inspectra™ calibrator and checked using the Inspectra™ system check for high and low point calibration checks. A self-adhesive foam pad used to house the 15 mm probe of the Inspectra™ was placed on the belly of the exercising forearm muscle prior to any exercise for 5 minutes to allow stabilisation of the signal.

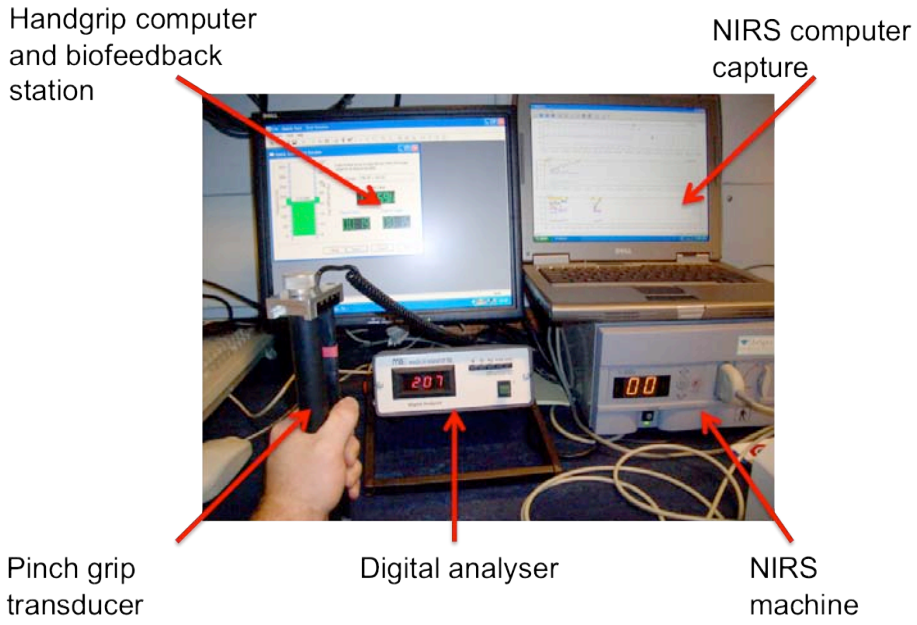
2.2.2.2 Handgrip dynamometry setup

An alloy pinch grip transducer (MIE medical research Ltd, Leeds, UK) was attached to a digital analyser (MIE medical research Ltd, Leeds, UK), which in turn was connected to computer running WINCAS software (MIE medical research Ltd, Leeds, UK) (see Appendix for software screen

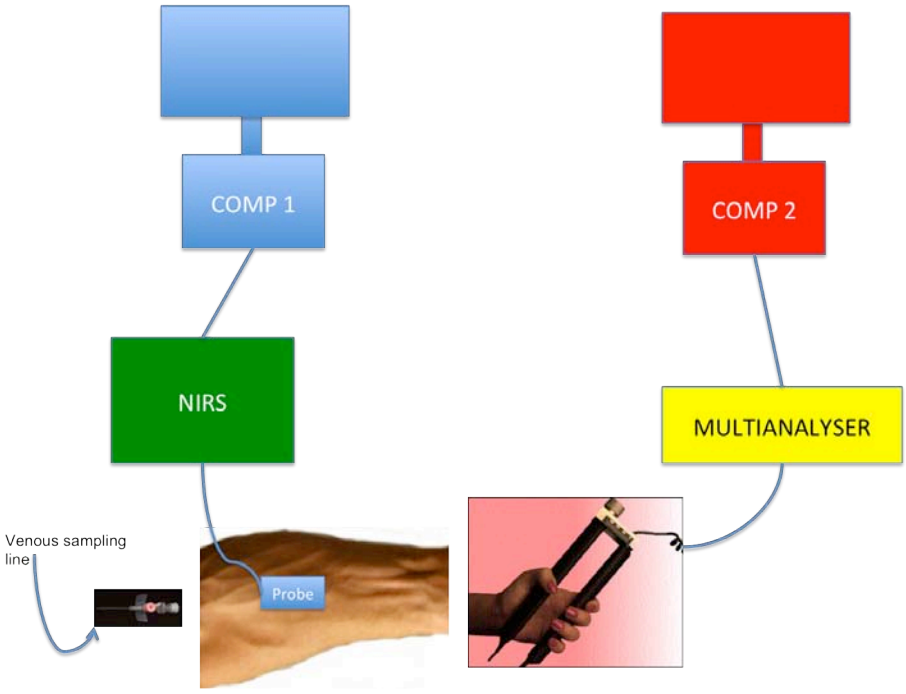
shots). The computer stored real time analogue data for the duration of the experiment for later analysis. In addition to data storage the WINCAS software provides a visual and audible feedback system to the subject. The width of the prongs on the pinch grip analyser was adjusted to the individual's hand size as per manufacturer's instructions. The pinch grip transducer was factory calibrated before testing and as per manufacturer's guidelines and only needs calibrating at 12 monthly intervals thereafter. The pinch grip apparatus was software calibrated before each individual experiment. Subjects were instructed to grip the transducer below the red marks, ensuring accurate force transduction. If necessary the subject's position was adjusted to keep the forearm parallel to the desk on which it rested and the transducer held in an upright position to ensure each subject used the same muscle groups - see Figures 2.2 a) & b).

Figure 2.2 a) Photograph of apparatus set-up. b) Schematic representation of total setup including near infrared spectroscopy (NIRS) probe on exercising forearm muscle group.

a)



b)



2.2.3 Protocol

Each subject had their maximal voluntary contraction established by taking the highest value from 3 maximal force exertions prior to cannulation or exercise and were allowed to rest for 10 minutes. A 20G indwelling intravenous cannula was inserted into the non-dominant forearm of the subject. The non-dominant arm was used because there is some evidence to suggest a reduced grip strength compared to the dominant arm and the muscles may not be as aerobically conditioned as the dominant arm, which may produce a more pronounced metabolic response [152]. A 3-way tap was attached and flushed with 5mls of 0.9% saline. Samples where then withdrawn at specified time intervals by first aspirating the dead space of the 3-way tap without any cuff occlusion and then aspirating into a blood gas syringe. A minimum of 5 minutes was given before the first sample was withdrawn to negate any effects of venous cuffing on muscle metabolism of oxygen use.

For cyclical exercise the subjects were asked to exert a maximal voluntary contraction (MVC) for 2 seconds then to relax for 3 seconds. This cycle was repeated for 300 seconds i.e. 60 cycles, followed by 300 seconds of rest before the final measurements were taken. Audible metronomic instructions were given by the computer to “squeeze” and “relax” coupled with visual strain gauges prompting the subjects when to squeeze and when to relax (see Figure 2.2).

Subjects were asked to rate the intensity of the exercise using the Borg scale, which is an asymmetric scale starting from 0 through to 20 (See Table 2.1)[242].

Table 2.1 Borg Scale rating- Subjective assessment of the intensity of exercise by subject.

Scale	Effort
6	20% effort
7	30% effort - Very, very light (Rest)
8	40% effort
9	50% effort - Very light - gentle walking
10	55% effort
11	60% effort - Fairly light
12	65% effort
13	70% effort - Somewhat hard - steady pace
14	75% effort
15	80% effort - Hard
16	85% effort
17	90% effort - Very hard
18	95% effort
19	100% effort - Very, very hard
20	Exhaustion

During exercise and the rest period venous samples were taken from the indwelling venous catheter at fixed time points of 0,60,120,180,300 and 600 seconds. Each time the dead space of the cannula was discarded and then flushed with 5mls of 0.9% saline after the sample had been withdrawn into a blood gas syringe. The samples were analysed immediately on a Radiometer 7200 blood gas analyser, which has excellent precision with 0.1% variability between sample measurements.

2.2.4 Statistical analysis

All analyses were done using Graphpad Prism 5 for Macintosh (Graphpad software, San Diego, California). All data are expressed as means (± standard deviation) where normally distributed unless otherwise stated. Statistical significance was set at $p<0.05$.

The study was powered on the assumption that a significant ($P<0.05$, double sided testing) correlation coefficient >=0.6 between anaerobic threshold and lactate production would require >=10 subjects.

2.3 RESULTS

2.3.1 Demographics

Ten subjects were enrolled into the study all of which completed the protocol in full. Eight of these subjects were male and two were female. They had a median age of 34 (28.5-36.5) years, a median height of 184 (175.5-187.25) cm, a median weight of 86 (70.25-88.5) Kg and a median exercise time per week of 195 (0-420) minutes, (see Table 2.2), with 3 subjects taking no exercise each week.

Table 2.2 Healthy volunteer demographics

Subject	Sex	Height	Weight	Age	Exercise time per week
1	M	182	86	24	420
2	M	179	100	36	100
3	M	179	71	35	0
4	M	188	88	40	180
5	M	196	90	32	420
6	F	165	68	20	420
7	M	186	78	38	420
8	M	186	87	34	210
9	F	160	47	30	0
10	M	187	86	34	0

Exercise time per week=Regular exercise undertaken per week in minutes, M=Male, F=Female
Height=cms, Weight=Kgs, Age=years, Exercise time per week=minutes

2.3.2 Handgrip dynamometry

The performance data from handgrip dynamometry shows a large range of strength and work done with a mean maximum strength value of 213.2 (± 68.17) N and mean work done of 28678 (± 8742) Ns (Table 2.3), but

relatively little variation in the Borg rating assigned by subjects with a mean rating of 13(± 1.25)(Table 2.3). There was no significant relationship between the Borg scale rating and the work done (r^2=0.05, p=0.52).

Table 2.3 Individual handgrip dynamometry values for all subjects and Borg rating

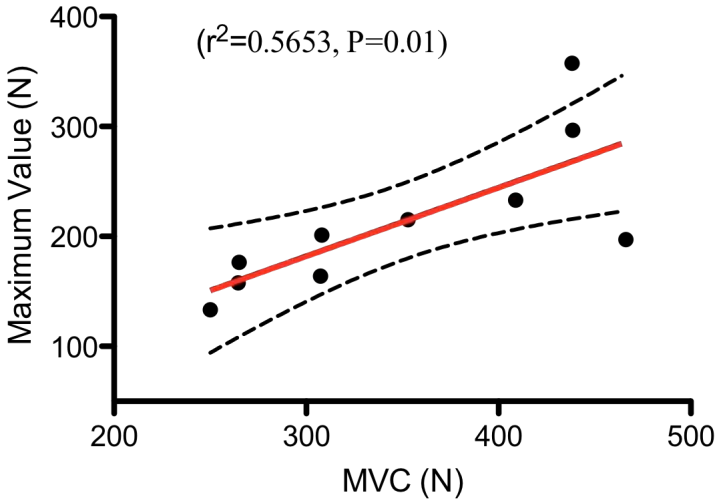
Subject	Max value (N)	Fatigue rate	Work done (Ns)	Borg rating
1	215.29	24.61	43627.84	13
2	296.57	59.79	29321.94	12
3	133.15	9.05	22361.13	12
4	201.23	46.83	35701.16	11
5	197.2	56.87	32785.22	13
6	157.82	35.47	15921.33	14
7	357.53	111.95	35228.88	14
8	164	37.03	28977.22	15
9	176.39	40.43	16580.47	14
10	232.94	65.58	26277.11	12

Max value=N, Fatigue rate=the average of the curve between max value and end of contraction, Work done=Ns, Borg rating=subjective assessment of exercise intensity-see Table 2.x

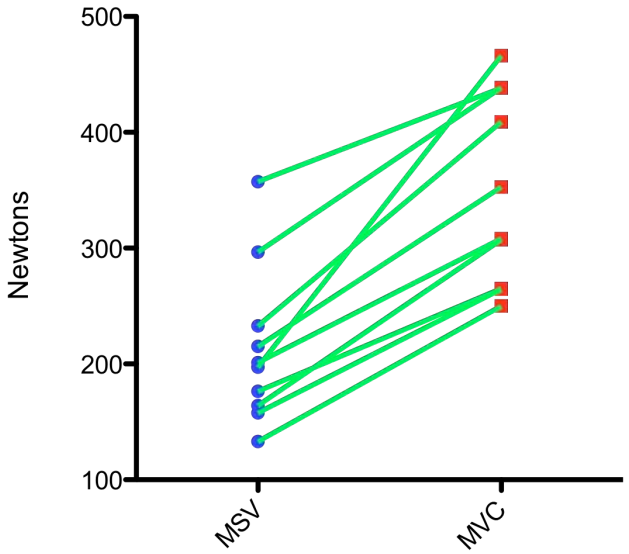
There was however a significant relationship between the maximum voluntary contraction of each subject and the maximum value they obtained during the cyclical exercise testing-see Figure 2.3 a). The maximum strength value achieved in the test was significantly lower than maximal voluntary contraction (MVC 350 ± 82.14 vs. MSV 218.32 ± 68.17, p = 0.0007). Each individual however had a higher maximal voluntary contraction than they did a maximal strength value-see Figure 2.3 b).

Figure 2.3 a) Linear regression plot of maximum value obtained during exercise and maximum voluntary contraction as tested prior to protocol commencement. b) Before and after plot of maximal strength value and corresponding maximal voluntary contraction for each individual

a)



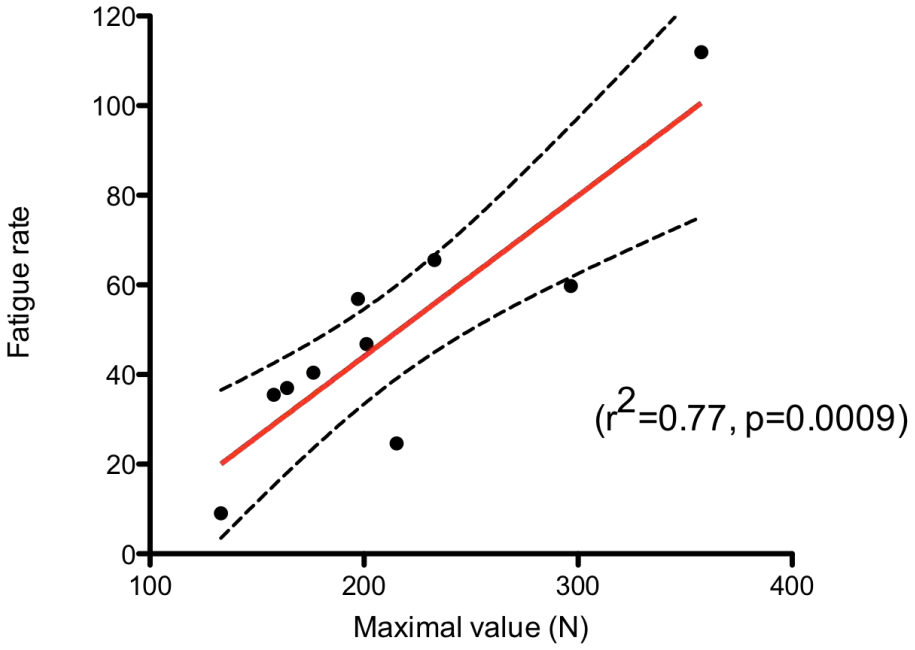
b)



MSV = Maximal Strength Value, MVC = Maximal Voluntary Contraction

The fatigue rate is a marker of reduction in strength over the course of the exercise, but again showed wide variation with a mean of 48.76 (± 27.91) and no significant relationship to work done (r^2=0.06, p=0.48). In addition the maximum grip strength achieved showed no clear relationship to total work done (r^2=0.21, p=0.18). There was however, a significant association with maximum strength achieved and the fatigue rate (r^2=0.77, p=0.0009) showing subjects with high maximum strength values fatiguing quicker (see Figure 2.4).

Figure 2.4 Relationship of fatigue rate and maximum strength achieved.



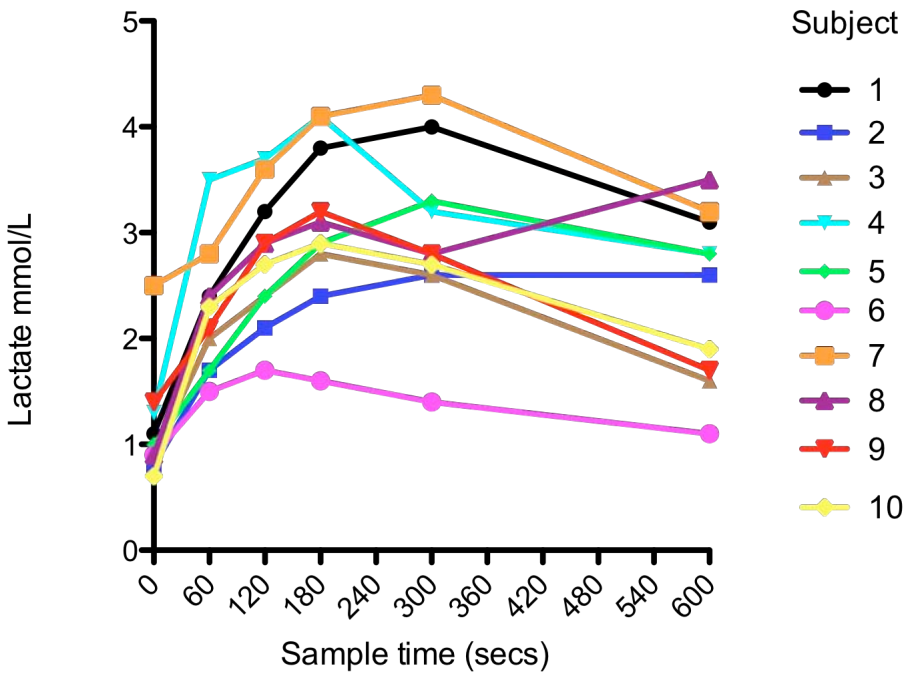
2.3.3 Metabolic performance

2.3.3.1 Fixed time sampling points

A graphical representation of the forearm lactate response to cyclical forearm exercise is shown in Figure 2.5.

The graph illustrates that for the majority of subjects forearm lactate values were falling by the termination of the test. For subject 2 there was no change in forearm lactate between sample times at 300 and 600 seconds, for subject 8 there was a paradoxical rise in forearm lactate from 300 to 600 seconds. All subjects had ceased exercise and were in a resting state by 300 seconds.

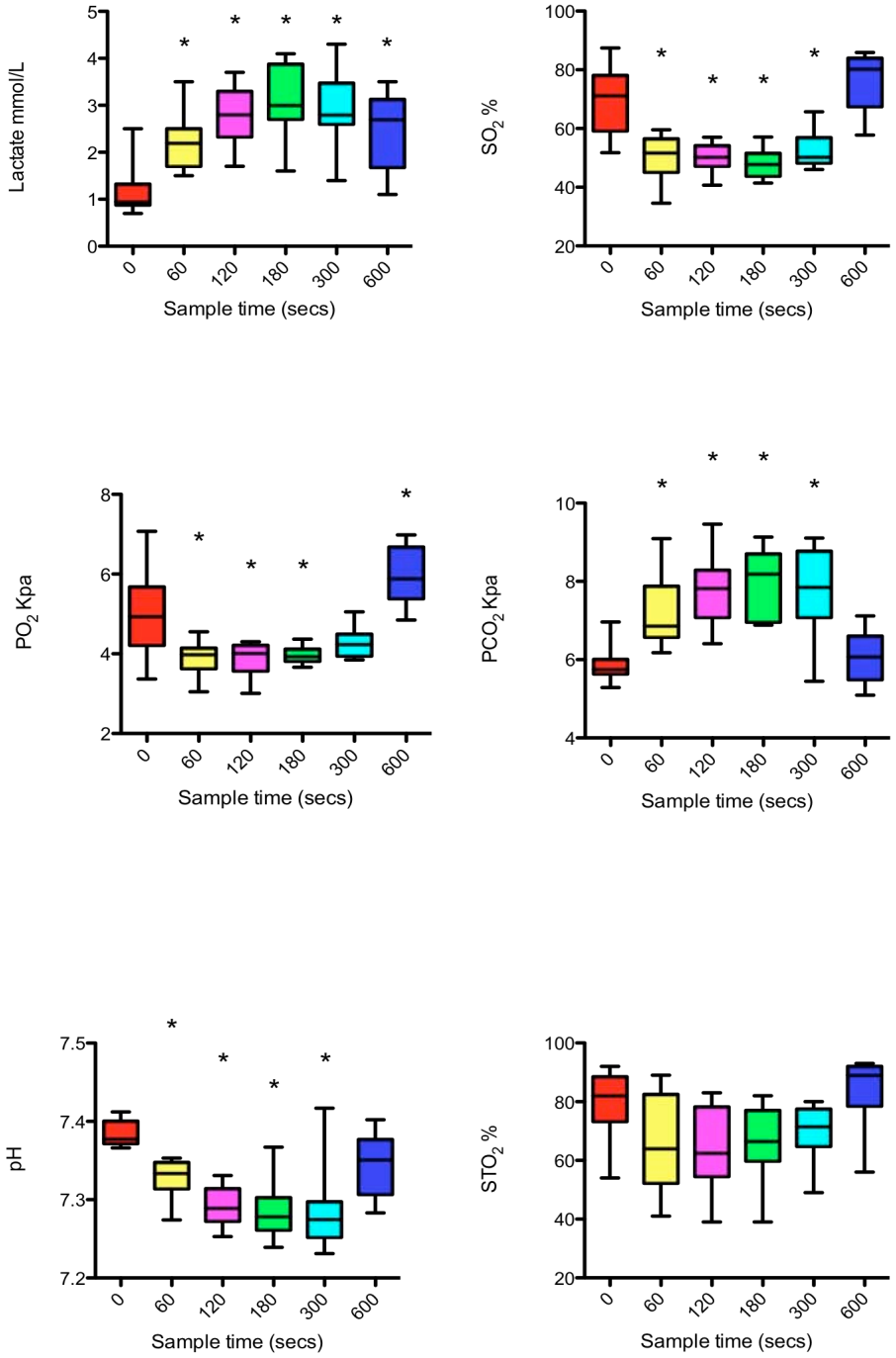
Figure 2.5 Forearm lactate curves for each subject, showing sampling points at 0,60,120,180,300 and 600 seconds.



Box and whisker summary plots of all subjects for forearm lactate, SO_2, PO_2, PCO_2, pH and STO_2 are shown in Figure 2.6

There were significant changes from baseline (time 0) for all measured blood gas variables (Forearm lactate, SO_2, PO_2, PCO_2, pH) but not for tissue oxygenation (STO_2). Only forearm lactate showed significant changes at all time points when compared to baseline. Forearm lactate and PO_2 values were significantly higher than baseline by the termination of sampling. The SO_2, pH and PCO_2 variables had returned to near baseline values by the last sampling time of 600 seconds.

Figure 2.6 Box and whisker plots of metabolic markers of metabolism plotted over 6 discrete sampling times for all 10 subjects.



*=Significant results showing deviation from baseline (0 seconds), one way ANOVA, $p<0.05$

2.3.3.2 Summary measures of metabolic performance

Markers of the performance of the model were evaluated through the static, dynamic and cumulative summary endpoints. Chapter 2: Appendix shows detailed calculations and explanations for all endpoints. The pH variables were transcribed into their equivalent $[H^+]$ for ease of computational analysis.

Performance summary measures for forearm lactate and CO_2 showed the most significant association with work done (see Tables 2.4 & 2.5 and Figures 2.7 & 2.8 respectively). Baseline levels showed no significant association with work done except for STO_2 (r^2=0.45, p=0.03)-see Figure 2.9 b). For CO_2 all performance endpoints were significant. For forearm lactate all expect (Lactate peak % change over baseline) were significant. Significance was just reached for hydrogen ion performance summary measures with ($[H]^+$ cumulative-baseline) (r^2=0.4, p=0.049)-see Figure 2.9 a).

All other performance measure summaries showed no significant association with work done and are shown in tabular form in Chapter 2: Appendix for completeness.

Table 2.4 Forearm lactate – Linear regression vs. Work done

Lactate	n=10		r^2	P value	
Lactate baseline	median(IQR)	0.95(0.875-1.325)	0.0727	0.4512	ns
Lactate peak	mean(SD)	3.24(0.7891)	0.5973	0.0088	*
Lactate peak-baseline	mean(SD)	2.09(0.6173)	0.5781	0.0107	*
Lactate peak % change over baseline	mean(SD)	203.8(82.05)	0.1296	0.3069	ns
Lactate cumulative	mean(SD)	1602(398.9)	0.6951	0.0027	*
Lactate cumulative - baseline	mean(SD)	912(315)	0.6212	0.0068	*
Lactate cumulative/sec	mean(SD)	2.67(0.6649)	0.6951	0.0027	*

* = Significant result ($p<0.05$), IQR=Interquartile range, SD=standard deviation

Figure 2.7 Significant linear regression plots Forearm lactate vs. Work done: a) Peak, b) Peak-Baseline, c) Cumulative, d) Cumulative-baseline, e) Cumulative/Second

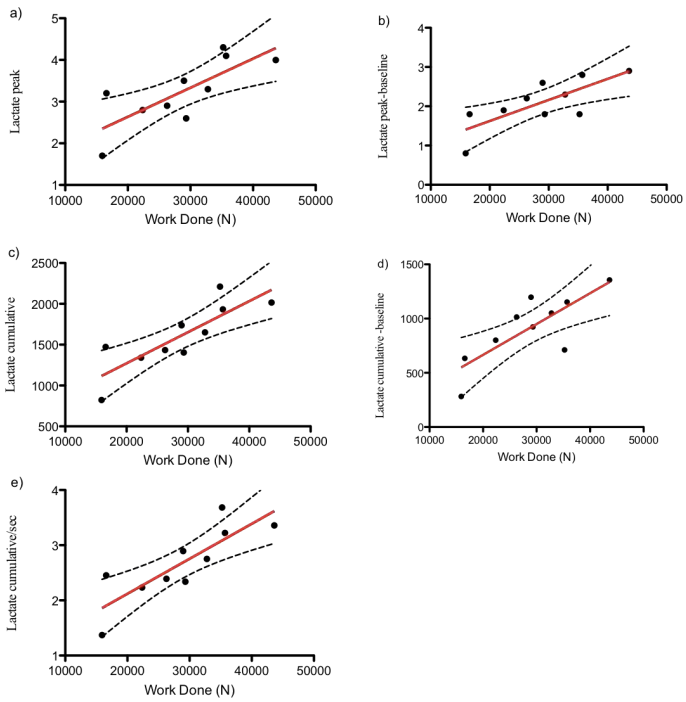


Table 2.5 CO_2 – Linear regression vs. Work done

CO_2	n=10		r^2	P value	
CO_2 baseline	median(IQR)	5.75(5.63-6.005)	0.1018	0.3688	ns
CO_2 peak	mean(SD)	8.244(0.8187)	0.7136	0.0021	*
CO_2 peak - baseline	mean(SD)	2.378(0.5724)	0.918	< 0.0001	*
CO_2 peak % change over baseline	mean(SD)	40.55(9.62)	0.8107	0.0004	*
CO_2 cumulative	mean(SD)	931.2(316.8)	0.624	0.0066	*
CO_2 cumulative - baseline	mean(SD)	810.5(301.9)	0.5101	0.0203	*
CO_2 cumulative/sec	mean(SD)	7.217(0.7437)	0.4566	0.032	*

* = Significant result (p<0.05), IQR=Interquartile range, SD=standard deviation

Figure 2.8 Significant linear regression plots CO_2 vs. Work done: a) Peak, b) Peak-Baseline, c) Peak % change over baseline, d) Cumulative, e) Cumulative-baseline, f) Cumulative/Second

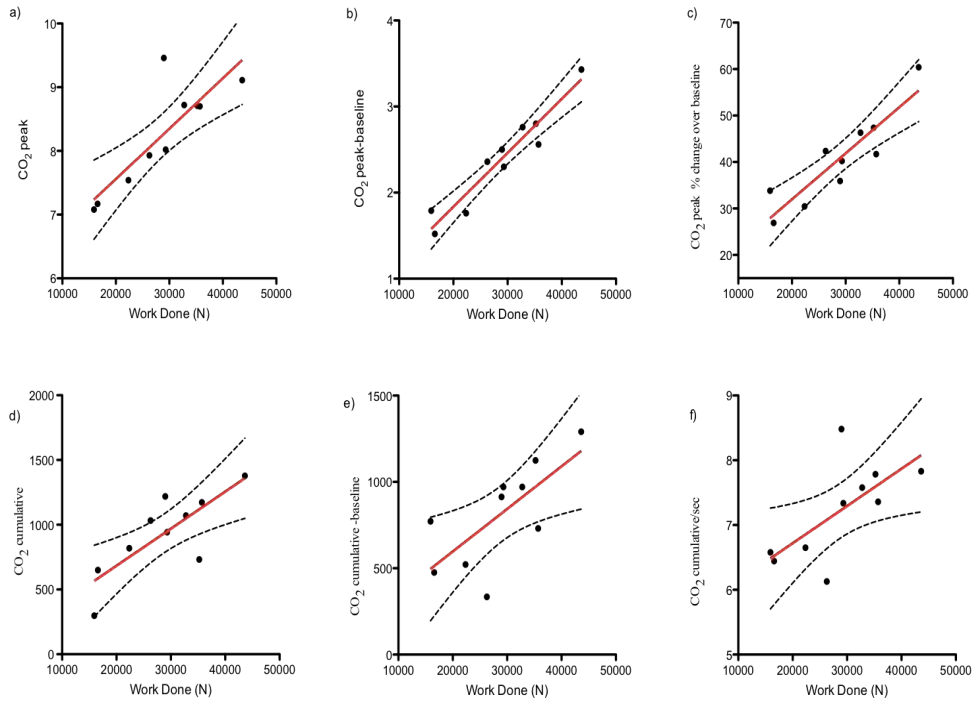
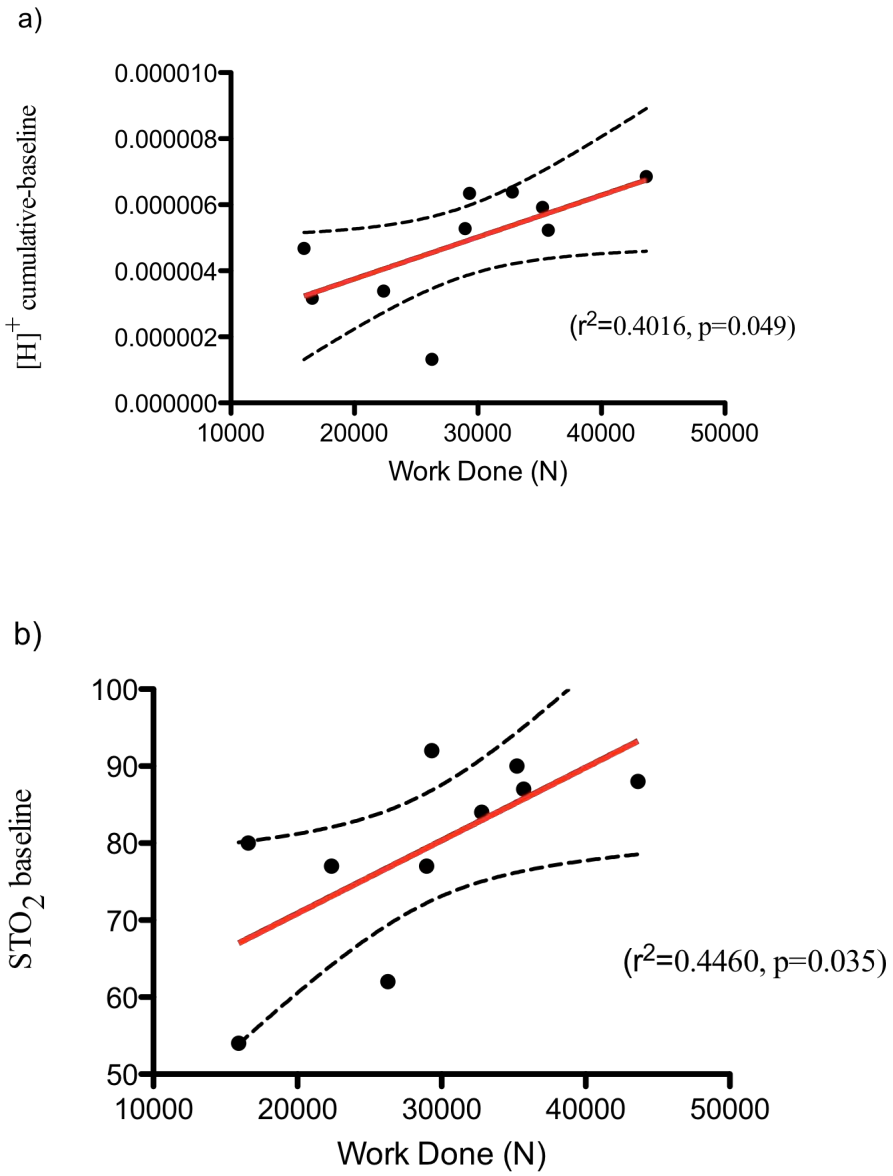


Figure 2.9 Significant linear regression plots of a) [H^+] cumulative-baseline, b) STO_2 baseline



2.4 DISCUSSION

The main aims of this study were to test a) if a cyclical approach to forearm exercise was practical and possible and b) if a proportionate biological response could be achieved that would clearly differentiate subjects.

As a bedside test it was clearly practical with all subjects managing to complete the testing. There were however a number of calibration issues and computer interface problems with the near infrared spectroscopy equipment that caused delay in testing for 3 of the subjects. These were easy to overcome and did not affect the overall result, but could be an issue in a busy ward setting if taken forward as a bedside test, but would present less of a problem in an outpatient setting such as a preoperative assessment clinic. There were also a number of adhesion issues of the near infrared spectroscopy probe to the skin which was resolved with additional adhesive tape to ensure no ambient light entry.

The test produced a clear biological response for all measured blood gas variables over time but not for near infrared spectroscopy. There was a wide range of values for STO_2 amongst individuals and relatively little difference between baseline and nadir values, which brings into question its ability and sensitivity to track changes in tissue oxygenation in this model. There are however a number of confounding aspects of the technique which may account for this. Firstly the degree of subcutaneous fat the light has to travel through will affect the depth the readings are taken from and it is likely that this was different across the individual

subjects. In addition although the emitted light frequencies are designed to detect oxy and deoxy haemoglobin the other structures such as bone, fat and skin all contribute to a variability that cannot be accounted for in such a fixed device. It also has to be remembered that NIRS gives an average of the readings and at any single time point there will be a balance of arterial and venous blood as well as tissue that will contribute to the readings at any given point. One would expect the consumption of oxygen and ATP (not measured in this model) to exhibit significant falls in measures of oxygen content [179]. There were indeed falls in both PO_2 and SO_2, which reflect the consumption of oxygen by exercising muscles. If the rate of supply of oxygen to the exercising muscle is sufficient to maintain aerobic metabolism, there should in theory be little change in these values. It is clear however that the muscles were using a mixture of aerobic and anaerobic metabolism as evidenced by the significant amounts of forearm lactate being produced during exercise. Lactate is predominantly an end intermediary of anaerobic respiration, with glucose being converted first to pyruvate with the liberation of 2 molecules of ATP and then to lactate. Hence it is reasonable to assume that near infrared spectroscopy lacked the sensitivity to track these changes in tissue oxygenation. Chudalla et al however provide a different explanation and suggest there is no relationship between PO_2 and venous lactate release in a forearm exercise model [243]. Furthermore they suggest that sympathetic stimulation as evidenced by epinephrine release also has no effect on lactate release [243].

Blood sampling form the 20G cannula inserted into the antecubital fossa represents sampling of blood from the deep forearm veins which drain blood almost exclusively from the forearm muscle both at rest [244, 245] and during exercise [246] but it is impossible to prove that in our model.

The forearm lactate levels at the termination of exercise were still significantly higher than those at the beginning of testing, as were the PO_2 values. It is most probable that this reflects ongoing anaerobic metabolism and release of lactate in the now resting muscle and reactive hyperaemia as blood flow is increased due to end products of metabolism causing local vasodilatation. We did not measure flow in our model but others have looked extensively at flow mediated brachial artery dilatation after forearm ischaemia and shown reactive hyperaemia to be a true phenomenon [220].

Because the test was based on fixed time point blood sampling a set of summary measures of the test were calculated to allow comparison of the overall output of the model amongst individuals. It is a potential weakness of this model and having the ability to sample the venous end products of metabolism continuously would have been advantageous and is being looked at in future work.

The subject group itself despite being predominantly male was reasonably well matched for age, weight and height but differed considerably in their routine exercise regime per week with 30% of subjects taking no regular exercise. Regular exercise has a considerable positive effect on cardiovascular and endothelial function and may have bearing on the performance during the forearm exercise, but our study

numbers were too small to be able to clearly discern that. Chapter 5 does however look at the anaerobic performance of each individual.

Despite that fact that there was a wide range of maximum strength and work done across the group the subjective rating of the intensity of the exercise using the Borg scale failed to reflect that. The scale is a 15 point scale designed in an asymmetric way (scores 6 – 20) to reduce the chance of bias [242]. It has been shown in athletes to correlate with their perceived rate of exertion and physiological variables such as heart rate, lactate levels and oxygen consumption [247], but there are known inconsistencies with it's use [247] and does not appear to be valid in discriminating exercise quantity in this model.

Due to the prolonged nature of the test it is not surprising that the maximal strength value achieved in the test was significantly less than the maximal voluntary contraction achieved in one off testing, as individuals switch psychologically to endurance rather than short term intensity. The Borg rating as already stated is clearly not useful to standardise the effort each individual puts into the test and it does not have the sensitivity to discriminate. For any exercise test it is important to be able to standardise the test so as to be able to apply it to a larger population. Using a maximal voluntary contraction to do this is well documented in the literature [179, 243, 248, 249]. In our study there is a clear relationship between MSV and MVC in that MVC is higher than MSV for all subjects. However the difference between MVC an MSV is not consistent with some subjects increasing their MVC by 2-3 times whilst others only increase by 20-30%. The impact of psychology on exercise performance is well known and is

difficult to control for during experimentation. All subjects however were given the same verbal and visual feedback and encouraged by me to work as hard as possible throughout the experiment. This has to be acknowledged as a potential weakness of this exercise regime.

The endurance capacity of each individual is clearly different as evidenced by their being no clear relationship between the MSV and work done. The test itself is a combination of grip strength and the ability to apply that overtime (endurance). Those subjects with higher grip strengths did fatigue earlier, reflecting their inability to maintain high intensity over time.

The forearm lactate curves for each subject as shown in Figure 2.5 show a relatively homogenous response with all subjects increasing their forearm lactate production over time and with the exception of subject 8, all showed a fall in forearm lactate in the resting period. The fact that the response was homogenous is good in that it suggests the input to the test is capable of eliciting a definable response, but less useful in that it does not clearly discriminate between individuals. For a test like this to be useful it must be able to separate individuals. It is possible that our subjects are too similar and the test simply reflects their homogeneity. It is interesting to speculate what the results would have been if I had repeated the experimental design in a group of elderly patients with multiple comorbidities in whom I am sure the I would have found more heterogeneity. This thesis did not examine that elderly population with this model and is a weakness that will be addressed in future work.

2.5 Conclusion

As a potential bedside test the model performed well. The setup of the test and the instructions given to subjects were easy to follow and no subject failed to finish the test. Fixed time point sampling was easy to achieve and to concurrently analyse.

It was easy to measure the input to the test in terms of the forces applied which were significantly and not surprisingly less than a one off test of strength (the maximal voluntary contraction), but made the test more difficult to standardise. There was also a wide variability amongst individuals in terms of grip strength and work done.

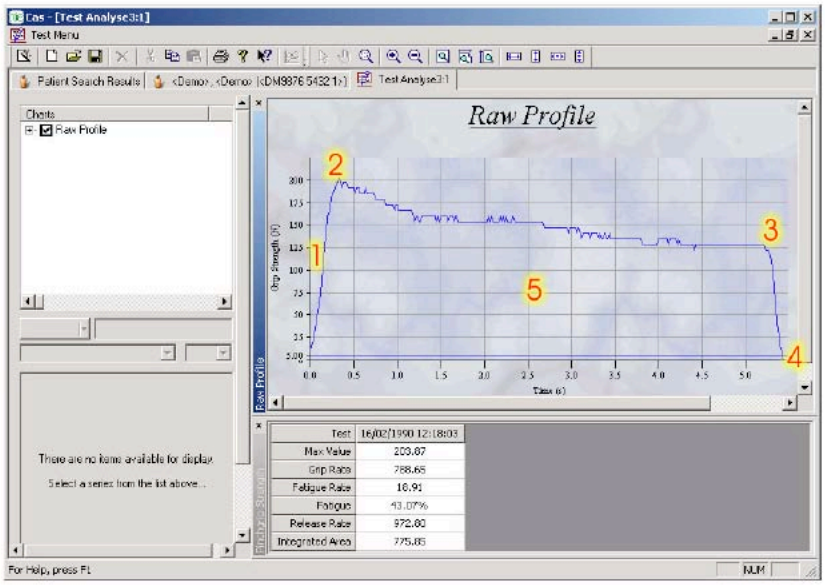
The test was equally successful in stimulating anaerobic metabolism with clear rises in lactate and falls in PO_2 and SO_2. It was clearly capable of producing well defined endpoints throughout the test that were significantly different from baseline for all variables for the majority of sampling points except for tissue oxygenation (STO_2). The continuous nature of STO_2 measurement was hoped to have given more time specific information but it's variability between subjects was too high, probably as a result of diference with subcytaneous tissue depth and differences in tissue structure below the probe.

It was also encouraging that the work done during the test was correlated to a number of markers of muscle metabolism seeing increasing amounts of lactate and PCO_2 as the workload increased.

2.6 Chapter 2 appendix

Isometric test example of dynamometer graph screen shot

Example of typical strength graph after single grip application and associated calculations (reproduced with permission from WINCAS manual MIE medical research Ltd)



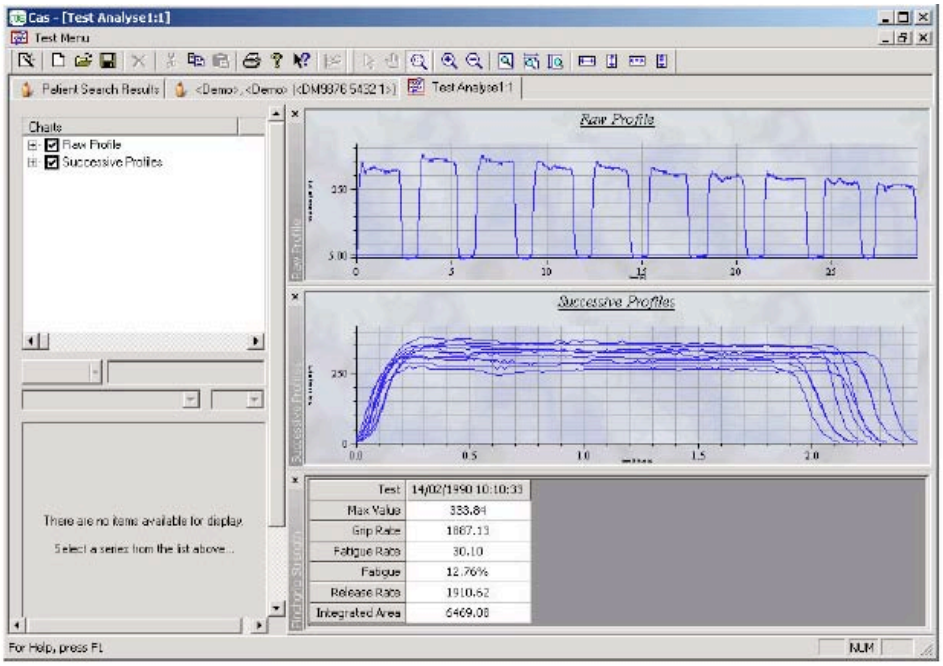
Below the graph is a table indicating the following parameters:

Maximum Value:	This is the peak force or moment achieved during the test (2)
Grip Rate:	The average value of the slope (1) excluding the first and last 10% of the curve. This value changes depending on joint pain and spacticity.
Fatigue Rate:	The average of the curve between the maximum value (2) and the end value (3). Fatigue rate should always be greater than zero if maximum contraction has been achieved. A flat curve would indicate either pain limitation or cheating.
Fatigue:	The drop in maximum grip (2-3) over the maximum grip (3) expressed as a percentage.
Release Rate:	The average value of the slope (3 to 4) excluding the first and last 10 percent of the curve. This value changes depending on joint stiffness and spacticity.
Integrated Area:	This is the total area under the curve (5), which is the measure of the work done.

Cyclical test example of dynamometer graph screen shot

Example a typical repeated (cyclical) strength endurance test

(reproduced with permission from WINCAS manual MIE medical research Ltd)



Calculations and definitions for summary test endpoints

1) Baseline
    a. The value at 0 seconds
2) Peak
    a. The highest recorded value during the test
3) Peak-baseline
    a. The highest recorded value during the test minus the value at 0 seconds
4) Peak % change over baseline
    a. (The peak or nadir value minus the baseline value) divided by the baseline value and multiplied by 100.
5) Cumulative
    a. The area under the curve for sampling points 0 to 600
6) Cumulative-baseline
    a. The area under the curve for sampling points 0 to 600 minus (the baseline value multiplied by 600)
7) Cumulative/sec
    a. The area under the curve for sampling points 0 to 600 divided by 600

Summary performance measures

Summary statistics and linear regression results for summary test endpoint variables vs. Work done, illustrated in full for completeness.

Hydrogen ion concentration

[H]+	n=10		r^2	P value	
$[H]^+$ baseline	mean(SD)	0.00000004124 (1.616E-09)	0.0421	0.5696	ns
$[H]^+$ peak	median(IQR)	0.00000005795 (5.228E-08-5.677E-08)	0.01164	0.7668	ns
$[H]^+$ peak-baseline	median(IQR)	0.00000001241 (9.862E-09-1.661E-08)	0.007292	0.8146	ns
$[H]^+$ peak % change over baseline	median(IQR)	29(23.25-41.36)	0.005708	0.8357	ns
$[H]^+$ cumulative	median(IQR)	0.0000303 (0.00002848-0.00003108)	0.1973	0.1984	ns
$[H]^+$ cumulative-baseline	mean(SD)	0.000004856 (0.00000175)	0.4016	0.0492	*
$[H]^+$ cumulative/sec	mean(SD)	0.00000004933 (3.414E-09)	0.1973	0.1984	ns

Partial pressure of oxygen (kPa) in venous blood

PO_2	n=10		r^2	P value	
PO_2 baseline	mean(SD)	4.986(1.072)	0.0004927	0.9515	ns
PO_2 nadir	mean(SD)	3.738(0.4258)	0.07618	0.4402	ns
PO_2 nadir-baseline	mean(SD)	-1.248(0.9714)	0.01044	0.7788	ns
PO_2 peak % change over baseline	mean(SD)	-22.85(13.21)	0.07289	0.4506	ns
PO_2 cumulative	mean(SD)	1290(103.3)	0.003925	0.8635	ns
PO_2 cumulative-baseline	mean(SD)	-1702(555)	0.0001976	0.9693	ns
PO_2 /sec	mean(SD)	2.149(0.1721)	0.003925	0.8635	ns

Dynamometer derived variables

Dynamometer	n=10		r^2	P value	
Maximum strength value (N)	mean(SD)	213.2(68.17)	0.2131	0.1793	ns
Fatigue rate	mean(SD)	48.76(27.91)	0.06434	0.4795	ns
Borg rating	mean(SD)	13(1.247)	0.05822	0.5019	ns

Saturation of oxygen (%) in venous blood

SO_2	n=10		r^2	P value	
SO_2 baseline	mean(SD)	69.15(11.33)	0.01422	0.7428	ns
SO_2 nadir	mean(SD)	46.58(6.236)	0.1405	0.2859	ns
SO_2-baseline	median(IQR)	-21.4(-27.08-(-16.6))	0.01695	0.72	ns
SO_2 peak % change over baseline	mean(SD)	-32.1(6.137)	0.03934	0.5828	ns
SO_2 cumulative	mean(SD)	16425(1621)	0.06475	0.478	ns
SO_2 cumulative -baseline	mean(SD)	-25065(5462)	0.00532	0.8413	ns
SO_2/sec	mean(SD)	27.37(2.702)	0.06475	0.478	ns

Near infrared spectroscopy derived summary test performance variables.

STO_2	n=10		r^2	P value	
STO_2 baseline	mean(SD)	79.1(12.4)	0.446	0.0348	*
STO_2 nadir	mean(SD)	56(15.28)	0.008362	0.8016	ns
STO_2 nadir-baseline	mean(SD)	-23.1(15.29)	0.2026	0.1917	ns
STO_2 peak % change over baseline	mean(SD)	-28.56(17.94)	0.1064	0.3577	ns
STO_2 cumulative	mean(SD)	20847(3479)	0.1825	0.2182	ns
STO_2 cumulative-baseline	mean(SD)	720.1(559.7)	0.01231	0.7603	ns
STO_2 /sec	mean(SD)	79.32(8.196)	0.04714	0.5468	ns
NIRS STO_2 slope	mean(SD)	33.63(35.91)	0.05549	0.5124	ns
NIRS THI average	mean(SD)	11.24(2.382)	0.2929	0.1062	ns
NIRS $V0_2$	mean(SD)	355(344.8)	0.009359	0.7903	ns

Chapter 3 - The development of a isometric handgrip exercise model

3.0 INTRODUCTION

In chapter 2 I demonstrated that the using a handgrip exercise model based on cyclical (intermittent) isometric exercise was practical to perform, stimulated anaerobic metabolism and that the endpoints of the test the measurable venous products of muscle respiration i.e. lactate and PCO_2 correlated well with work done by the model.

There are fundamental differences however between isometric (resistance) and cyclical (rhythmic) exercise. This chapter will aim to evaluate the use of an isometric exercise strategy to produce a standardised forearm handgrip exercise model.

The overall setup and use of equipment is similar between the two forearm exercise models and has been described already in Chapter 2. Where there are significant differences these will be highlighted in the method section.

3.1 MATERIALS AND METHODS

3.1.1 Subjects

Healthy adult individuals were recruited by local advertisement. All subjects gave written informed consent to the study as had been previously agreed by the local research ethics committee of University College London Hospitals. All subjects were screened as healthy by questionnaire and medical examination by the study investigator prior to participating in the study.

3.1.2 Equipment

3.1.2.1 Near Infrared spectroscopy measurement of tissue oxygenation.

This setup has already been described in Chapter 2, see pages 81-82.

3.1.2.2 Handgrip dynamometry setup

The overall setup of the equipment has already been described in Chapter 2, see pages 82-84.

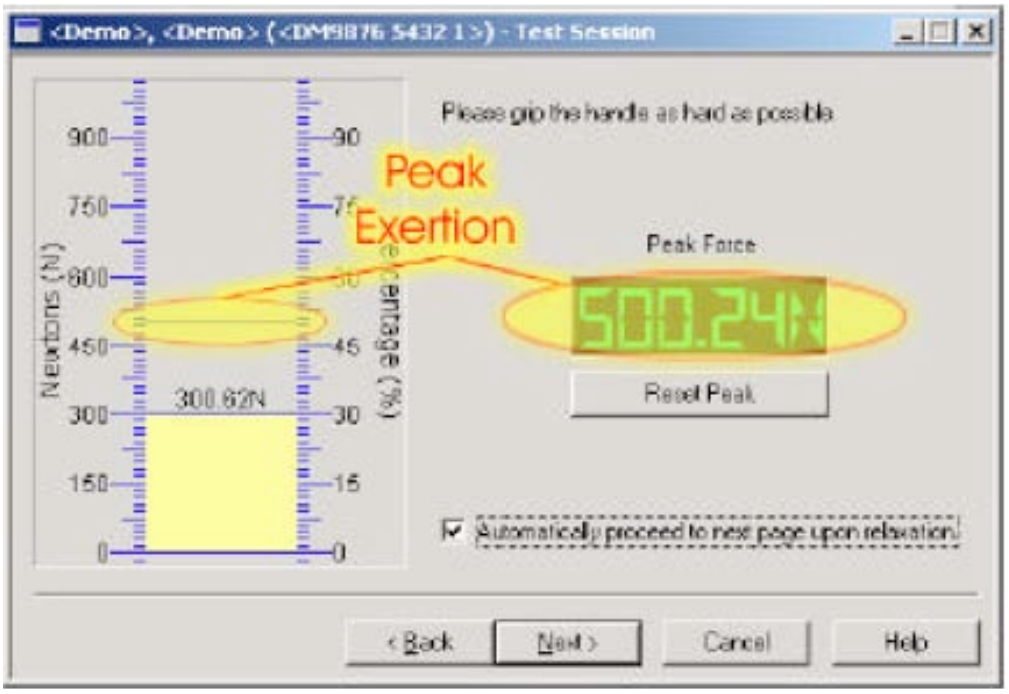
3.1.3 Protocol

A 20G indwelling intravenous cannula was inserted into the non-dominant forearm of the subject. A 3 way tap was attached and flushed with 5mls of 0.9% saline. Samples where then withdrawn at specified time intervals by first aspirating the dead space of the 3 way tap without any cuff occlusion and then aspirating into a blood gas syringe. A minimum of 5 minutes was given before the first sample was withdrawn to negate any effects of venous cuffing on muscle metabolism of oxygen use.

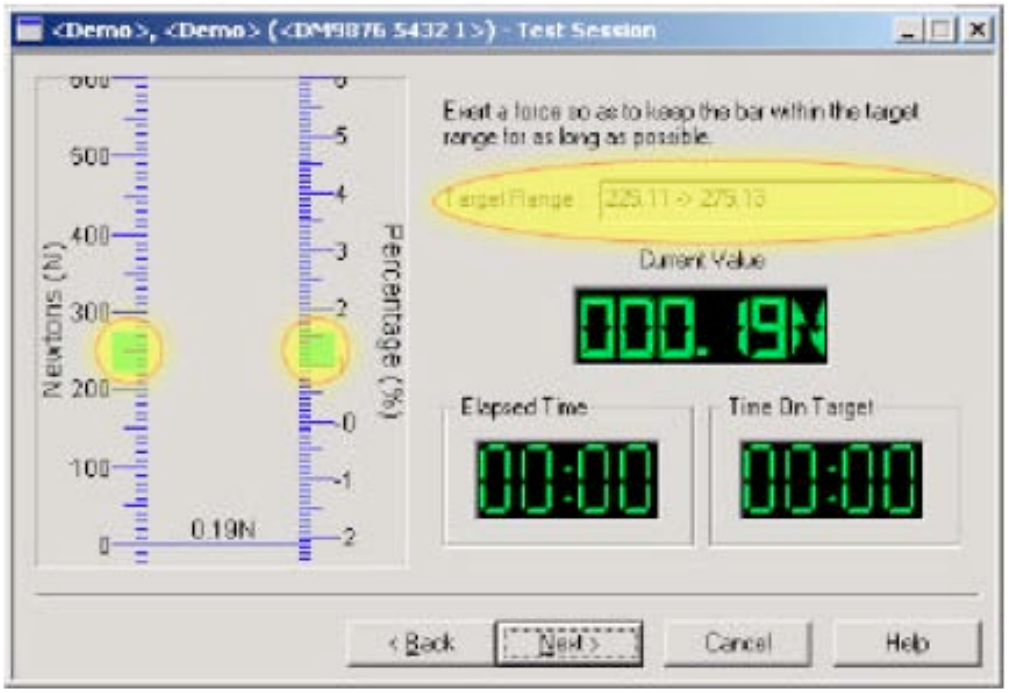
Subjects were seated and the apparatus set up as described in Chapter 2. A maximal voluntary contraction (MVC) was established prior to a baseline venous gas sample was taken, by asking the subject to briefly grip the transducer as hard as possible. This was repeated 3 times and the average reading taken as the subjects true MVC, subjects were then rested for 10 minutes. The MVC was recorded by the computer and a target zone set as 50% of that MVC with a tolerance of +/-5%, (see Figure 3.1). Subjects were given visual feedback from a graphical force transducer graph on the computer screen and received audible encouragement from myself. Subjects were then rested for a minimum of 5 minutes and their STO_2 reading had returned to baseline.

Figure 3.1 Demo screen shots illustrating recording of MVC and setting of 50% MVC target with ±5% tolerance band, (reproduced with permission from WINCAS manual MIE medical research Ltd), a) Recording of MVC b) target values and tolerance bands

a) Recording of MVC



b) Screenshot of test showing target value and ±5% tolerance bands



Once each subject had been rested and was seated and positioned correctly they were asked to grip the transducer so as to exert a force equivalent to 50% of their MVC. To assist them they were shown a visual bar graph of force applied that contained a green target area with a 5% tolerance band (see Figure 3.1). They were instructed to keep the within the green area for as long as possible or until exhaustion. If they exerted too little or too much force the bar turned red indicating they were outside of the target zone and they were given audible instructions to alter the force of their grip to return to the green zone. If they strayed outside this tolerance zone for more than 3 seconds the test was automatically terminated.

The study lasted for 10 minutes from the onset of exercise. During this time multiple venous sampling was made at specified time points of 60,120,180,300 and 600 seconds after exercise had started and NIRS readings recorded at 3 second intervals onto a computer as described in Chapter 2. Prior to each venous sample being taken a dead space volume of 2 mls was discarded from the venous effluent cannula after which the venous blood gas sample was taken. The cannula was then flushed with 2 mls of 0.9% saline to prevent blockage of the cannula. Once exercise had finished due to patient fatigue, readings and blood sampling continued for the full 10 minutes of the study, subjects were asked to rest after cessation of exercise to prevent further voluntary muscle contraction.

3.1.4 Statistical analysis

All analyses were done using Graphpad Prism 5 for Macintosh (Graphpad software, San Diego, California). All data are expressed as means (± standard deviation) where normally distributed unless otherwise stated. Statistical significance was set at $p<0.05$. Linear regression.

3.2 RESULTS

3.2.1 Demographics

Eleven subjects were enrolled in the study, ten of which had already completed the cyclical forearm exercise study in a previous sitting. All subjects completed the study without any problems. There were nine male and two female subjects.

Group demographics were obviously broadly similar to those of Chapter 2. They were 34 (30-36) years old, had a median height of 183(179-187) cm, a median weight of 86 (71-88) Kg and a median exercise time per week of 210 (0-420) minutes.

The demographics for the group are shown below in Table 3.1.

Table 3.1 Healthy volunteer demographics

Subject	Sex	Height	Weight	Age	Exercise time per week
1	M	182	86	24	420
2	M	179	100	36	100
3	M	179	71	35	0
4	M	188	88	40	180
5	M	196	90	32	420
6	F	165	68	20	420
7	M	186	78	38	420
8	M	186	87	34	210
9	F	160	47	30	0
10	M	187	86	34	0
11	M	183	85	35	420

Exercise time per week=average exercise undertaken per week in minutes

3.2.2 Handgrip dynamometry

The performance data from handgrip dynamometry shows a large range of strength and work done with a mean MVC of 355.6 (± 80.07) N and mean work done of 26257 (± 11388) Ns (see Table 3.2), but relatively little variation in the Borg rating assigned by subjects with a high mean rating of 15.91 (± 2.43), (see Table 3.2). There was no significant relationship between the Borg scale rating and the work done (r^2=0.15, p=0.24).

Table 3.2 Individual handgrip dynamometry data for all subjects with Borg ratting

Subject ID	MVC	Work done	Exercise time	Borg rating
1	352.88	29797.49	185.76	16
2	438.66	34708.62	164.72	18
3	250.02	9226.31	68.88	14
4	308.16	25371.17	183.89	15
5	466.31	41554.4	190.33	13
6	264.66	8675.61	72.64	16
7	438.25	39390.4	196.7	18
8	307.35	25206.91	173.81	18
9	265.07	19114.8	147.92	12
10	408.98	19258.47	102.72	15
11	411.02	36526.41	183.88	20

Exercise time=seconds, Work done=NS

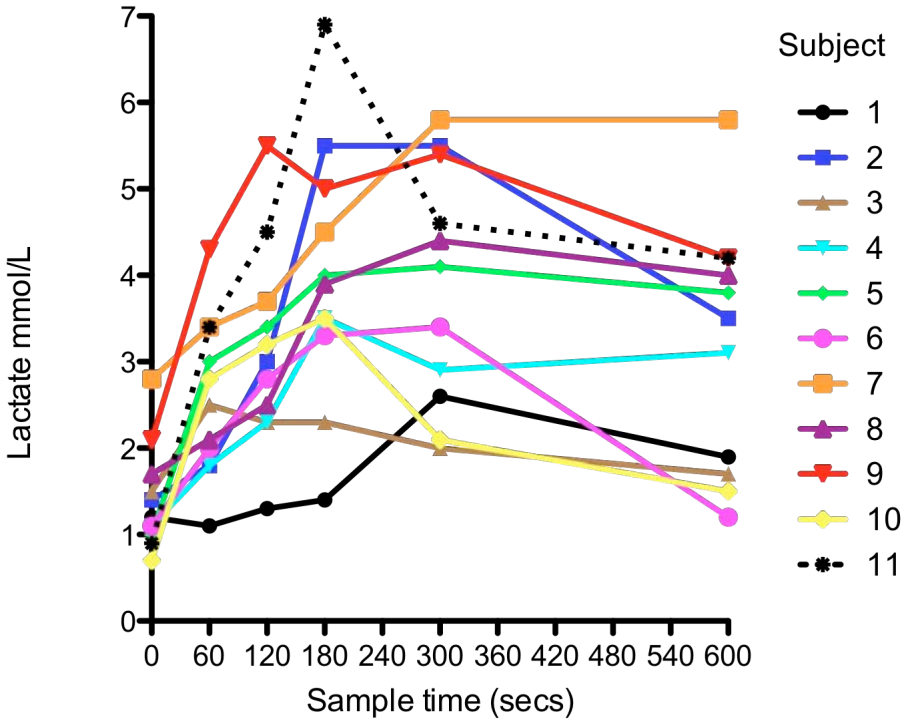
As expected there was a significant association of MVC and work done (r^2=0.73, p=0.0008), but no significant relationship between the Borg rating and exercise time.

3.2.3 Metabolic performance

3.2.3.1 Fixed time sampling points

There was a relatively wide and heterogeneous variation in the pattern of forearm lactate production between subjects (See Figure 3.2). All subjects had ceased to exercise by 190.33 seconds and all but one (subject 4) showed declining levels of forearm lactate from 300-600 seconds.

Figure 3.2 Forearm lactate curves for each subject, showing sampling points at 0,60,120,180,300 and 600 seconds.



Box and whisker summary plots of all subjects for forearm lactate, SO_2, PO_2, PCO_2, pH and STO_2 are shown in Figure 3.3.

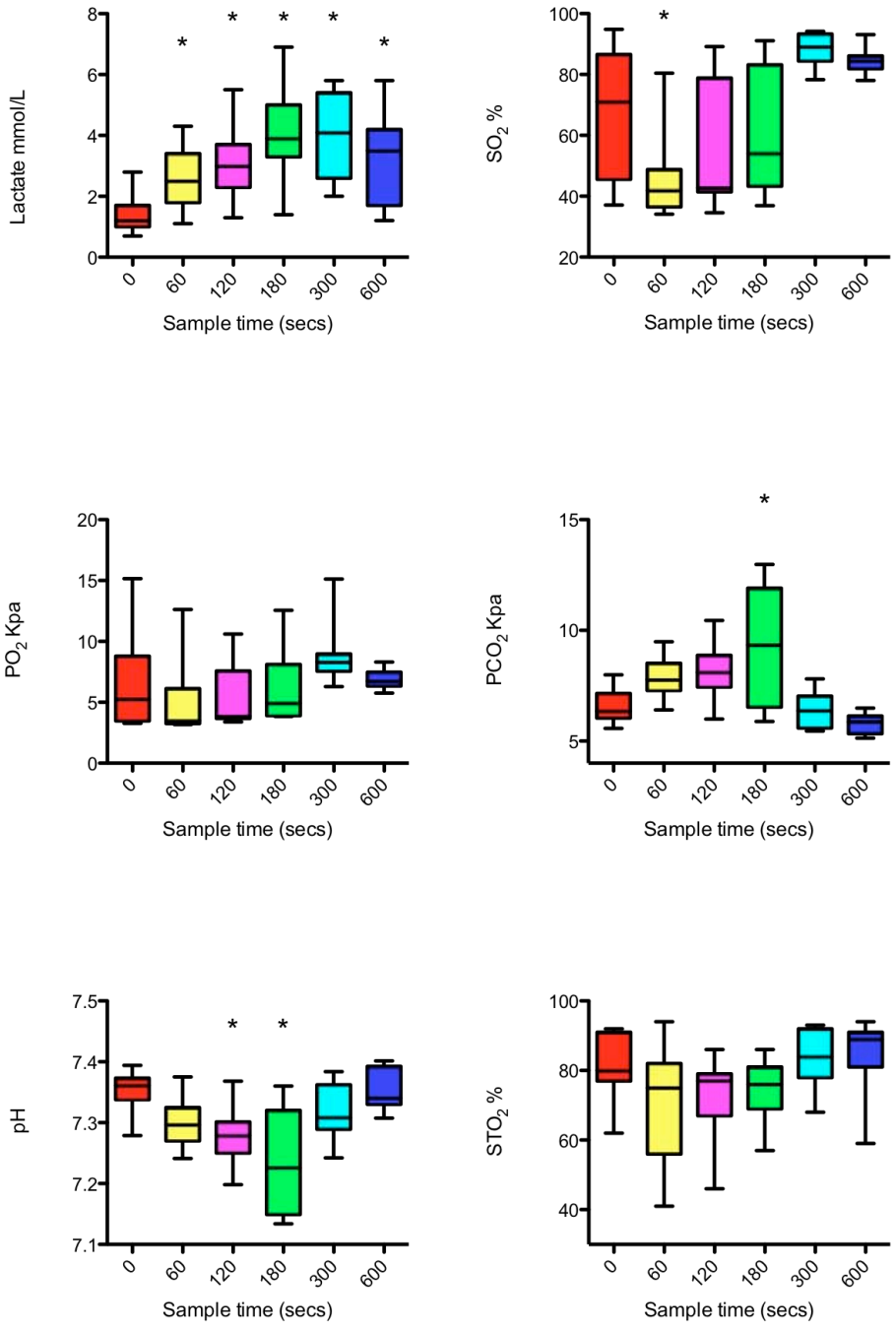
There were significant changes from baseline (time 0) for all sampling points for forearm lactate, but not for PO_2 or STO_2. The first sampling point at 60 seconds was significantly less than baseline for SO_2, as were sampling points at 120 and 180 seconds when compared to baseline pH. When compared to baseline, PCO_2 at 180 seconds was significantly higher. All other variables and sampling points showed no significant changes when compared to baseline, (see Figure 3.3).

There was no significantly detectable difference from baseline by the termination of the tests for any of the variables except for Forearm lactate, which remained significantly higher, (see Figure 3.3).

3.2.3.2 MVC

There was no significant relationship between MVC and any fixed time point sample or of summary measures of metabolic performance for forearm lactate, SO_2, PO_2, PCO_2, pH or STO_2.

Figure 3.3 Box and whisker plots of metabolic markers of metabolism plotted over 6 discrete sampling times for all 11 subjects.



*=Significant results showing deviation from baseline (0 seconds), one way ANOVA, $p<0.05$

3.2.4 Summary measures of metabolic performance

Markers of the performance of the model were evaluated through the static, dynamic and cumulative summary endpoints. Chapter 2: Appendix shows detailed calculations and explanations for all endpoints. The pH variables were transcribed into their equivalent $[H^+]$ for ease of computational analysis.

3.2.4.1 Forearm lactate

The only significant association with work done was for cumulative minus baseline lactate, with more lactate being produced at higher workloads, (see table 3.3 and Figure 3.4).

3.2.4.2 PCO_2

There was a significant variability between subjects for baseline PCO_2, with a median of 6.58(0.72) kPa and although a weak association with an r^2 value 0f 0.27 those with higher levels of baseline PCO_2 appear to do more work-see Table 3.4 and Figure 3.5 a).

There were significant and stronger relationships between PCO_2 cumulative and PCO_2 cumulative per second versus work done, with higher levels of both being associated with more work having been done-see Table 3.4 and Figures 3.5 b) & c).

3.2.4.3 Hydrogen ion concentration

With the exception of baseline values the only significant associations were similar to PCO_2 with cumulative and cumulative per second $[H]^+$ having stronger associations with r^2 values of 0.77, (see Table 3.5 and

Figures 3.6 a) & b) respectively). More work done was associated with a higher measurable concentration of $[H]^+$ and consequently a lower pH.

3.2.4.4 SO_2

The values for oxygen saturation followed a similar pattern to both PCO_2 and $[H]^+$ with cumulative and cumulative per second variables being significantly associated with work done. The more work done the greater the drop in cumulative SO_2 and the lower the SO_2 per second-see Table 3.6 and Figures 3.7 a) & b).

3.2.4.5 Dynamometry & Borg scale ratings

There was no significant association between the Borg rating given by each subject to the amount of work done during the exercise, (see Table 3.7).

Not surprisingly however there were significant associations for MVC and exercise time versus work done, (see Table 3.7 and Figures 3.8 a) & b) respectively).

3.2.4.6 STO_2 and PO_2

There were no significant associations with work done and either STO_2 or PO_2, (see Tables 3.8 & 3.9 respectively).

Table 3.3 Summary statistics and linear regression results for Forearm lactate derived variables vs. Work done

Lactate	n=11		r^2	P value	
Lactate baseline	median(IQR)	1.409(0.6057)	0.1754	0.6755	ns
Lactate peak	mean(SD)	4.336(1.419)	0.544	0.0692	ns
Lactate peak-baseline	mean(SD)	2.927(1.336)	0.3523	0.0885	ns
Lactate peak % change over baseline	mean(SD)	246.2(170.9)	0.04469	0.2955	ns
Lactate cumulative	mean(SD)	2036(686.3)	0.7475	0.0623	ns
Lactate cumulative -baseline	mean(SD)	1190(560)	0.6206	0.0435	*
Lactate cumulative/sec	mean(SD)	3.393(1.144)	0.7475	0.0623	ns

- = Significant result ($p<0.05$), IQR=Interquartile range, SD=standard deviation

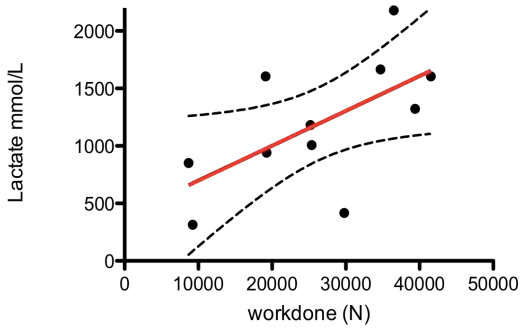


Figure 3.4 Linear regression plot for cumulative lactate-baseline Vs. Work done. ---- = 95% confidence intervals

Table 3.4 Summary statistics and linear regression results for PCO_2 derived variables Vs. Work done.

PCO_2	n=11		r^2	P value	
PCO_2 baseline	median(IQR)	6.582(0.7222)	0.2723	0.0345	*
PCO_2 peak	mean(SD)	9.49(2.19)	0.3624	0.1687	ns
PCO_2 peak -baseline	mean(SD)	2.908(2.017)	0.2178	0.4473	ns
PCO_2 peak % change over baseline	mean(SD)	44.39(31.04)	0.1792	0.5466	ns
PCO_2 cumulative	mean(SD)	4181(528.1)	0.5337	0.0059	*
PCO_2 cumulative -baseline	mean(SD)	232.1(426.2)	0.1403	0.3677	ns
PCO_2 cumulative/sec	mean(SD)	6.969(0.8802)	0.5337	0.0059	*

* = Significant result ($p<0.05$), IQR=Interquartile range, SD=standard deviation

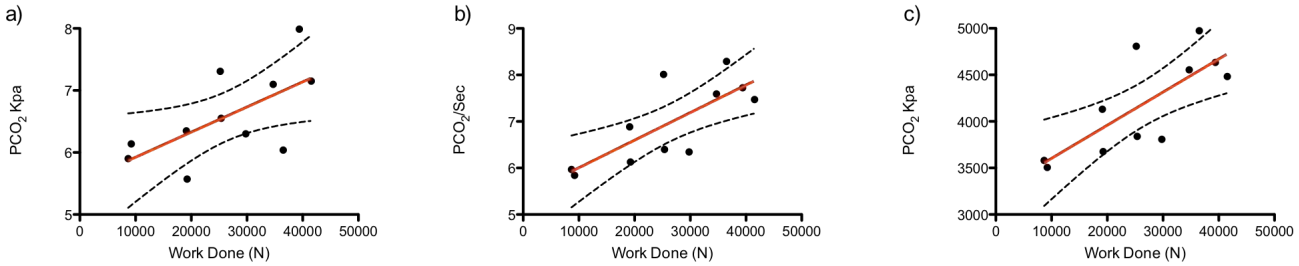


Figure 3.5 Significant Linear regression plots for PCO_2 derived variables vs. Work done. ---- = 95% confidence intervals a) PCO_2 baseline, b) PCO_2 cumulative c) PCO_2 cumulative/sec

Table 3.5 Summary statistics and linear regression results for $[H]^+$ derived variables Vs. Work done.

$[H]^+$	n=11		r^2	P value	
$[H]^+$ baseline	mean(SD)	0.00000004458(3.26E-09)	0.2687	0.296	ns
$[H]^+$ peak	median(IQR)	0.00000006018(9.305E-09)	0.4351	0.2838	ns
$[H]^+$ peak-baseline	median(IQR)	0.0000000156(9.345E-09)	0.2265	0.4912	ns
$[H]^+$ peak % change over baseline	median(IQR)	35.38(21.74)	0.1952	0.4952	ns
$[H]^+$ cumulative	median(IQR)	0.00002973(0.000002753)	0.7721	0.0394	*
$[H]^+$ cumulative-baseline	mean(SD)	0.000002981(0.000002211)	0.404	0.1422	ns
$[H]^+$ cumulative/sec	mean(SD)	0.00000004954(4.589E-09)	0.7721	0.0394	*

* = Significant result ($p<0.05$), IQR=Interquartile range, SD=standard deviation

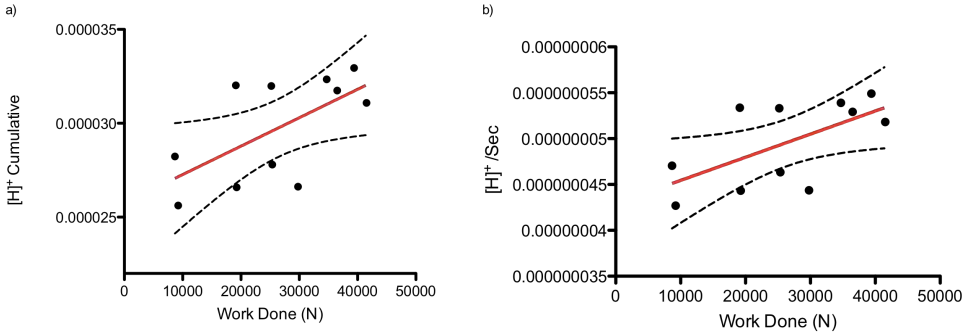


Figure 3.6 Significant Linear regression plots for $[H]^+$ derived variables vs. Work done. ---- = 95% confidence intervals. a) $[H]^+$ cumulative, b) $[H]^+$ cumulative/sec

Table 3.6 Summary statistics and linear regression results for SO_2 derived variables Vs. Work done.

SO_2	n=11		r^2	P value	
SO_2 baseline	mean(SD)	68.69(19.63)	0.1827	0.2046	ns
SO_2 nadir	mean(SD)	39.4(36.5-48.8)	0.5034	0.2753	ns
SO_2-baseline	median(IQR)	-23.34(17.76)	0.01053	0.6261	ns
SO_2 peak % change over baseline	mean(SD)	-31.03(19.93)	0.05404	0.6574	ns
SO_2 cumulative	mean(SD)	44975(4740)	0.4947	0.0063	*
SO_2 cumulative -baseline	mean(SD)	3761(9226)	0.03393	0.6874	ns
SO_2/sec	mean(SD)	74.96(7.9)	0.4947	0.0063	*

* = Significant result ($p<0.05$), IQR=Interquartile range, SD=standard deviation

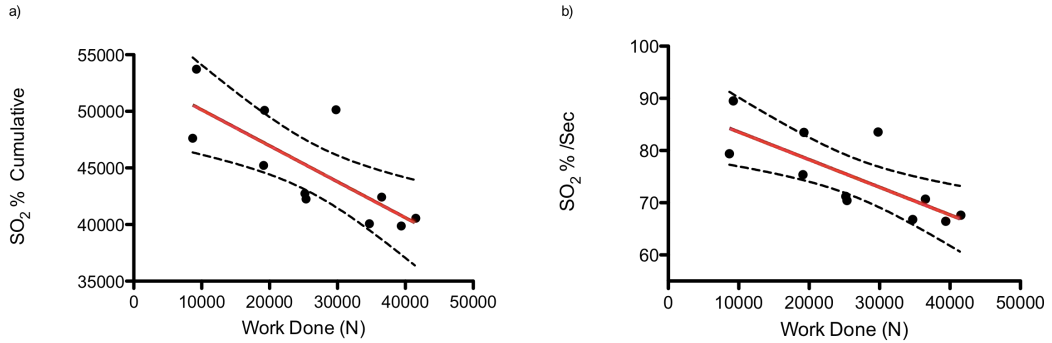


Figure 3.7 Significant Linear regression plots for SO2 vs. Work done. ---- = 95% confidence intervals a) SO2 cumulative, b) SO2/sec

Table 3.7 Summary statistics and linear regression results for Borg & Dynamometer derived variables Vs. Work done.

Dynamometer	n=11		r^2	P value	
MVC (N)	mean(SD)	355.6(80.07)	0.7324	0.0008	*
Exercise time (seconds)	mean(SD)	151.9(47.89)	0.1974	0.0002	*
Borg rating	mean(SD)	15.91(2.427)	0.001378	0.2406	ns

*= Significant result (p<0.05), IQR=Interquartile range, SD=standard deviation

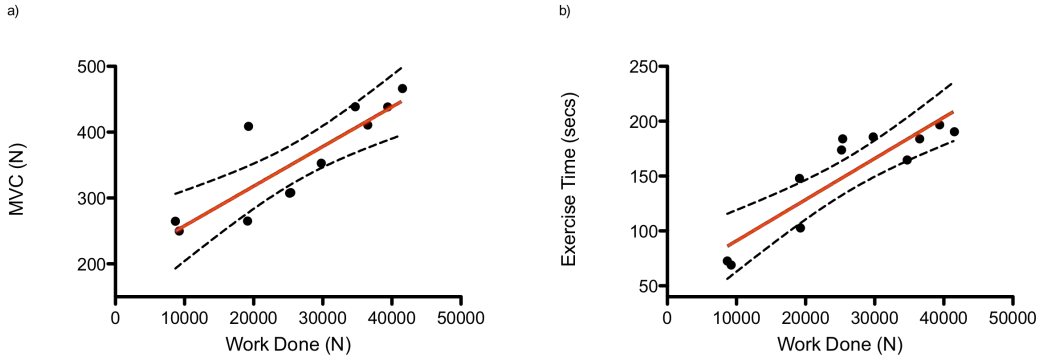


Figure 3.8 Significant Linear regression plots for Dynamometer derived variables vs. Work done. ---- = 95% confidence intervals. a) MVC, b) Exercise time

Table 3.8 Summary statistics and linear regression results for STO_2 derived variables Vs. Work done.

STO_2	n=11		r^2	P value	
STO_2 baseline	mean(SD)	80.09(9.428)	0.0199	0.0743	ns
STO_2 nadir	mean(SD)	60.27(15.23)	0.009659	0.1345	ns
STO_2 nadir-baseline	mean(SD)	-19.82(11.32)	0.0002181	0.5926	ns
STO_2 peak % change over baseline	mean(SD)	-25.31(16.53)	0.0005629	0.336	ns
STO_2 cumulative	mean(SD)	47768(4702)	0.1455	0.1792	ns
STO_2 cumulative-baseline	mean(SD)	-286.4(3268)	0.09284	0.3095	ns
STO_2 /sec	mean(SD)	81.25(79.25-82.55)	0.1455	0.1792	ns
NIRS STO_2 slope	mean(SD)	11.94(6.481-41)	0.02826	0.0507	ns
NIRS THI average	mean(SD)	11.33(2.495)	0.09253	0.0723	ns
NIRS $V0_2$	mean(SD)	152.8(62.16-475.4)	0.03315	0.0598	ns

Table 3.9 Summary statistics and linear regression results for PO_2 derived variables Vs. Work done.

PO_2	n=11		r^2	P value	
PO_2 baseline	mean(SD)	6.9(4.054)	0.001522	0.5608	ns
PO_2 nadir	mean(SD)	3.43(3.25-5.44	0.1342	0.182	ns
PO_2 nadir-baseline	mean(SD)	-1.64(-5.36-(-0.23))	0.008611	0.7987	ns
PO_2 peak % change over baseline	mean(SD)	-29.83(22.2)	0.004594	0.7035	ns
PO_2 cumulative	mean(SD)	4265(911.8)	0.00447	0.1093	ns
PO_2 cumulative-baseline	mean(SD)	782.7(-1343-1476)	0.0003852	0.9793	ns
PO_2 /sec	mean(SD)	7.108(1.52)	0.00447	0.1093	ns

3.3 DISCUSSION

This study was designed as was the cyclical model in Chapter 2 to test a) if an isometric approach to forearm exercise was practical and possible and b) if a proportionate biological response could be achieved that would clearly differentiate subjects. It was clearly practical to perform and measure static isometric and in many ways easier than cyclical isometric exercise due to the simplicity of the exercise regime used. The pattern of response for individuals was heterogeneous as shown in Figure 3.2 for the forearm lactate curves, which may have the added benefit of differentiating individuals. The group as a whole exhibited a broad range of static strength (MVC) and work done, which may be responsible for the differences in forearm lactate patterns seen. The subjective rating of exercise using the Borg scale showed more variation than in Chapter 2 but no association with the actual work done or exercise time. This suggests that there was not a significant difference in perception of how hard the exercise was between individuals, but was poor at predicting the final amount of work done. This is not entirely surprising in that it is an individual and subjective measure of exercise intensity and there was a large variation in the MVC and exercise time between individuals, which had the most significant bearing on the amount of work done. MVC being the largest of the components making up work done was significantly associated with work done, but did not show any significant relationship wit exercise time. Strength (MVC) and endurance however are two separate exercise entities and one does not necessarily belie the other. A difference in muscle fibre types may explain why individuals with slow

twitch fibres may be more adapted to endurance exercise whilst those with type 1 or fast twitch may be more suited to short term intense exercise. My model was a mixture of the two entities, but we cannot comment further as no histological analysis of muscle fibre was undertaken.

All subjects had ceased to exercise by 190 seconds but over half the group continued to see rises in forearm lactate after the cessation of exercise. This reflects the ongoing respiration in the muscle with regeneration of high-energy compounds and is consistent with other models of intense exercise. All subjects apart from one had falling concentrations of forearm lactate by the termination of the test, which may have a number of explanations, 1) due to measurement error 2) an increase in lactate production or 3) an increase in lactate clearance as blood flow is restored to the forearm. Explanations 1) and 3) are the most likely.

The test produced significant changes in all variables from fixed time point samples except PO_2 and STO_2. It is likely that exercise occurred in predominantly anaerobic conditions as evidenced by the rise in forearm lactate, PCO_2 and hydrogen ion concentration along with data from other authors [179]. Soller et al show that even during exercise changes in venous measures for SO_2 and PO_2 may not reflect absolute changes at the cellular level and it is most probable that our model reflects that. The early drop in SO_2 may reflect acute use of venous oxygen stores to fuel aerobic respiration, but it is difficult to explain why this was restored within 60 seconds during the exercise period. The failure of STO_2 to track

changes may in part be due to the wide variation in readings between individuals despite the changes in median values and probably reflects the inaccuracy in the monitor – which can be affected by probe depth, size and placement. The placement of the probe probably varied between subjects, as does the amount of subcutaneous fat, which may have led to the variability in readings.

It is disappointing not to find a relationship between MVC and any of the fixed time point samples or the summary measures of performance. Strength, however, is only one aspect of exercise as mentioned above and endurance as measured by work done may be the better variable to measure. This is borne out by relating work done to the summary measures of performance that showed significant relationships for forearm lactate, PCO_2, hydrogen ion concentration and SO_2. Fixed time point sampling in my model has some disadvantages in that it can only give an approximation of metabolic flux at certain points in time as the sampling frequency was at best 60 seconds. Changes that occur between these points will be missed and have to be extrapolated which has obvious potential for error. Alternative approaches have been used such a placing continuous catheters in muscle [179], but the aim of the model was to keep it simple as a bedside test and insertion of such catheters would have negated that benefit. The strongest associations were seen in hydrogen ion concentration with r^2 values of up to 0.77. Sustained forearm exercise above 30% of MVC is known to cause anaerobic respiration and as explained in Chapter 1, acidosis is the main waste product of anaerobic respiration with hypoxia being only one of

many stimuli for the release of forearm lactate production. This adds weight to the argument that the model effectively induced anaerobic respiration in exercising muscle.

3.4 CONCLUSION

The static isometric model again performed well and was simpler to setup due to the reduced complexity of the instructions given than the cyclical isometric model.

Standardisation of the test worked well with each subject achieving results comparable to an age matched control group and the input of an individual was easy to calculate from the test apparatus.

Fixed time point sampling was possible and analysis straightforward.

The endpoints of the test were easily definable with significant changes from base line for venous markers of anaerobic respiration i.e. lactate, hydrogen ion concentration and PO_2, but less significant changes from baseline were seen most probably due to the decreased duration of exercise in this test compared to the cyclical model.

Again the model showed good correlation with work done and the measureable venous summary endpoints of anaerobic respiration.

CHAPTER 4 - A COMPARISON OF ISOMETRIC AND CYCLICAL HANDGRIP MODELS

4.0 INTRODUCTION

In chapter 2 I showed that a cyclical forearm exercise model was practical to perform and produced a measurable and reproducible metabolic response, with clearly identifiable endpoints and relationship to work done. The metabolic response of individual was relatively homogenous.

In chapter 3 I showed that an isometric forearm exercise model was also practical to perform and produced a measurable and reproducible metabolic response, with clearly identifiable endpoints and relationship to work done. The metabolic response of individual was in contrast relatively heterogeneous.

This chapter will compare and contrast the performance, the input and the metabolic output of the isometric and cyclical forearm exercise models. It will establish identifiable endpoints for each model, which will be compared with the anaerobic threshold measured by formal cardiopulmonary exercise testing in the same group of subjects in Chapter 5.

4.1 MATERIALS AND METHODS

4.1.1 Handgrip dynamometry

Both method and experimental setup have been described in Chapters 2 & 3 in full. I will briefly outline each test again here for the sake of clarity.

The cyclical forearm exercise test consisted of a maximal voluntary contraction for 2 seconds followed by a relaxation phase of 3 seconds. This was repeated 60 times and the exercise part of the test terminated at 300 seconds.

The isometric forearm exercise test was simpler with subjects asked to exert a maximal voluntary contraction and then sustain a contraction rated at 50% of that maximal voluntary contraction for as long as possible or until exhaustion.

Both exercise tests had visual and auditory feedback and venous sampling was performed at 0,60,120,180,300 and 600 seconds with STO_2 measurements recorded every 3 seconds.

4.2 Results

Comparison results will be presented below.

4.2.1 Comparison of isometric and cyclical forearm exercise models

4.2.1.1 Demographics

These have been described in full chapters 2 & 3. There were no significant differences between the two groups for age, height, weight or exercise time per week.

4.2.1.2 Work done

Work done by each exercise model was calculated as the integrated area under the force time curves. Table 4.1 shows the respective work done and Borg rating for each subject by exercise model.

Table 4.1 Comparison of work done and Borg scale for isometric and cyclical handgrip models.

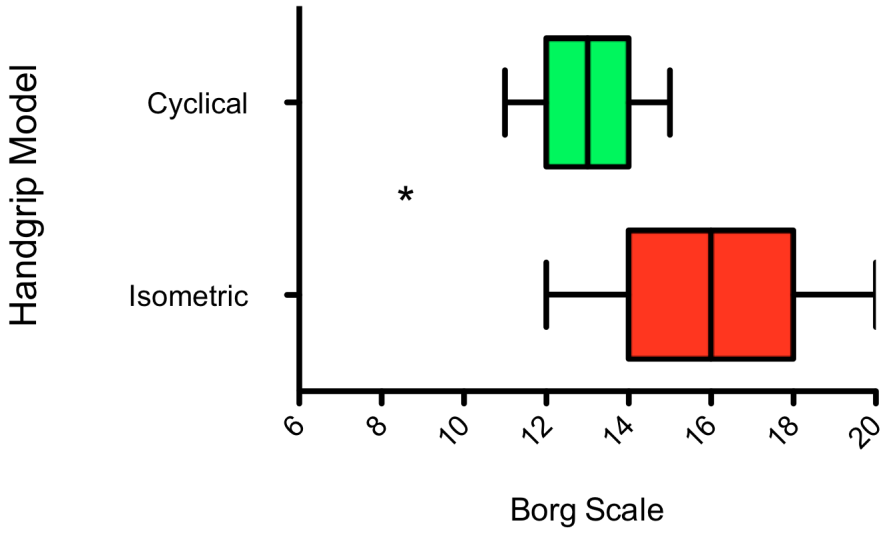
	Isometric		Cyclical	
Subject	**Work done (N)**	**Borg rating**	**Work done (N)**	**Borg rating**
1	29797.49	16	43627.84	13
2	34708.62	18	29321.94	12
3	9226.31	14	22361.13	12
4	25371.17	15	35701.16	11
5	41554.4	13	32785.22	13
6	8675.61	16	15921.33	14
7	39390.4	18	35228.88	14
8	25206.91	18	28977.22	15
9	19114.8	12	16580.47	14
10	19258.47	15	26277.11	12
11	36526.41	20		

Figure 4.1 shows a comparison between each exercise model with respect to the subjective rating of the intensity of the exercise they experienced according to the Borg rating scale. There is a clearly significant difference between the two models with subjects finding the isometric model harder. There was also a wider variation in the rating of the intensity of the exercise than the cyclical model, (mean Borg cyclical 13 (± 1.25) vs. mean Borg isometric 15.91 (± 2.43).

Figure 4.2 however demonstrates that there was no significant difference between the total amounts of work done by subjects for each exercise model, despite the Borg rating suggesting that the isometric exercise was harder.

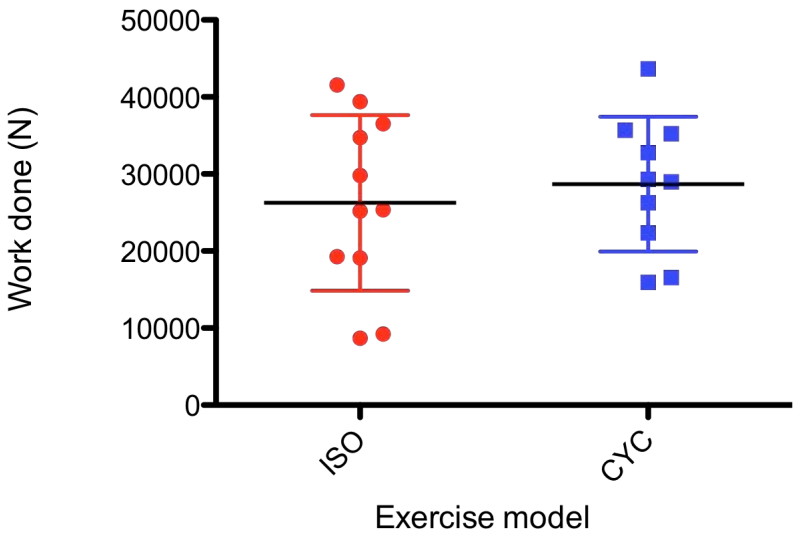
There was however a significant difference in the MVC in the isometric model and the MSV in the cyclical model, (mean ± (SD), MVC (ISO) 355.6 (80.07) vs. 213.2 (68.17), P=0.0003).

Figure 4.1 Comparison of Borg scale rating (difficulty of exercise-subjective rating) for each handgrip model.



*indicates significant difference between groups, 2 tailed unpaired t test p=0.003.

Figure 4.2 Vertical scatter plot of work done by isometric and cyclical exercise models respectively. Individual subject plots with Mean and SD bar indicators.



4.2.1.3 Metabolic performance

Metabolic performance has been described in chapter 1 and refers to the measurable venous products of metabolism i.e. Forearm lactate, SO_2, PO_2, PCO_2 and pH at fixed time points and a their cumulative summary analysis.

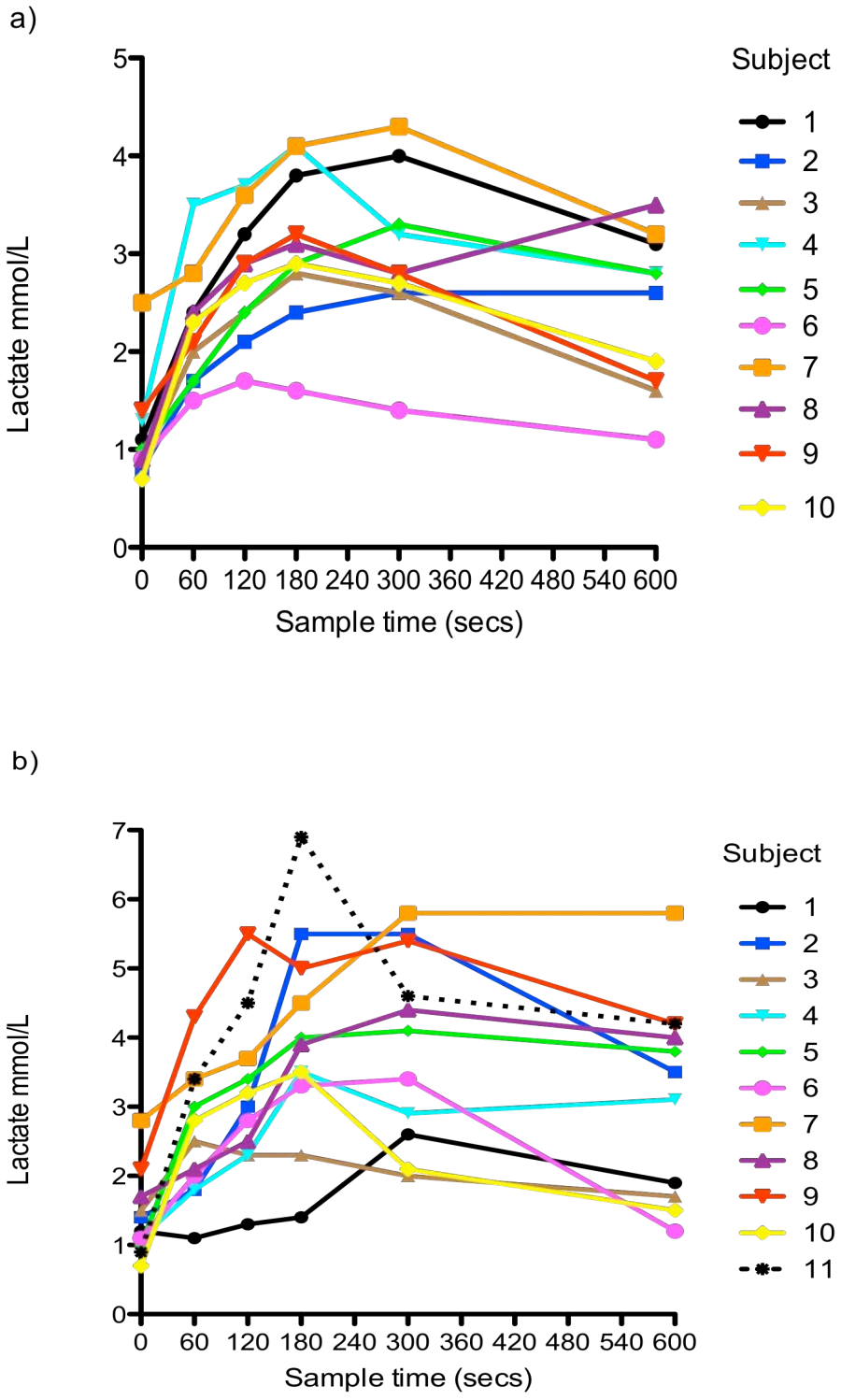
4.2.1.3.1 Fixed time point sampling

This section will describe the results of handgrip dynamometry from the fixed sampling points i.e. 0,60,120,180,300 and 600 seconds.

4.2.1.3.1.1 Pattern of forearm lactate production

Overall both models were able to elicit a metabolic response as evidenced by the production of lactate measured in venous blood during exercise. As can be seen from Figure 4.3 however the pattern of production was subtly different. The cyclical model produced a more homogenous pattern of production, with less differentiation between subjects. The isometric model on the other hand shows more variation in forearm lactate production with sharp and higher rises in at least 4 of the subjects but over differing time scales, with 7 of them reaching peak lactate levels by 300 seconds in comparison to 5 in the cyclical model.

Figure 4.3 Comparison of forearm lactate production by sampling point for each individual a) Cyclical, b) Isometric.

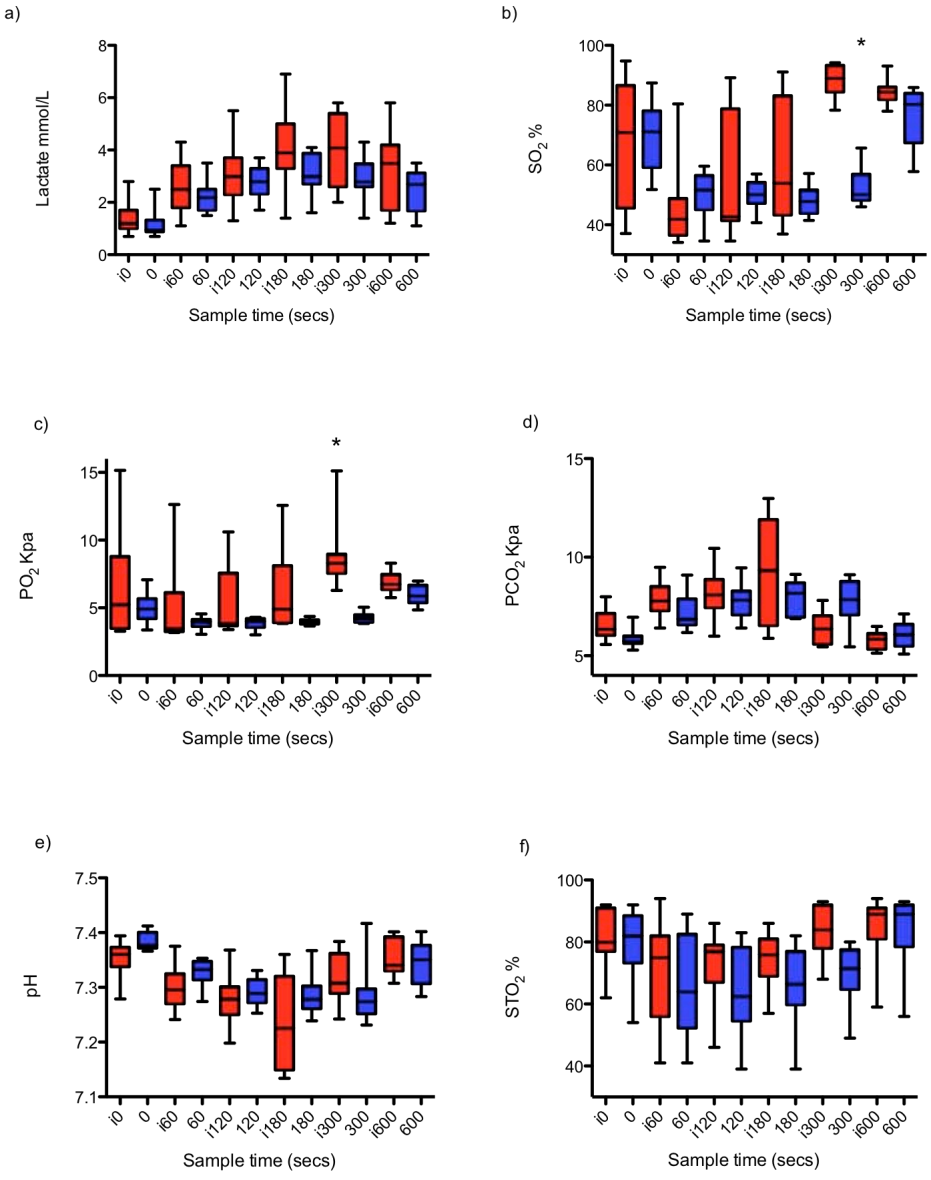


4.2.1.3.1.2 Release patterns for all blood gas variables and STO_2

Figure 4.3 suggests that there may be a difference between the way forearm lactate is released over time by each respective model. Figure 4.4 a) also suggests that forearm lactate release is higher at each time point for the isometric exercise, this is however untrue as there is no statistical difference between each respective time point from 0 to 600 seconds.

The same observation is true for all other variables measured except for SO_2 and PO_2 which both show significant differences between the two exercise models at 300 seconds, with the isometric having higher SO_2 and PO_2 values-see Figures 4.4 b) & c).

Figure 4.4 Box and whisker plots (min to max) of venous blood gas variables and tissue oxygen saturations (STO_2) at all sampling points. Comparison of isometric and cyclical models.



*=Significant difference between groups by one way ANOVA analysis ($p<0.05$), i prefix denotes Isometric model values.

4.2.1.3.2 Summary measures of metabolic performance

4.2.1.3.2.1 Forearm lactate

The only significant difference between the models was for peak lactate production, with isometric exercise producing higher peak lactate values, (see Table 4.2 and Figure 4.5)

4.2.1.3.2.2 PCO_2

There were a number of significant differences between the exercise models for PCO_2. Table 4.3 shows there were significant differences for baseline levels with isometric values being higher and for cumulative and cumulative minus baseline values, (see Figures 4.6 a), b) and c) respectively).

Cumulative PCO_2 was significantly higher for the isometric model but because of a higher baseline value the isometric model had lower PCO_2 values when corrected for baseline-see Figure 4.6 c).

4.2.1.3.2.3 Hydrogen ions

Similar to PCO_2 there was a significant difference in baseline $[H]^+$ with the isometric model having higher values which upon correction for baseline saw levels fall to below those of the cyclical model for cumulative-see Table 4.4 and Figures 4.7 a) & b)

4.2.1.3.2.4 PO_2

Table 4.5 shows that there were three significant differences for PO_2 derived variables; cumulative, cumulative minus baseline and PO_2 per

second, (see Figures 4.8 a), b), & c) respectively). In each case the values for isometric exercise were higher.

4.2.1.3.2.5 SO_2

The derived variables for SO_2 followed a similar pattern to PO_2 with cumulative, cumulative minis baseline and SO_2 per second all being significantly higher in the isometric model, (see Table 4.6 and Figures 4.9 a), b) & c) respectively).

4.2.1.3.2.6 STO_2

The only significant difference between groups was for cumulative STO_2 change, with the isometric model changing more over time, (see table 4.7 and Figure 4.10).

Table 4.2 Comparison of cyclical and isometric handgrip models for forearm lactate based summary measures of handgrip performance

	Test	Significance	p value
Lactate baseline	1	ns	0.31
Peak Lactate	1	*	0.045
peak lactate-baseline	1	ns	0.086
peak % change over baseline lactate	1	ns	0.48
Cumulative lactate	1	ns	0.097
Cumulative lactate-baseline	1	ns	0.18
Average Lactate per sec	1	ns	0.097

1=unpaired t test, * =significant ($p<0.05$)

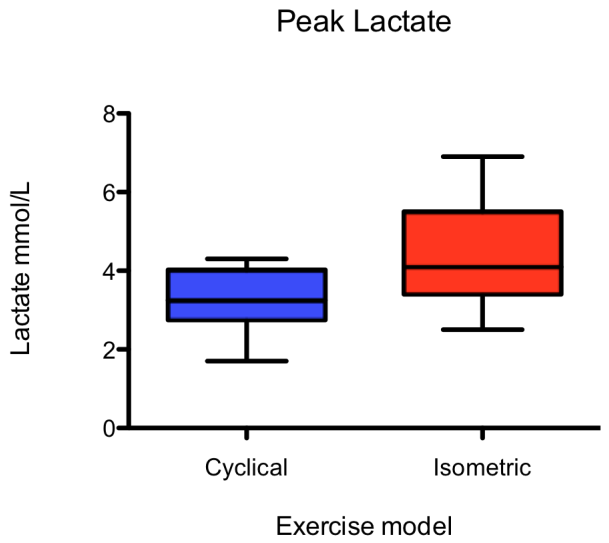


Figure 4.5 Box and whisker plot for peak lactate

Table 4.3 Comparison of cyclical and isometric CO_2 based summary measures of handgrip model

	Test	Significance	p value
CO_2 baseline	1	*	0.014
Peak CO_2	1	ns	0.11
Peak CO_2 -baseline	1	ns	0.43
Peak % change over baseline CO_2	1	ns	0.71
Cumulative CO_2	1	*	<0.0001
Cumulative CO_2 -baseline	1	*	0.0021
CO_2 per sec	1	ns	0.49

1=unpaired t test, * =significant ($p<0.05$)

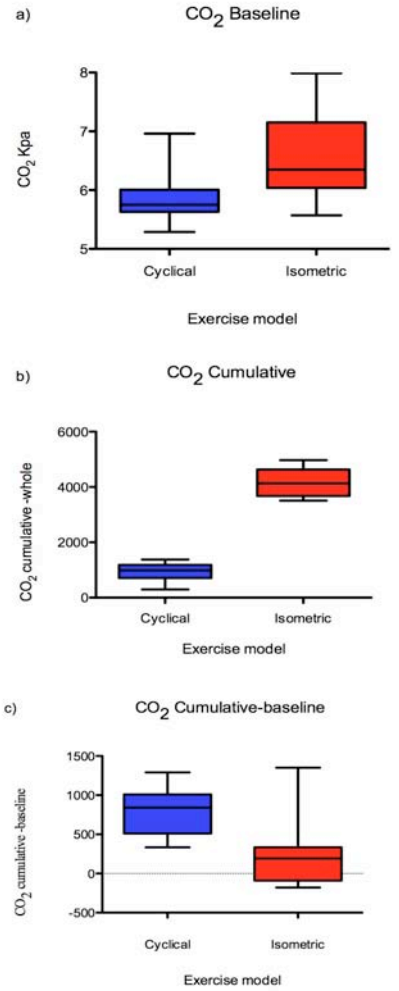


Figure 4.6 Box and whisker plot a) baseline CO_2, b) Cumulative CO_2, c) Cumulative CO_2 minus baseline

Table 4.4 Comparison of [H]+ based summary measures of handgrip model

$[H]^+$	Test	Significance	p value
$[H]^+$ baseline	1	*	<0.0001
$[H]^+$ peak	2	ns	0.26
$[H]^+$ peak-baseline	2	ns	0.97
$[H]^+$ peak % change over baseline	2	ns	0.92
$[H]^+$ cumulative	1	ns	0.91
$[H]^+$ cumulative-baseline	1	*	0.045
$[H]^+$ cumulative/sec	2	ns	0.91

1=unpaired t test, 2=Mann-Whitney, *=significant (p<0.05)

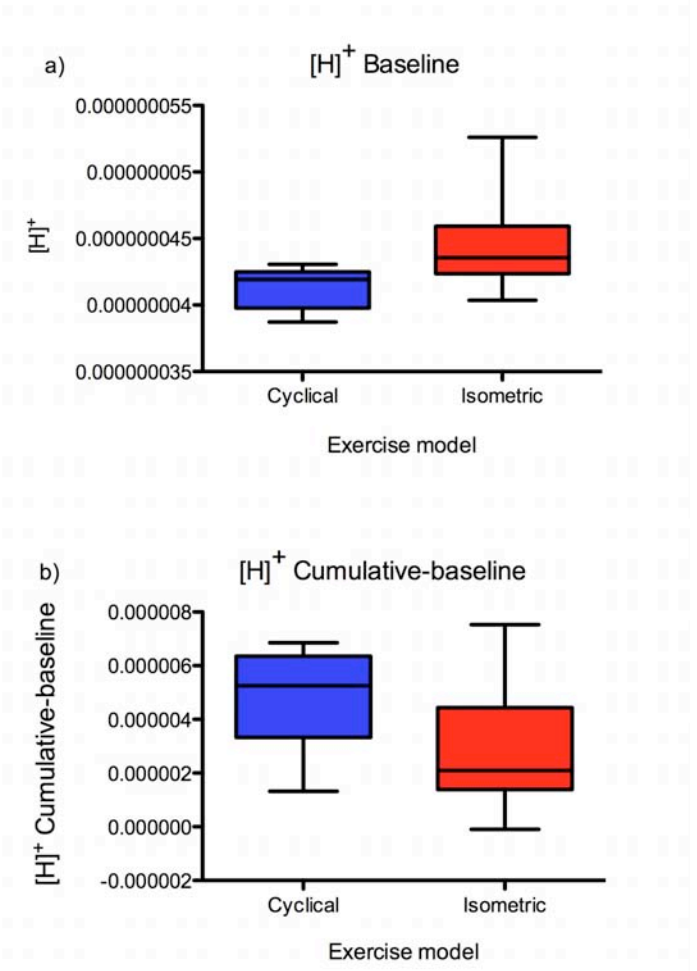


Figure 4.7 Box and whisker plot a) baseline $[H]^+$, b) Cumulative $[H]^+$ minus baseline

Table 4.5 Comparison of PO_2 based summary measures of handgrip model

	Test	Significance	p value
PO_2 baseline	1	ns	0.165
Nadir PO_2	2	ns	0.97
Nadir-baseline PO_2	2	ns	0.59
peak % change over baseline PO_2	1	ns	0.39
Cumulative PO_2 change	1	*	<00001
Cumulative PO_2 change-baseline	2	*	0.018
PO_2 per sec	1	*	<0.0001

1=unpaired t test, 2=Mann-Whitney, *=significant ($p<0.05$)

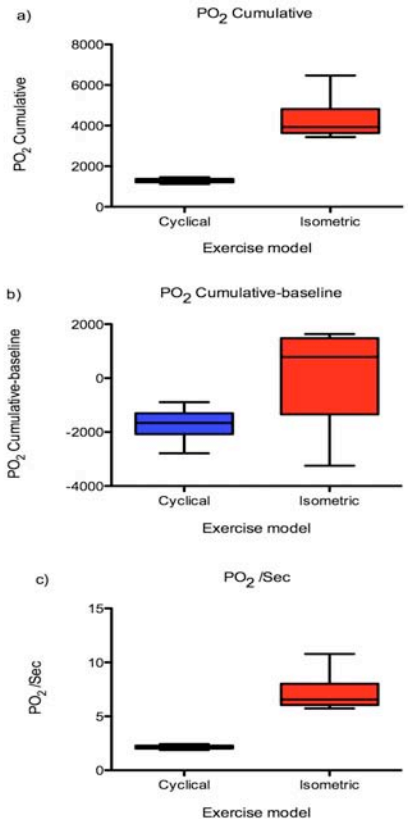


Figure 4.8 Box and whisker plot a) cumulative PO_2 change b) Cumulative PO_2 change minus baseline, c) PO_2 per second

Table 4.6 Comparison of SO_2 based summary measures of handgrip model

	Test	Significance	p value
SO_2 baseline	1	ns	0.95
Nadir SO_2	2	ns	0.2
Nadir SO_2 -baseline	1	ns	0.9
Peak % change over baseline SO_2	1	ns	0.87
Cumulative SO_2 change	1	*	<0.0001
Cumulative SO_2 change-baseline	1	*	<0.0001
SO_2 per sec	1	*	<0.0001

1=unpaired t test, 2=Mann-Whitney, *=significant (p<0.05)

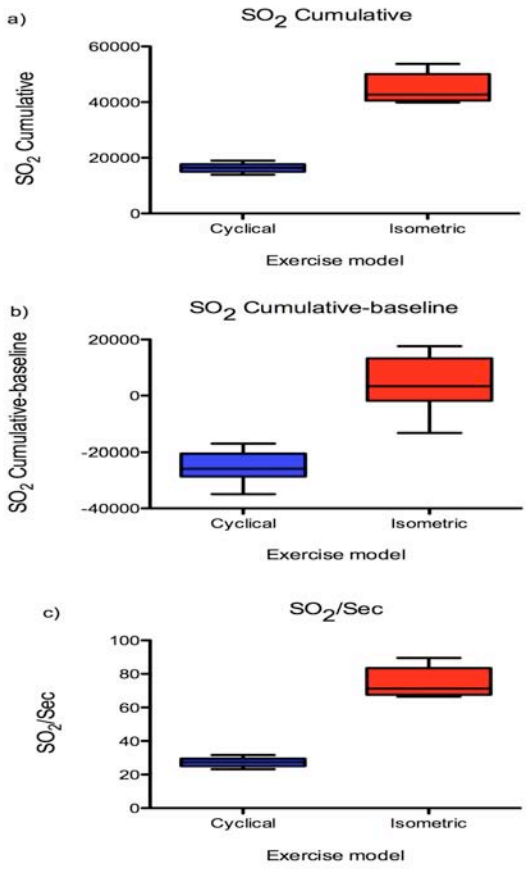


Figure 4.9 Box and whisker plot a) cumulative SO_2 change b) Cumulative SO_2 change minus baseline, c) SO_2 per second

Table 4.7 Comparison of STO_2 based summary measures of handgrip model

	Test	Significance	p value
STO_2 baseline	1	ns	0.84
Nadir STO_2	1	ns	0.53
Nadir STO_2 -Baseline	1	ns	0.58
Peak % change over baseline STO_2	1	ns	0.67
Cumulative STO_2 change	2	*	0.0001
Cumulative STO_2 change-baseline	2	ns	0.42
STO_2 per sec	2	ns	0.86
NIRS time to nadir STO_2	2	ns	1
NIRS STO_2 slope	2	ns	1
NIRS THI average STO_2	1	ns	0.94
NIRS VO_2	2	ns	0.97

1=unpaired t test, 2=Mann-Whitney, *=significant ($p<0.05$)

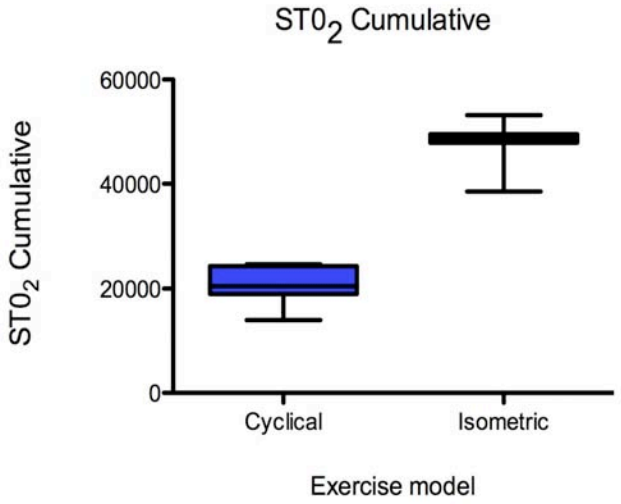


Figure 4.10 Box and whisker plot STO_2 cumulative

4.2.1.4 Forearm lactate – Increase and Decrease between tests

For 10 of the subjects it was possible to compare their performance in the cyclical versus isometric exercise models. It is clear that there are two distinct groups, 1) a group that produces less lactate in the isometric model than the cyclical model and 2) a group that produces more lactate in the cyclical model than they do in the isometric model, (see Figure 4.11).

The group was evenly split with 5 subjects seeing an increase from cyclical to isometric and 5 who saw a decrease in lactate production from cyclical to isometric, (see Figures 4.12 a) & b) respectively).

These differences with respect to anaerobic threshold will be explored further in Chapter 5.

Figure 4.11 Total forearm lactate expression minus baseline lactate by each subject paired between cyclical and isometric handgrip models.

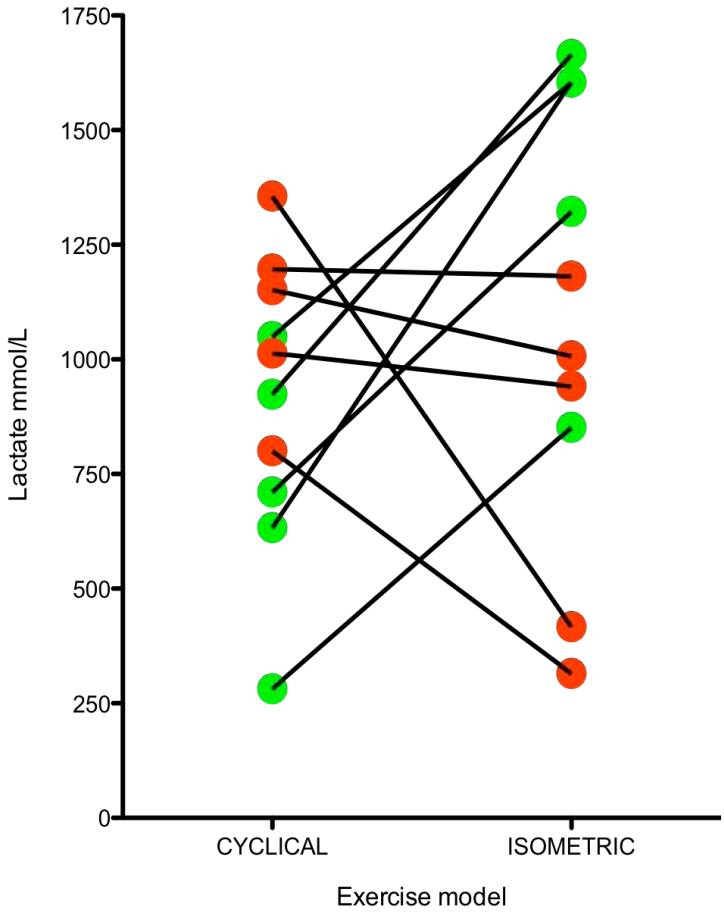
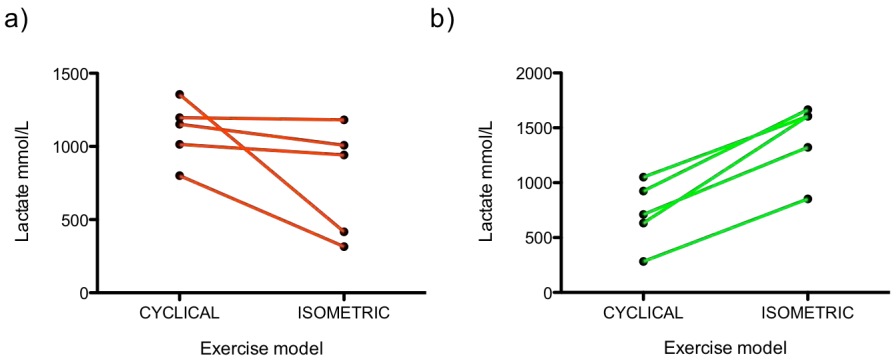


Figure 4.12 Before and after plots of cumulative forearm lactate minus baseline expression for a) Increase between test group & b) decrease between test group.



4.3 DISCUSSION

Both models successfully produced a measureable metabolic response to exercise. There were however a number of significant differences between the two models.

From a practical standpoint the static isometric model was much easier to administer, due to the simplicity of instructions and produced a more defined endpoint. There was no difference between the total amount of work done between either model (see Figure 4.2), but subjects found the static isometric model much harder (Borg scale 13 (±1.25) vs. 15.91 (±2.43), with a greater variability in subjective rating between subjects. The fact that subjects found the isometric test harder is probably explainable by the fact that maximal grip strength was much higher and subjects felt like they were working harder even though the exercise duration of the test was less as subjects fatigued quicker. This is partly explainable by looking at factors causing fatigue in muscle during exercise, although there is considerable doubt regarding the underlying physiology. Anaerobic exercise is known to cause more acidosis and if not cleared, accumulation of the end products of metabolism than aerobic exercise an may be a limiting factor in endurance exercise. There are a number of target candidates for causing fatigue during exercise and the most popular is the increase in acidity as the concentration of hydrogen ions increases. This has been recently challenged by Cairns et al who suggest that acidosis may have little detrimental effect on muscle performance in isolated muscle preparations and may even improve function [250]. Whilst they also acknowledge this may not hold true for

whole body systems. Figure 4.4 suggests that there is a greater production of hydrogen ions and a subsequent fall in pH in the static isometric model but it does not reach significance, so does not confirm that theory. Other candidates are inorganic phosphate [251] and the accumulation of potassium ions in the interstitium [252], but these were not measured, making additional comment difficult. The most likely cause of fatigue is likely to be a combination of the above factors rather than a single variable.

The only significant differences between the models for the fixed time point sampling was at 300 seconds for SO_2 and PO_2. The most likely explanation for this is the timing of exercise in each model. All subjects in the cyclical model exercised for 300 seconds whereas all subjects had completed exercise by 190.33 seconds in the isometric model. Figure 4.4 b) to e) show this nicely with much earlier recovery to normal or supranormal levels seen in the isometric group. There is undoubtedly a significant contribution of reactive hyperaemia to the resupply of oxygenated blood in the isometric model, which occurs earlier than the cyclical model. Figure 4.4 a) also suggests that there is a higher level of forearm lactate production than the cyclical model, but there was no significant difference between the groups. There was a significant difference in peak lactate between the two models with the isometric model producing significantly higher levels of forearm lactate but not overall greater amounts (mean ± (SD) 4.33 (1.42) vs. 3.24 (0.79), p=0.045), (see Table 4.2 and Figure 4.5).

There were significant differences between the groups for endpoint summaries for forearm lactate, PO_2, SO_2, CO_2, hydrogen ion concentration and STO_2, but not for all endpoint summary variables. In all cases isometric exercise produced greater values for forearm lactate, CO_2, and hydrogen ion concentration and lower values for PO_2, SO_2 and STO_2. The most rational explanation is that despite there being no significant difference in the work done, the intensity of exercise performed was significantly higher in the isometric model and was a greater stimulus to anaerobic respiration, (mean ± (SD), MVC (ISO) 355.6 (80.07) vs. 213.2 (68.17), P=0.0003).

The most surprising difference between the two models was in the comparison of the performance of each individual in each test. Figure 4.11 shows the total forearm lactate expression for each individual in the cyclical model and in the isometric model, what is clear from the graph is that the group was evenly split into those that produced higher levels of forearm lactate in the isometric test and those that produce lower levels of forearm lactate in the isometric test compared to their performance in the cyclical model. To the best of my knowledge this is the first time this has been demonstrated in the literature. It is possible that this reflects differing types of muscle fibres present in different individuals [211] or different levels of aerobic conditioning between individuals making some more tolerant of anaerobic conditions than others. The recent work describing differences between monocarboxylate transport (MCT) systems not only between individuals but between different muscle fibres may also explain the difference in performance of the two tests as this

system is primarily responsible for lactate transport between cells and blood and changes with exercise [253]. This will be explored further in Chapter 5.

It is important to highlight the fact that essentially the same cohort of volunteers was used for both studies. This has advantage in that it reduces variability in the study population, but may also introduce bias as the same confounding variables are carried across both studies i.e extremes of exercise capacity may skew the results and prior knowledge of the testing environment may influence subsequent performance.

4.4 CONCLUSIONS

In chapters 2 and 3 I have already shown that both cyclical and isometric forearm exercise tests were easy to perform and produced well defined endpoints with respect to measurable venous markers of anaerobic metabolism.

There was no discernable difference in work done by either model, but subjects found the isometric model harder and fatigued quicker i.e. they did the same amount of work but in a shorter time frame in the isometric model.

As hypothesised in chapter 1 there were a number of key differences in the metabolic output of each model. By 300 seconds PO_2 and SO_2 were significantly higher in the isometric model than the cyclical model, reflecting probable restoration of oxygenated blood to the muscle, whereas the cyclical model was still actively exercising.

The differences between the two models were most pronounced on analysis of the summary measures of metabolic performance. The isometric model produced significantly higher peak forearm lactate levels, higher cumulative PCO_2, higher cumulative hydrogen ion production, more deoxygenation and desaturation as judged by PO_2, SO_2 and STO_2 changes.

The most likely explanation for the differences being a stronger stimulus to anaerobic metabolism in the isometric model as opposed to the cyclical model, which fits with our original hypothesis.

Of note was a clear increase in lactate in the isometric model compared to the cyclical model for half of the subjects tested. The opposite was true for the remaining half. This will be explored further in chapter 5.

Both models will be compared with formal exercise testing in chapter 5 to find which is best suited to take forward in patient testing to predict surgical outcome, with the hypothesis that the isometric model will show the strongest relationship to anaerobic threshold as measured by cardiopulmonary exercise testing.

Chapter 5: The relationship of isometric and cyclical forearm exercise models to cardiopulmonary exercise testing

5.0 INTRODUCTION

In Chapters 2-4 I have shown that both a cyclical and isometric based forearm exercise model is possible as a bedside test, produces a defined metabolic response than can be used as an endpoint for the test and that the isometric model appears to stimulate anaerobic metabolism to a greater extent.

In addition in chapter 4 there appeared to be the emergence of two distinct groups. One that increased lactate production on isometric exercise and one that decreased lactate production on isometric exercise when compared with cyclical exercise. This concept will be explored further in relationship to anaerobic threshold of those individual's in this chapter.

In chapter 1 I have already described the utility of cardiopulmonary exercise testing as a marker of exercise and functional capacity and it's ability to help predict surgical outcome. This chapter will compare the results from formal cardiopulmonary exercise testing, (from which an anaerobic threshold will be derived) to the endpoints of both isometric

and cyclical forearm exercise testing. If a significant relationship can be demonstrated a distinct test endpoint will be defined.

5.1 MATERIALS AND METHODS

All eleven subjects who completed the isometric exercise program underwent cardiopulmonary exercise testing in a separate session and on a different day.

5.1.1 Cardiopulmonary exercise testing

The basis and interpretation of cardiopulmonary exercise testing has been described in Chapter 1, see pages 46-52.

5.1.2 Equipment and Protocol

Cardiopulmonary exercise testing was performed on a lode electronically braked bicycle ergometer that was controlled through Breeze (Medgraphics, UK) software. The bike height was set to ensure approximately 5 degrees of flexion in the knee at the bottom of the pedal crank so the subjects did not have to extend at the hip in order to reach the pedals. Handlebars were adjusted for comfort at the same time and each subject had an indication of their leg speed (rpm) displayed and were told to keep this between 50 and 60 rpm for the duration of the test.

A 12 lead exercise ECG was recorded concurrently and was linked into the Breezesuite™ software package (Medgraphics, UK), as was non-invasive blood pressure and continuous pulse oximetry.

The metabolic cart (CPX Ultima metabolic monitor, Medgraphics, UK) was connected to the subject by way of a sealed mouthpiece which was then connected to a Medgraphics preVent™ pneumotach device.

Before each test the metabolic cart was gas and flow calibrated according to its internal software as was the pneumotacograph using a super syringe. Gas calibration was done using the two-point method. During calibration adjustments for barometric pressure, humidity and temperature were made. The metabolic cart has oxygen and carbon dioxide analysers with a response time of 90 m/s or less to enable breath-by-breath measurement of carbon dioxide and oxygen.

Results were presented in a standard 9-panel plot format and V-slope comparison plot compiled by Breeze (Medgraphics, UK). These were stored in a separate database and later analysed by an independent assessor who was blinded to the subjects identity and forearm exercise results.

The rate of increment in work rate was predetermined using an estimate of expected work capacity. This was done in an objective manner to aim for test duration of approximately 6 to 10 minutes. Work rate was determined using the following equations:

1) VO_2 unloaded (ml/min) = 150 + (6 x weight (kg)

2) a) Peak VO_2 (ml/min) Men = height (cm) – age (years) x 20

b) Peak VO_2 (ml/min) Women = height (cm) – age (years) x 14

3. Work Rate increment (W/min) = (Peak VO_2 –VO_2 Unloaded) / 100

Subjects were allowed to rest for 5 minutes during which data was recorded to ensure that the subject was comfortable with the mouthpiece. During this time the respiratory exchange ratio was observed until it fell below 1, indicating that the subject was not hyperventilating.

The rest period was then followed by a period of 3 minutes of unloaded cycling. This allows for the oxygen cost of just turning the legs to be evaluated, provides minimum resistance and ensures that oxygen kinetics were not disrupted prior to the measurement of anaerobic threshold. After the rest cycle there was a continuous change into the ramp protocol that was predetermined as detailed above. Subjects were given verbal feedback and encouragement at all stages.

Core data displayed and recorded were Oxygen Consumption, Carbon dioxide production, Ventilation, Tidal Volume, Heart Rate, Ventilatory equivalents for Oxygen and Carbon Dioxide, Work Rate and Respiratory Exchange Ratio.

Subjects continued to exercise for 3 minutes beyond the attainment of perceived anaerobic threshold as judged by an independent cardiopulmonary testing technician to try and reduce any false positives.

The following criteria were used in combination to determine anaerobic threshold

1) Rising ventilatory efficiency for Oxygen

2) Plateau in Ventilatory efficiency for Carbon Dioxide

3) RER >1

4) Rising End Tidal Oxygen

5) Cross over of VCO_2 and VO_2 when plotted on same axis

6) Increase in gradient of VCO_2 vs. VO_2

As stated the raw data was stored and later analysed by an independent assessor who was blinded to the subjects identity and forearm exercise results.

5.2 RESULTS

5.2.1 Demographics

Eleven subjects underwent formal cardiopulmonary exercise testing to sub maximal levels of exercise. The demographics and weekly exercise patterns have already been described in chapter 3, (see Table 3.1).

Each subject completed the testing without error, except for one subject who had to repeat the test on the following day due to an inability to calibrate the gas sensors because of temperature fluctuations.

Table 5.1 shows individual data for anaerobic threshold and resting oxygen consumption. There is a broad range of anaerobic thresholds recorded ranging from 18.2 to 36.4 mls/Kg/min, but a high group mean (± SD), 27.4 (± 7.23) anaerobic threshold, as would be expected form a young and healthy cohort.

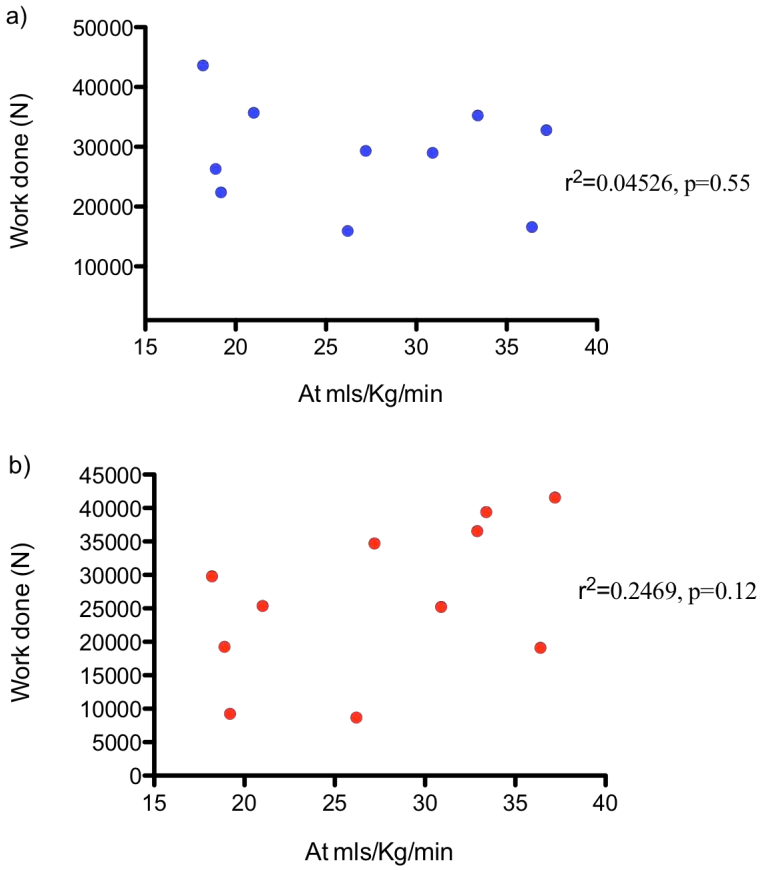
Table 5.1 Individual data from cardiopulmonary exercise testing.

	Anaerobic Threshold (At)		Resting oxygen consumption (VO_2)	
Subject	**mls/kg/min**	**mls/min**	**mls/kg/min**	**mls/min**
1	18.2	1563	6.5	556
2	27.2	2716	3.7	368
3	19.2	1366	4.3	304
4	21	1847	2.8	240
5	37.2	3532	3.7	351
6	26.2	1779	3.4	232
7	33.4	2605	5.6	434
8	30.9	2690	6.5	566
9	36.4	1711	4.5	212
10	18.9	1624	3.9	259
11	32.9	2746	6.1	506
Mean(SD)	27.41(7.23)	2198(686.8)	4.636(1.32)	366.2(131.7)

5.2.2 Work done vs. anaerobic threshold

When compared with work done during isometric and cyclical forearm exercise there was no clear relationship to anaerobic threshold, (see Figure 5.1).

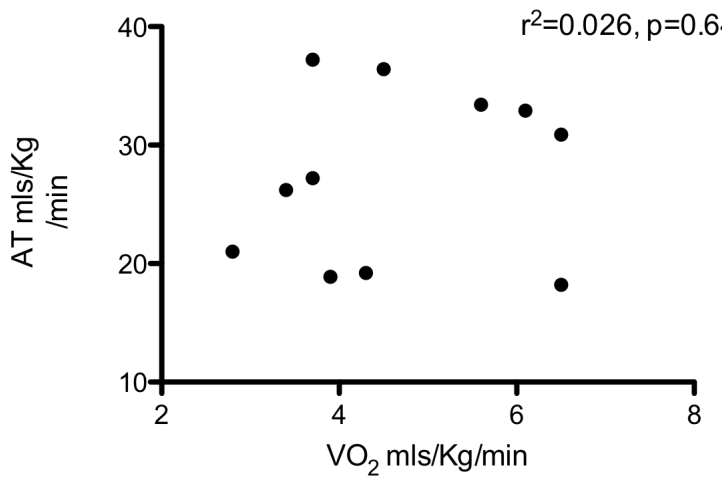
Figure 5.1 Scatter plots of work done vs. anaerobic threshold for a) cyclical and b) isometric exercise models.



5.2.3 Relationship between anaerobic threshold and resting oxygen consumption (VO_2)

Figure 5.2 demonstrates that there is no statistically significant relationship between resting oxygen consumption and anaerobic threshold.

Figure 5.2 Scatter plot of anaerobic threshold vs. resting oxygen consumption for all subjects.

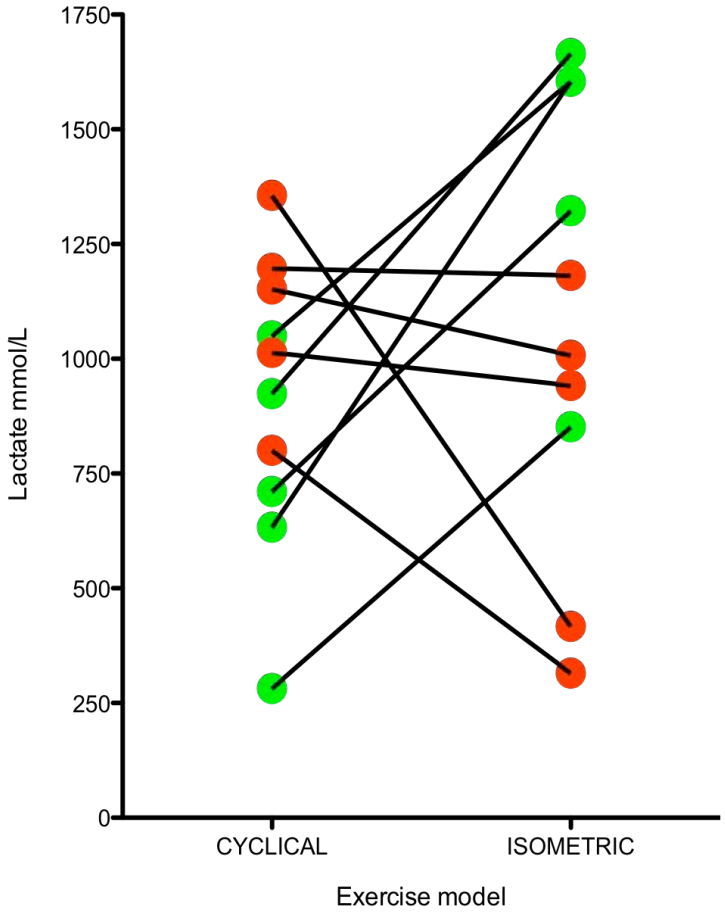


5.2.4 Difference in forearm lactate rise between isometric and cyclical models and relationship to anaerobic threshold

In chapter 4 it was shown there was a clear separation of two groups that either increased or decreased their forearm lactate production between cyclical and isometric exercise, (see Figure 5.3).

Figure 5.3 has been reproduced here for clarity to illustrate this point.

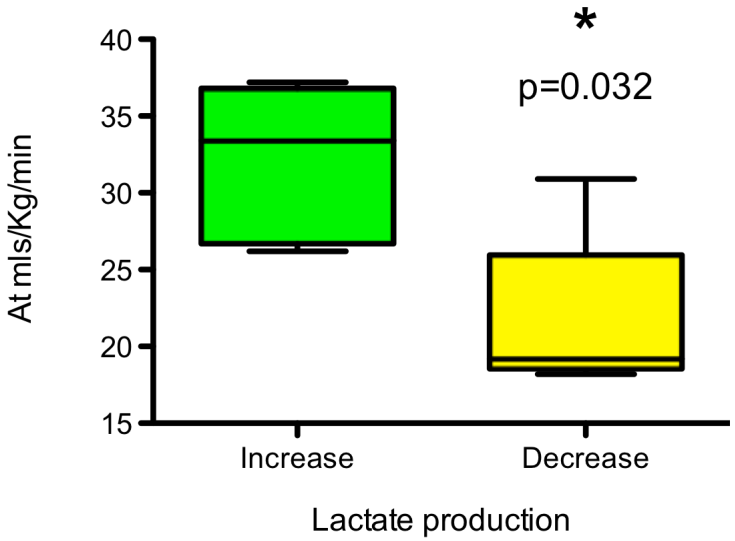
Figure 5.3 Total forearm lactate expression minus baseline lactate by each subject paired between cyclical and isometric handgrip models.



If the groups are separated into two, based on whether they increased or decreased their forearm lactate production during isometric exercise when compared to cyclical exercise, there is a clear and significant difference in the anaerobic threshold of these groups, (see Figure 5.4). Those subjects who increased their forearm lactate production had higher anaerobic thresholds, the lowest of which (26.2) is just below the group

mean of 27.4: (median (IQR) anaerobic threshold; Increase 33.4 (26.7 - 36.8) vs. Decrease 19.2 (18.55 – 25.95), p=0.032).

Figure 5.4 Box and whisker plot of anaerobic threshold vs. increase or decrease in forearm lactate production from cyclical to isometric exercise model



5.2.5 Isometric time points and anaerobic threshold

There were significant associations between forearm lactate, PO_2, SO_2, CO_2, and hydrogen ion concentration at all sampling intervals expect baseline (see Table 5.2).

There were no significant associations for STO_2 at any time point.

The strongest associations were with forearm lactate and pH, which showed significant associations at all time points except baseline. Significant associations were seen for SO_2 at 60, 120 and 180 seconds, for PO_2 at 180 seconds and for PCO_2 at 60, 120,180 and 300 seconds (see Figures 5.5 to 5.9 for linear regression scatter plots).

Those subjects with higher anaerobic thresholds produced more lactate, more CO_2 and more hydrogen ions. They also had lower values for PO_2, SO_2.

Table 5.2 Linear regression r^2 and significance level for Isometric handgrip exercise venous blood gas and NIRS STO_2 variables vs. Anaerobic threshold

	Lactate		**SO_2**		**PO_2**		**PCO_2**		**pH**		**STO_2**	
Sample Time	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p
0	0.1754	ns	0.1827	ns	0.001522	ns	0.2723	ns	0.2713	ns	0.0199	ns
60	0.4681	0.0202	0.4385	0.0264	0.04949	ns	0.572	0.0071	0.6085	0.0046	0.03252	ns
120	0.5512	0.0089	0.5666	0.0075	0.008259	ns	0.6495	0.0027	0.6105	0.0045	0.004651	ns
180	0.4581	0.0222	0.3873	0.0409	0.3888	0.0404	0.3949	0.0384	0.5236	0.0118	0.0001942	ns
300	0.6779	0.0018	0.1138	ns	0.09231	ns	0.3774	0.0443	0.5393	0.0101	0.1212	ns
600	0.5997	0.0051	0.008214	ns	0.004474	ns	0.0833	ns	0.6415	0.0031	0.346	ns

Significant results are highlighted in yellow. Sample time-seconds, Lactate=mmo/L, SO_2=Venous blood gas oxygen saturation, PO_2=Venous blood gas oxygen tension in Kpa, PCO_2=Venous blood gas carbon dioxide tension in Kpa, STO_2=Tissue oxygen saturation from NIRS in %

Figure 5.5 Scatter plots for Forearm lactate vs. anaerobic threshold. i) All sampling points with best fit line and ii) Significant linear regression plots with best fit line and 95% confidence intervals for sampling points at a) 60, b) 120, c) 180, d) 300, & e) 600 seconds.

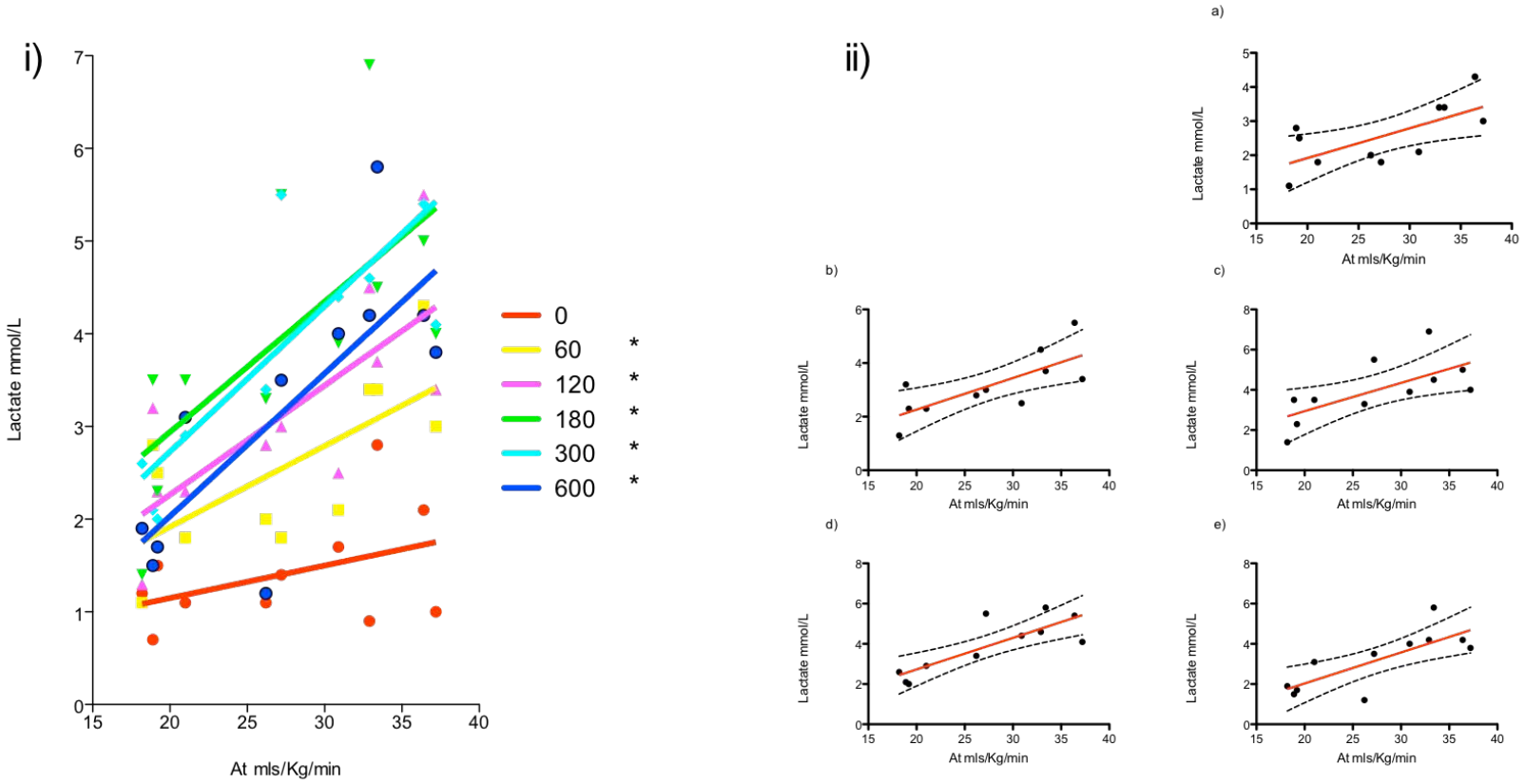


Figure 5.6 Scatter plots for SO_2% vs. anaerobic threshold. i) All sampling points with best fit line and ii) Significant linear regression plots with best fit line and 95% confidence intervals for sampling points at a) 60, b) 120, c) 180 seconds.

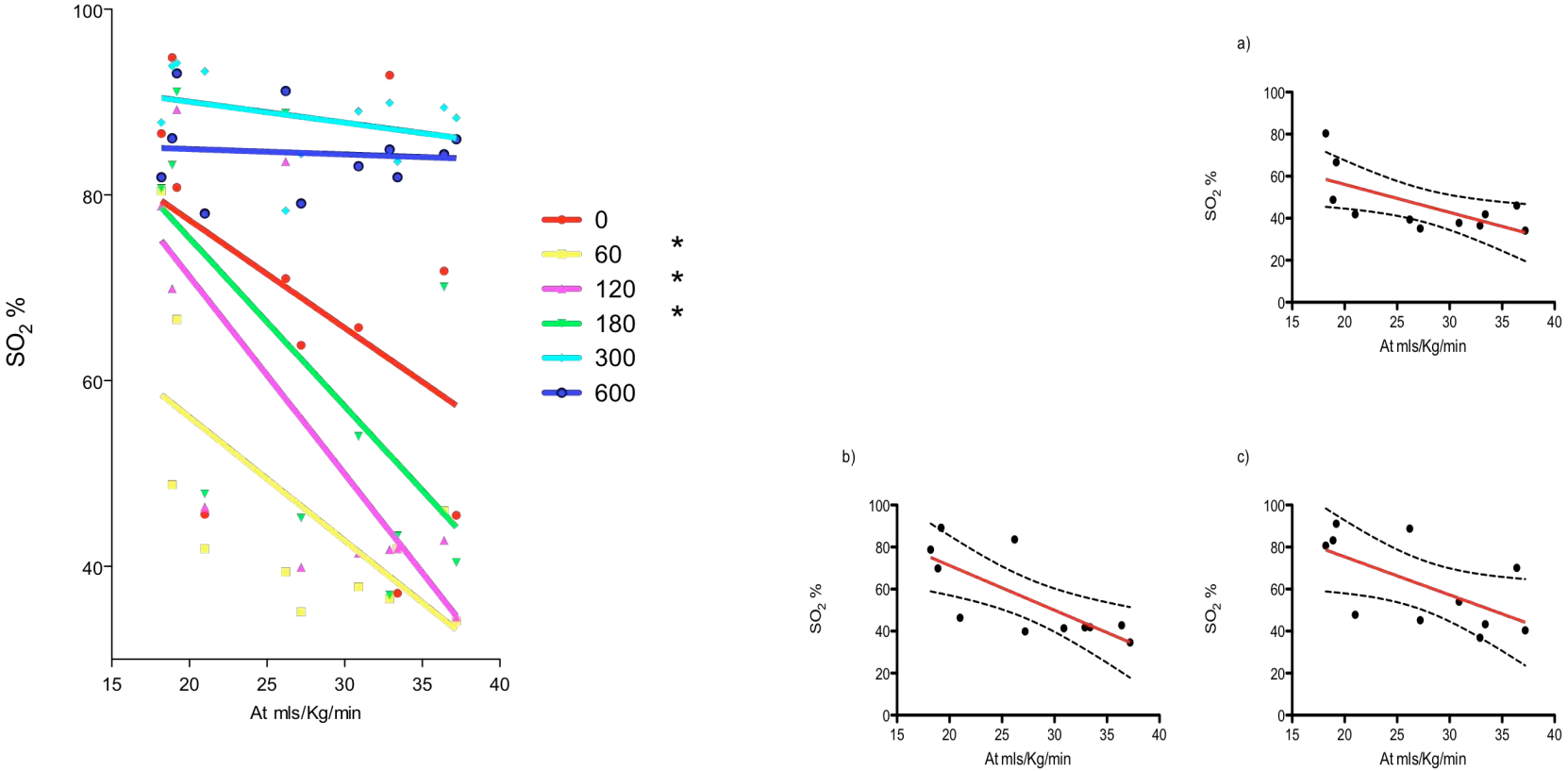


Figure 5.7 Scatter plots for PCO_2 vs. anaerobic threshold. i) All sampling points with best fit line and ii) Significant linear regression plots with best fit line and 95% confidence intervals for sampling points at a) 60, b) 120, c) 180 & d) 300 seconds.

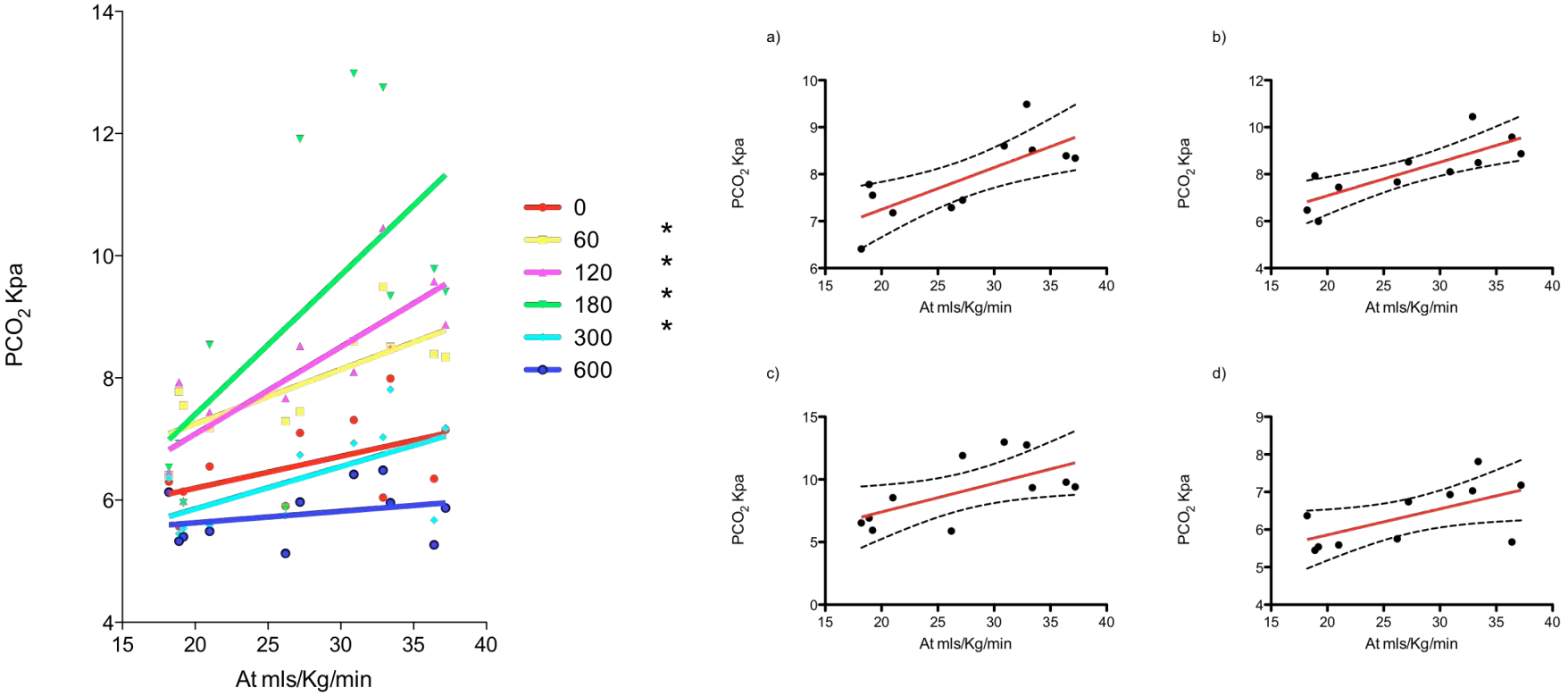


Figure 5.8 Scatter plots for pH vs. anaerobic threshold. i) All sampling points with best fit line and ii) Significant linear regression plots with best fit line and 95% confidence intervals for sampling points at a) 60, b) 120, c) 180 & d) 300 & e) 600 seconds.

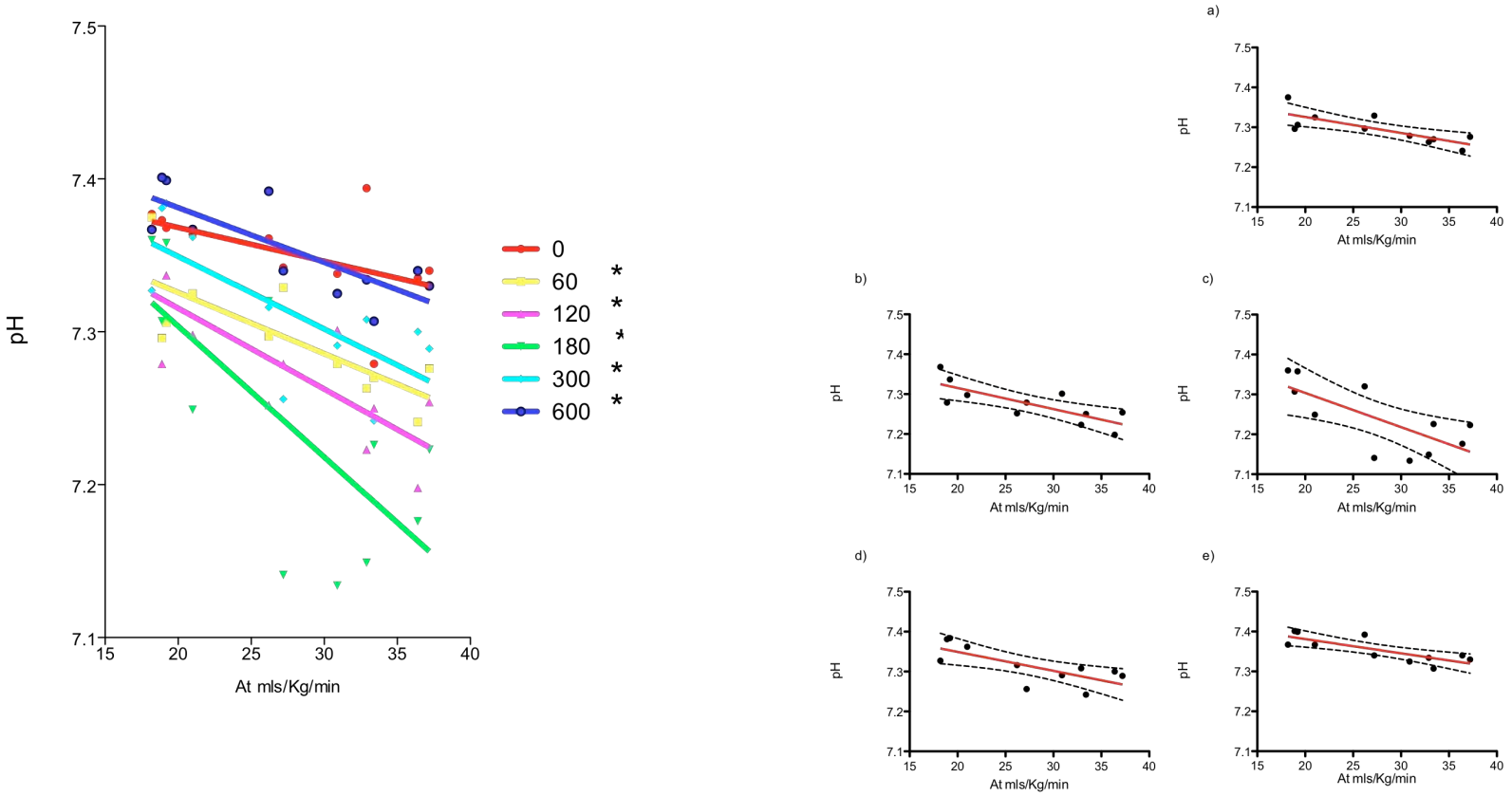
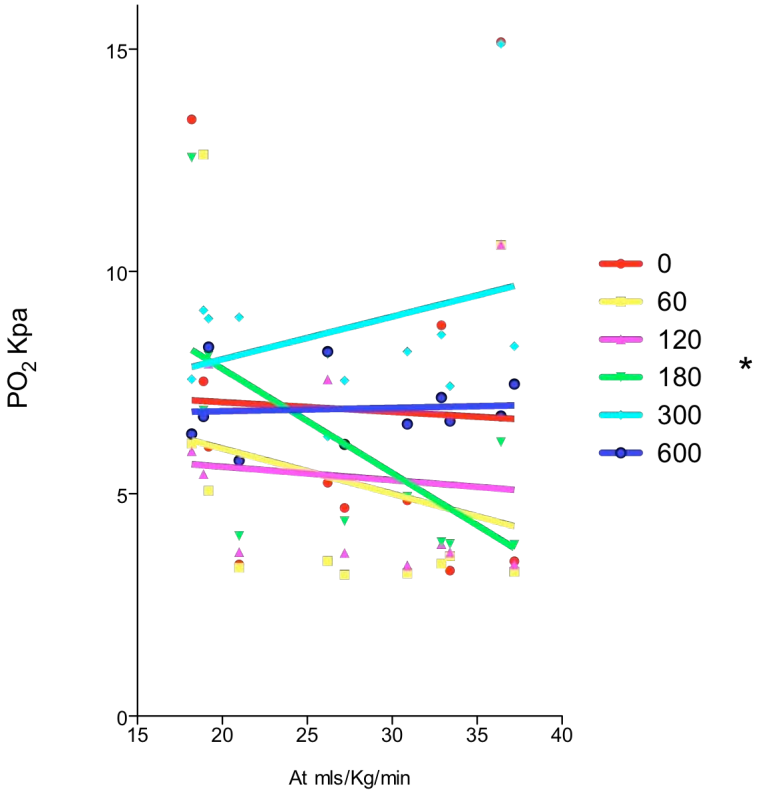
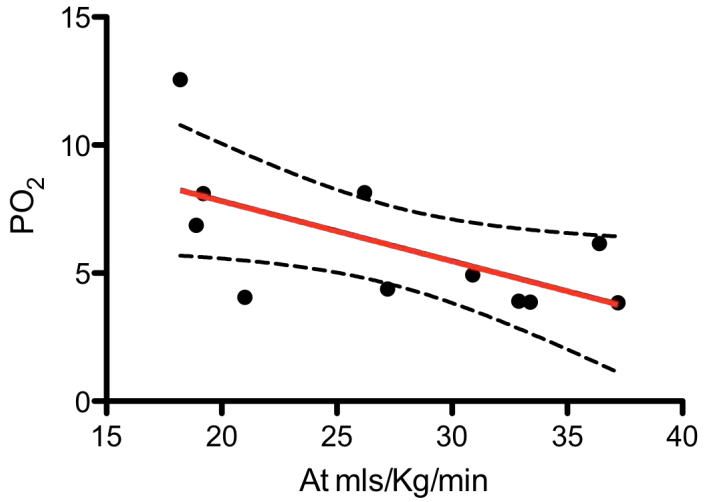


Figure 5.9 Scatter plots for PO_2 vs. anaerobic threshold. i) All sampling points with best fit line and ii) Significant linear regression plots with best fit line and 95% confidence intervals for sampling point at 180 seconds.





5.2.6 Isometric endpoint summary measures and anaerobic threshold

There were fewer significant associations between the endpoint summaries for isometric exercise and anaerobic threshold.

Forearm lactate, SO_2, CO_2, and hydrogen ion concentration all showed significant associations with anaerobic threshold, but not for all variables, (see Tables 5.3, 5.4, 5.6 & 5.7 and Figures 5.10, 5.11, 5.12 & 5.13 respectively).

There were no significant associations for PO_2, STO_2 or dynamometry, (see Tables 5.5, 5.8 & 5.9 respectively).

Table 5.3 Linear regression results for forearm lactate vs. anaerobic threshold

Lactate	n=11		r^2	P value	
Lactate baseline	median(IQR)	1.409(0.6057)	0.1754	0.1999	ns
Lactate peak	mean(SD)	4.336(1.419)	0.544	0.0096	*
Lactate peak-baseline	mean(SD)	2.927(1.336)	0.3523	0.0542	ns
Lactate peak % change over baseline	mean(SD)	246.2(170.9)	0.04469	0.5326	ns
Lactate cumulative	mean(SD)	2036(686.3)	0.7475	0.0006	*
Lactate cumulative - baseline	mean(SD)	1190(560)	0.6206	0.004	*
Lactate cumulative/sec	mean(SD)	3.393(1.144)	0.7475	0.0006	*

Figure 5.10 Linear regression scatter plots with best fit line and 95% CI for significant forearm lactate results

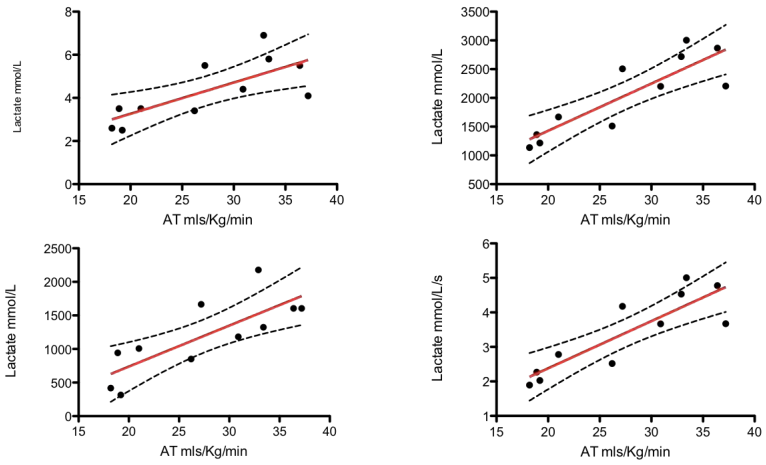


Table 5.4 Linear regression results for SO_2 vs. anaerobic threshold

SO_2	n=11		r^2	P value	
SO_2 baseline	mean(SD)	68.69(19.63)	0.1827	0.1898	ns
SO_2 nadir	mean(SD)	39.4(36.5-48.8)	0.5034	0.0145	*
SO_2-baseline	median(IQR)	-23.34(17.76)	0.01053	0.764	ns
SO_2 peak % change over baseline	mean(SD)	-31.03(19.93)	0.05404	0.4915	ns
SO_2 cumulative	mean(SD)	44975(4740)	0.4947	0.0157	*
SO_2 cumulative -baseline	mean(SD)	3761(9226)	0.03393	0.5877	ns
SO_2/sec	mean(SD)	74.96(7.9)	0.4947	0.0157	*

Figure 5.11 Linear regression scatter plots with best fit line and 95% CI for significant SO_2 results

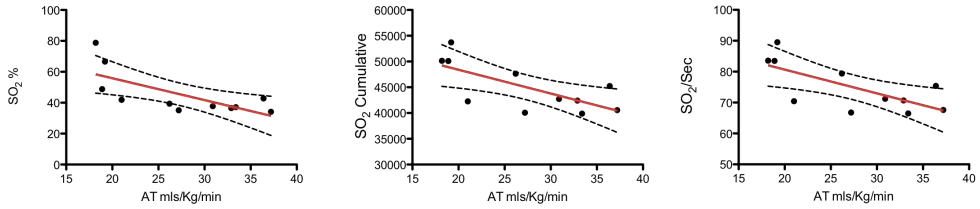


Table 5.5 Linear regression results for PO_2 vs. anaerobic threshold

PO_2	n=11		r^2	P value	
PO_2 baseline	mean(SD)	6.9(4.054)	0.001522	0.9093	ns
PO_2 nadir	mean(SD)	3.43(3.25-5.44	0.1342	0.2678	ns
PO_2 nadir-baseline	mean(SD)	-1.64(-5.36-(-0.23))	0.008611	0.7861	ns
PO_2 peak % change over baseline	mean(SD)	-29.83(22.2)	0.004594	0.843	ns
PO_2 cumulative	mean(SD)	4265(911.8)	0.00447	0.8452	ns
PO_2 cumulative-baseline	mean(SD)	782.7(-1343-1476)	0.0003852	0.9543	ns
PO_2 /sec	mean(SD)	7.108(1.52)	0.00447	0.8452	ns

Table 5.6 Linear regression results for CO_2 vs. anaerobic threshold

CO_2	n=11		r^2	P value	
CO_2 baseline	median(IQR)	6.582(0.7222)	0.2723	0.0997	ns
CO_2 peak	mean(SD)	9.49(2.19)	0.3624	0.05	ns
CO_2 peak -baseline	mean(SD)	2.908(2.017)	0.2178	0.1478	ns
CO_2 peak % change over baseline	mean(SD)	44.39(31.04)	0.1792	0.1945	ns
CO_2 cumulative	mean(SD)	4181(528.1)	0.5337	0.0107	*
CO_2 cumulative -baseline	mean(SD)	232.1(426.2)	0.1403	0.2563	ns
CO_2 cumulative/sec	mean(SD)	6.969(0.8802)	0.5337	0.0107	*

Figure 5.12 Linear regression scatter plots with best fit line and 95% CI for significant CO_2 results

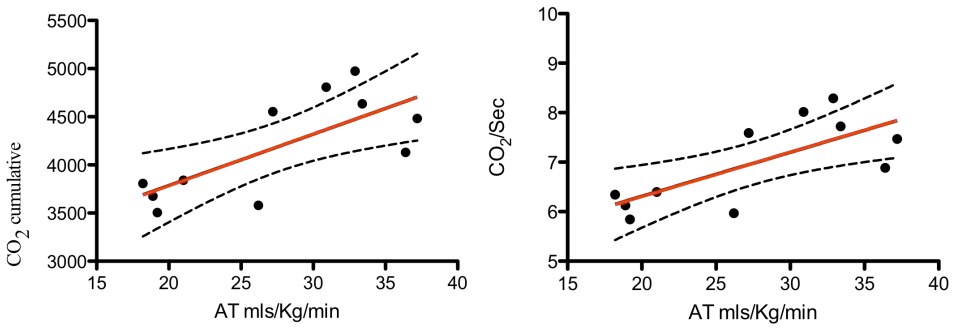


Table 5.7 Linear regression results for Hydrogen ion concentration vs. anaerobic threshold

$[H]^+$	n=11		r^2	P value	
$[H]^+$ baseline	mean(SD)	0.00000004458(3.26E-09)	0.2687	0.1023	ns
$[H]^+$ peak	median(IQR)	0.00000006018(9.305E-09)	0.4351	0.0272	*
$[H]^+$ peak-baseline	median(IQR)	0.0000000156(9.345E-09)	0.2265	0.1389	ns
$[H]^+$ peak % change over baseline	median(IQR)	35.38(21.74)	0.1952	0.1737	ns
$[H]^+$ cumulative	median(IQR)	0.00002973(0.000002753)	0.7721	0.0004	*
$[H]^+$ cumulative-baseline	mean(SD)	0.000002981(0.000002211)	0.404	0.0356	*
$[H]^+$ cumulative/sec	mean(SD)	0.00000004954(4.589E-09)	0.7721	0.0004	*

Figure 5.13 Linear regression scatter plots with best fit line and 95% CI for significant $[H]^+$ results

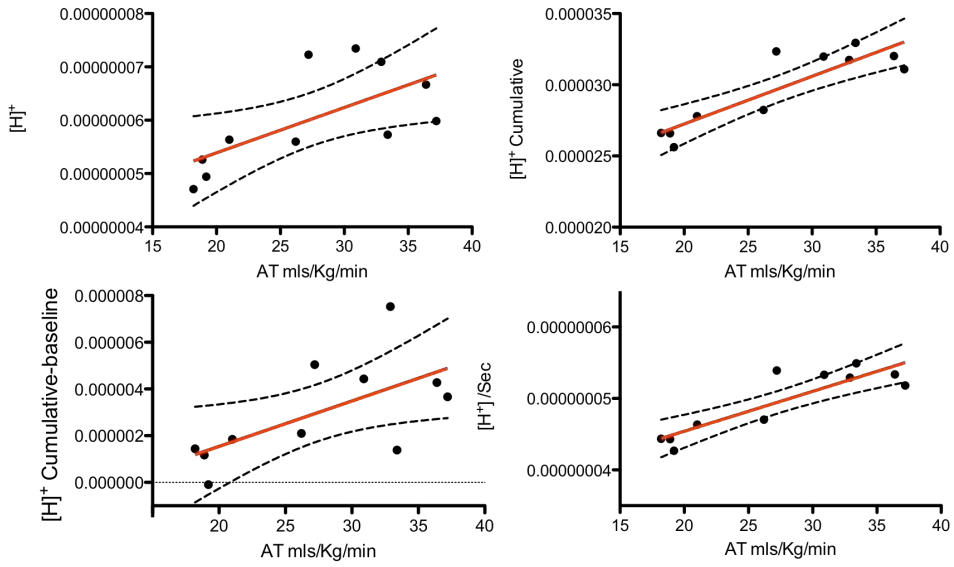


Table 5.8 Linear regression results for NIRS vs. anaerobic threshold

STO_2	n=11		r^2	P value	
STO_2 baseline	mean(SD)	80.09(9.428)	0.0199	0.6791	ns
STO_2 nadir	mean(SD)	60.27(15.23)	0.009659	0.7737	ns
STO_2 nadir-baseline	mean(SD)	-19.82(11.32)	0.0002181	0.9656	ns
STO_2 peak % change over baseline	mean(SD)	-25.31(16.53)	0.0005629	0.9448	ns
STO_2 cumulative	mean(SD)	47768(4702)	0.1455	0.247	ns
STO_2 cumulative-baseline	mean(SD)	-286.4(3268)	0.09284	0.3623	ns
STO_2 /sec	mean(SD)	81.25(79.25-82.55)	0.1455	0.247	ns
NIRS STO_2 slope	mean(SD)	11.94(6.481-41)	0.02826	0.6425	ns
NIRS THI average	mean(SD)	11.33(2.495)	0.09253	0.3928	ns
NIRS $V0_2$	mean(SD)	152.8(62.16-475.4)	0.03315	0.6146	ns

Table 5.9 Linear regression results for dynamometry vs. anaerobic threshold

Dynamometer	n=11		r^2	P value	
Maximum strength value	mean(SD)	355.6(80.07)	0.08996	0.3702	ns
Exercise time (secs)	mean(SD)	151.9(47.89)	0.1974	0.171	ns
Borg rating	mean(SD)	15.91(2.427)	0.001378	0.9137	ns
work done	mean(SD)	26257(11388)	0.2469	0.12	ns

5.2.7 Cyclical time points and anaerobic threshold

There were no significant associations for forearm lactate, PO_2, SO_2, CO_2, hydrogen ion concentration or STO_2 at any of the sampling intervals. Table 5.10 shows the linear regression results for all time points.

5.2.8 Cyclical endpoint summary measures and anaerobic threshold

There were no significant associations for any endpoint summary measures for forearm lactate, PO_2, SO_2, CO_2, hydrogen ion concentration or STO_2 and anaerobic threshold. Results are shown in the Appendix for completeness.

Table 5.10 Linear regression r^2 and significance level for cyclical handgrip exercise venous blood gas and NIRS STO_2 variables vs. Anaerobic threshold

	Lactate		**SO_2**		**PO_2**		**PCO_2**		**pH**		**STO_2**	
Sample Time	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p	r^2	p
0	0.1581	ns	0.2197	ns	0.2745	ns	0.05482	ns	0.05482	ns	0.07423	ns
60	0.061	ns	0.02658	ns	0.02554	ns	0.01413	ns	0.01413	ns	0.002694	ns
120	0.006956	ns	0.0004449	ns	0.00592	ns	0.0009365	ns	0.0009365	ns	0.02133	ns
180	0.0013	ns	0.08377	ns	0.01777	ns	0.002931	ns	0.002931	ns	0.01702	ns
300	0.01028	ns	0.1386	ns	0.03741	ns	0.1217	ns	0.1217	ns	0.13	ns
600	0.03383	ns	0.03157	ns	0.04382	ns	0.07896	ns	0.07896	ns	0.1068	ns

Significant results are highlighted in yellow. Sample time-seconds, Lactate=mmo/L, SO_2=Venous blood gas oxygen saturation, PO_2=Venous blood gas oxygen tension in Kpa, PXO_2=Venous blood gas carbon dioxide tension in Kpa, STO_2=Tissue oxygen saturation from NIRS in %

5.3 Discussion

Demographically the group of subjects displayed a broad range of anaerobic thresholds (18.2 to 36.4 mls/Kg/min), with those at the upper end of the spectrum demonstrating higher than average levels of exercise capacity implying a partially aerobically trained cohort, with weekly exercise times of up to 410 minutes.

There is no documented link between resting oxygen consumption and anaerobic threshold, which was confirmed in this study [254].

As hypothesised there was no clear demonstrable relationship between work done in either the isometric or cyclical forearm model and anaerobic threshold or resting oxygen consumption. There was however a trend towards more work done in those with a higher anaerobic threshold for the isometric model.

The difference in performance of each subject in the cyclical and isometric forearm models as touched upon in chapter 4 is of interest when examined by anaerobic threshold. There was a significant difference in anaerobic threshold for those subjects who saw an increase in their total forearm lactate in isometric compared to cyclical forearm exercise, median (IQR) anaerobic threshold (increase vs. decrease) 33.4 (26.7-36.8) vs. 19.2 (18.55-25.95), P=0.032. There are a number of possible explanations for this of which the most probable is that isometric forearm is predominantly an ischemic model and relies heavily on anaerobic respiration for sustained muscle contraction. Those subjects with high anaerobic thresholds may better tolerate the lactate

accumulation due to conditioning and be better able to use the lactate produced to regenerate ATP. This is consistent with observations in elite athletes who may produce less lactate at a given workload than untrained individuals but are capable of producing larger amounts of lactate as workload increases, as they seemingly do not fatigue to the same extent and may use the lactate produced in a far more efficient way to refuel the metabolic processes [205].

The most striking finding however is the consistent and significant relationship of fixed time point and endpoint summaries of metabolic performance in the isometric forearm exercise model being related to anaerobic threshold but not those from the cyclical forearm exercise model. STO_2 however showed no significant association with either model, brining into question it's suitability for monitoring in this model.

As has been stated above the most probable explanation for the relationship to isometric testing and not to cyclical testing is the strong anaerobic and high intensity exercise undertaken in isometric testing. Although the physiological mechanism may be different between whole body exercise, which has equal reliance on the cardiorespiratory system and exercise in a small muscle group such as the forearm, they may be measuring a similar process of anaerobic respiration.

It is important to state however that although the relationships were statistically significant the strength of the relationship was moderate at best with the best r^2 value being 0.68 for lactate at 300 seconds.

It is equally important to state that the numbers in this study were small and statistical error due to the small sample size must be noted, but the consistency of the result is encouraging. One of the consistent deficiencies in this thesis is the lack of testing in an elderly population with significant comorbidities. It is possible that for patients with very low anaerobic thresholds close to 11 mls/Kg/min that the signal may be stronger as they are likely to be similar to those with chronic heart failure who show persistently poor peripheral oxidative capacity. I plan to look at this population however in work that will follow this thesis.

It is also probable that using a continuous analysis technique with catheters such as the Paratrend™ in the antecubital vein we may be able to improve the sensitivity of the test and be able to identify an inflection point in the venous metabolic markers of metabolism. It is unlikely that there will be a sharp change in any variable such as oxygen or the production of lactate, but the use of a continuous technique would allow the identification of the beginning of a rise or fall in the substrate for or the metabolites of aerobic respiration. There are many devices on the market that could have potential usefulness, for instance the improvement in microdialysis equipment would allow for an implantable that may extend its life into the Intraoperative and postoperative period, but that is not the subject of this thesis. Again future wok is planned to look at this possibility.

Because of the relationship seen with isometric exercise testing and anaerobic threshold this model was taken forward to test in an orthopaedic group of patients which is the subject of Chapter 6.

5.4 Conclusions

Of the two forearm exercise tests it was the isometric one that showed a positive and consistent relationship with anaerobic threshold as measured by cardiopulmonary exercise testing.

Based on the linear regression data the most promising test endpoints are cumulative lactate, cumulative hydrogen ion production and forearm lactate at 300 seconds. These will be identified as possible predictors of surgical outcome in substitution of anaerobic threshold as measured by cardiopulmonary exercise testing and will be used in chapter 6 to try and predict outcome in an orthopaedic surgical population undergoing joint replacements.

Of note there were no significant relationships demonstrable between cyclical exercise testing and cardiopulmonary exercise testing.

Of additional and unique interest is the finding that as a group, those who produced more lactate in the isometric model of exercise had significantly higher anaerobic threshold levels. This has not been shown before but may reflect the phenomena shown in elite athletes that are much better able to utilise lactate as a fuel by transporting it to other parts of the body where it can be processed.

5.5 Appendix

Cyclical endpoint summary measures and anaerobic threshold

Table 5.11 Cyclical endpoint summary measures vs. anaerobic threshold

Lactate

Lactate	n=10		r^2	P value	
Lactate baseline	median(IQR)	0.95(0.875-1.325)	0.1581	0.2551	ns
Lactate peak	mean(SD)	3.24(0.7891)	0.00441	0.8554	ns
Lactate peak-baseline	mean(SD)	2.09(0.6173)	0.06296	0.4844	ns
Lactate peak % change over baseline	mean(SD)	203.8(82.05)	0.195	0.2014	ns
Lactate cumulative	mean(SD)	1602(398.9)	0.006053	0.8308	ns
Lactate cumulative - baseline	mean(SD)	912(315)	0.08778	0.4058	ns
Lactate cumulative/sec	mean(SD)	2.67(0.6649)	0.006053	0.8308	ns

Hydrogen ion concentration

$[H]^+$	n=10		r^2	P value	
$[H]^+$ baseline	mean(SD)	0.00000004124(1.616E-09)	0.07423	0.4463	ns
$[H]^+$ peak	median(IQR)	0.00000005795(5.228E-08-5.677E-08)	0.1008	0.3713	ns
$[H]^+$ peak-baseline	median(IQR)	0.00000001241(9.862E-09-1.661E-08)	0.123	0.3204	ns
$[H]^+$ peak % change over baseline	median(IQR)	29(23.25-41.36)	0.1275	0.311	ns
$[H]^+$ cumulative	median(IQR)	0.0000303(0.00002848-0.00003108)	0.1171	0.3331	ns
$[H]^+$ cumulative-baseline	mean(SD)	0.000004856(0.00000175)	0.06235	0.4866	ns
$[H]^+$ cumulative/sec	mean(SD)	0.00000004933(3.414E-09)	0.1171	0.3331	ns

PCO_2

CO_2	n=10		r^2	P value	
CO_2 baseline	median(IQR)	5.75(5.63-6.005)	0.05482	0.515	ns
CO_2 peak	mean(SD)	8.244(0.8187)	0.0003728	0.9578	ns
CO_2 peak -baseline	mean(SD)	2.378(0.5724)	0.02431	0.6671	ns
CO_2 peak % change over baseline	mean(SD)	40.55(9.62)	0.05975	0.4961	ns
CO_2 cumulative	mean(SD)	931.2(316.8)	0.08666	0.409	ns
CO_2 cumulative -baseline	mean(SD)	810.5(301.9)	0.02747	0.6473	ns
CO_2 cumulative/sec	mean(SD)	7.217(0.7437)	0.0642	0.48	ns

PO_2

PO_2	n=10		r^2	P value	
PO_2 baseline	mean(SD)	4.986(1.072)	0.2745	0.1201	ns
PO_2 nadir	mean(SD)	3.738(0.4258)	0.00301	0.8803	ns
PO_2 nadir-baseline	mean(SD)	-1.248(0.9714)	0.3441	0.0747	ns
PO_2 peak % change over baseline	mean(SD)	-22.85(13.21)	0.3075	0.0962	ns
PO_2 cumulative	mean(SD)	1290(103.3)	0.08215	0.422	ns
PO_2 cumulative-baseline	mean(SD)	-1702(555)	0.3065	0.0968	ns
PO_2 /sec	mean(SD)	2.149(0.1721)	0.08215	0.422	ns

SO_2

SO_2	n=10		r^2	P value	
SO_2 baseline	mean(SD)	69.15(11.33)	0.2197	0.1718	ns
SO_2 nadir	mean(SD)	46.58(6.236)	0.04538	0.5546	ns
SO_2-baseline	median(IQR)	-21.4(-27.08-(-16.6))	0.2766	0.1184	ns
SO_2 peak % change over baseline	mean(SD)	-32.1(6.137)	0.2202	0.1712	ns
SO_2 cumulative	mean(SD)	16425(1621)	0.1021	0.3681	ns
SO_2 cumulative - baseline	mean(SD)	-25065(5462)	0.2388	0.1518	ns
SO_2/sec	mean(SD)	27.37(2.702)	0.1021	0.3681	ns

STO_2

STO_2	n=10		r^2	P value	
STO_2 baseline	mean(SD)	79.1(12.4)	0.04367	0.5623	ns
STO_2 nadir	mean(SD)	56(15.28)	0.008093	0.8048	ns
STO_2 nadir-baseline	mean(SD)	-23.1(15.29)	0.06729	0.4692	ns
STO_2 peak % change over baseline	mean(SD)	-28.56(17.94)	0.06507	0.4769	ns
STO_2 cumulative	mean(SD)	20847(3479)	0.005003	0.846	ns
STO_2 cumulative-baseline	mean(SD)	720.1(559.7)	0.3422	0.0757	ns
STO_2 /sec	mean(SD)	79.32(8.196)	0.133	0.3001	ns
NIRS STO_2 slope	mean(SD)	33.63(35.91)	0.01308	0.7531	ns
NIRS THI average	mean(SD)	11.24(2.382)	0.05588	0.5108	ns
NIRS $V0_2$	mean(SD)	355(344.8)	0.02319	0.6745	ns

Dynamometry

Dynamometer	n=10		r^2	P value	
Maximum strength value	mean(SD)	213.2(68.17)	0.03142	0.6242	ns
Fatigue rate	mean(SD)	48.76(27.91)	0.1746	0.2296	ns
Borg rating	mean(SD)	13(1.247)	0.3726	0.0609	ns

Chapter 6: PILOT STUDY OF HANDGRIP EXERCISE TO PREDICT POSTOPERATIVE OUTCOME IN AN ORTHOPAEDIC POPULATION

6.0 Introduction

In chapter 1 the difficulty of predicting surgical outcome, the basis of exercise physiology, the potential advantages of functional capacity testing and the perioperative use of handgrip dynamometry were detailed.

In chapters 2 & 3 the development and performance of cyclical and isometric forearm exercise models were described. Each was possible and found to produce a biological signal worthy of further investigation.

In chapter 4 both forearm exercise models were compared and their advantages and disadvantages discussed.

In chapter 5 the clear relationship between formal cardiopulmonary exercise testing and the isometric handgrip model was shown and taken forward to test in an orthopaedic surgical population. In particular the strong association between cumulative lactate, cumulative hydrogen ion production and forearm lactate at 300 seconds.

This chapter will present the results of the use of an isometric forearm exercise model to predict surgical outcome in a prospective study of orthopaedic patients undergoing joint replacement surgery.

6.1 Materials and Methods

6.1.1 Study design

A prospective observational trial of a preoperative handgrip exercise model in single joint replacement orthopaedic surgery to predict surgical outcome. Full permission for the study was obtained from the local research and ethics committee of UCLH.

6.1.2 Patient selection

6.1.2.1 Inclusion criteria

Any adult patient (>18 years old) undergoing primary joint replacement surgery by one of three named surgeons.

6.1.2.2 Exclusion criteria

Any adult patient with hand or elbow joint deformity problems that would prevent handgrip exercise.

6.1.3 Protocol

Patients were approached 24 hours before their planned surgery for possible inclusion in the study. Full written informed consent was obtained from willing patient volunteers. Before entering the study a medical history was taken and a physical examination performed.

All patients were admitted to the Middlesex hospital the night before surgery and had their operation performed at the Middlesex hospital. Isometric exercise testing was performed in the non-fasted state the

evening before surgery by myself. All patients were given instructions and verbal coaching prior to and during the forearm exercise period.

A specialised trolley was constructed to allow the transport of the testing equipment to the patient's bedside. Patients were tested whilst sitting up in bed, with the arm supported on a bedside table to mimic the same conditions as achieved in the healthy volunteers. A 20G cannula was inserted into the antecubital fossae of the patient's non-dominant forearm and a baseline blood gas sample taken for analysis, five minutes after venous occlusion had ceased to allow for venous congestion and potential alterations in oxygen and forearm lactate metabolism to stabilise, as demonstrated in chapter 2. The patient's MVC was established as described in the handgrip dynamometry section.

Patients followed the isometric exercise regime as described in chapter 3 with sampling at 0,60,120,180,300 and 600 seconds. The dead space of the cannula was discarded and the cannula flushed with 2 mls of 0.9% saline before and after each sampling respectively. Once the patients MVC had been established the computer was set to a target of 50% of MVC and exercise commenced in exactly the same manner as described in chapter 3.

6.1.4 Data collected

The apparatus setup and data collected were exactly the same as in the isometric model and have already been described in detail in chapter 3.

In addition data on postoperative complications was recorded on days 3,5,8 and 15 using the postoperative morbidity survey (POMS) [8]. This

was collected by a research nurse form the surgical outcomes research centre and UCLH, to ensure blinding to the results of forearm exercise testing.

Patients were additionally risk scored preoperatively using Detsky, Lee, American College of Cardiology/American Heart Association and POSSUM methodologies.

Length of stay and hospital mortality was recorded retrospectively upon patient discharge or death.

Anaesthesia was left to the discretion of the anaesthetist.

6.1.5 Statistical analysis

All analyses were done using Graphpad Prism 5 for Macintosh (Graphpad software, San Diego, California). All data are expressed as means (± standard deviation) where normally distributed unless otherwise stated. Statistical significance was set at $p<0.05$.

The study was powered on the basis of results from the healthy volunteer data and a similar cohort of patients who had undergone elective orthopaedic surgery at University College London Hospitals, where 50% of patients sustained postoperative morbidity. From the healthy volunteer data, our primary hypothesis was that a minimum detectable difference in venous lactate of 2mmol/l, with an anticipated standard deviation of 1mmol/l, would occur in the 50% patients predicted from our extensive previous POMS outcome studies in orthopaedic patients to sustain postoperative morbidity. Thus, 21 patients would be required (alpha= 0.01; power=90%). Kaplan-Meier survival plots were also used to assess

the relationship between the handgrip metabolic variables and length of stay, stratified according to peak lactate values < >median for the whole patient population (log-rank test).

6.2 Results

Twenty two patients were recruited to the study. One patient withdrew their consent prior to any study procedures for personal reasons; hence 21 patients were included in the final analysis.

6.2.1 Demographics

Individual patient demographics are shown in Table 6.1. Eight patients had hip replacements and 14 patients had knee replacement operations. Three different consultant surgeons performed the operations. The distribution of male and female patients was approximately equal with 10 female and 11 male patients. The average age of the population was 69.67(±10.51) years and there was no significant difference between males and females, Male=69.55(±10.64) and Female=69.8-(±10.93).

Male patients were not significantly heavier 87(70-105) vs. 74.5(70-77.5) Kg, p=0.23), but were significantly taller 1.73(±0.11) vs. 1.61(±0.09), p=0.009).

Table 6.1 Individual Patient Demographics

PAT	AGE	SEX	WT	HT	BMI	Hand	ASA	Procedure	OT
1	65	M	105	1.75	34	L	1	HR(L)	160
2	66	F	67	1.47	31	R	2	HR(R)	180
3	88	M	63	1.55	26	R	2	KR(R)	132
4	62	F	70	1.57	28	L	1	KR(R)	123
5	65	M	127	1.83	38	R	2	KR(R)	136
6	63	M	80	1.83	24	R	2	KR(L)	150
7	54	M	114	1.78	36	R	1	KR(R)	145
8	55	F	75	1.65	28	R	2	KR(R)	132
9	77	F	74	1.63	28	R	2	THR(L)	206
10	83	F	70	1.52	30	L	2	TKR(R)	167
11	71	M	101	1.85	30	R	3	KR(R)	95
12	75	F	73	1.65	27	R	2	TKR(L)	140
13	88	F	75	1.57	30	R	2	THR(L)	136
14	60	F	82	1.75	27	L	3	TKR(L)	110
15	66	M	61	1.63	23	R	1	THR(L)	156
16	72	F	116	1.72	39	R	2	TKR(L)	155
17	72	M	87	1.73	29	R	1	TKR(L)	140
18	60	F	76	1.52	33	R	2	KR(L)	140
19	59	M	103	1.8	32	R	2	KR(R)	132
20	87	M	76	1.7	26	R	2	THR(L)	200
21	75	M	70	1.57	28	L	1	KR(R)	152

PAT=patient, WT=weight, HT=height, BMI=body mass index, Hand=hand dominance, ASA=ASA score, OT=operative time(minutes), LOS=length of stay, THR=Total Hip replacement, TKR=Total Knee replacement, HR=Hip replacement, KR=Knee replacement

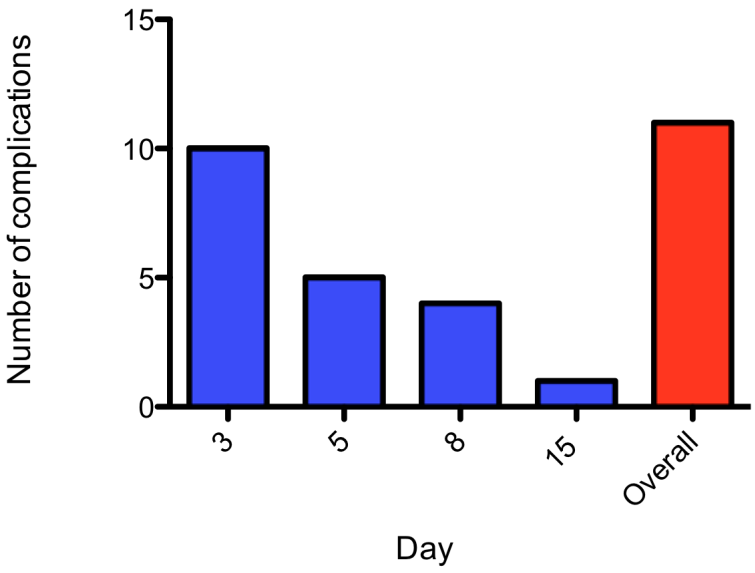
For overall complications there was an excess of female patients developing one or more complications as defined by POMS during their hospital stay (see Table 6.2). Figure 6.1 shows the decline in complications over time as well as the number of patients with a complication at any point in their stay, indicating that just over half the patients developed at least one complication during their stay. There was

a significant difference in the proportion of complications between male and female patients (p=0-001) with a relative risk of 0.202 for developing complications for male patients. Complication data for each patient is shown in Table 6.3.

Table 6.2 Proportions of patients developing complications at some point during their hospital stay, grouped by sex.

	Complications	**No Complications**
Male	2	9
Female	9	1

Figure 6.1 Number of complications per day as recorded by POMS. Blue bars represent the number of patients with a complication on the defined sample day. The red bar represents the number of patients with at least one complication during their stay.



The median hospital stay for female patients was also longer at 8(5.75-11.75) vs. 4(2-9) but failed to reach statistical significance at p=0.05.

No patients died within 30 days of their operation, which was the limit for the follow up of this study.

6.2.2 Risk scoring

Table 6.2 shows individual patient risk scores, length of stay and complications according to POMS by days 3,5,8,15 and overall. The Goldman, Detsky and Lee scores did not vary significantly between individuals or show any association with length of stay or complications (see Table 6.3). There was greater spread of scores for the American College of Cardiology/American Heart Association score but again this showed no relationship to length of stay or complications.

The POSSUM morbidity and mortality scores did however show significant relationships with length of stay (see Table 6.4) and with overall compilations,. POSSUM morbidity scores for those with complications vs. no complications, median (IQR), 21.08 (16.24 – 26.89) vs. 11.81 (7.59 – 16.25), P=0.005). POSSUM mortality scores for complications vs. no complications, median (IQR), 0.97 (0.69– 1.36) vs. 0.52 (0.31 – 0.7), P=0.005.

Table 6.3 Individual patient risk scoring and outcome data

	Risk Scores							Post operative Morbidity Survey(POMS)				
Patient No.	**Goldman**	**Detsky**	**Lee**	**ACC/AHA**	**POSSUM Morbidity**	**POSSUM Mortality**	**LOS**	**Day 3**	**Day 5**	**Day 8**	**Day 15**	**Overall**
1	0	0	0	0	7.59	0.31	2	n	n	n	n	n
2	0	5	1	2	21.08	0.97	26	y	y	y	y	y
3	5	5	2	4	21.08	0.97	9	n	n	n	n	n
4	0	0	0	0	16.25	0.69	6	y	n	n	n	y
5	0	0	0	0	16.25	0.69	5	n	n	n	n	n
6	0	0	0	0	7.59	0.31	2	n	n	n	n	n
7	0	0	0	0	7.59	0.31	2	n	n	n	n	n
8	0	0	0	0	12.68	0.49	6	y	n	n	n	y
9	5	5	0	3	46.26	2.39	11	y	n	n	n	y
10	5	5	0	1	26.89	1.36	8	n	n	y	n	y
11	0	0	1	4	13.47	0.60	4	n	n	n	n	n
12	5	5	0	1	21.08	0.97	4	y	n	n	n	y
13	5	5	1	5	23.87	1.15	8	y	y	n	n	y
14	0	0	1	3	16.25	0.69	14	y	n	y	n	y
15	0	0	0	0	12.35	0.50	9	y	y	y	n	y
16	5	0	0	0	23.87	1.15	8	y	y	n	n	y
17	5	0	0	0	16.25	0.69	3	n	n	n	n	n
18	0	0	0	0	10.16	0.43	5	n	n	n	n	n
19	0	0	0	0	7.59	0.31	5	n	n	n	n	n
20	5	0	0	3	37.29	2.23	21	y	y	y	n	y
21	5	0	1	3	15.84	0.70	4	n	n	n	n	n

LOS=length of stay

Table 6.4 Linear regression results for risk scoring and operative time vs. Length of stay

n=21	r^2	p value	
Goldman	0.01113	0.649	ns
Detsky	0.1202	0.1236	ns
Lee	0.07955	0.2155	ns
ACC/AHA	0.1523	0.0803	ns
POSSUM morbidity	0.301	0.01	*
POSSUM mortality	0.318	0.0078	*
ASA	0.09569	0.1724	ns
Operation time	0.2379	0.0249	*

6.2.3 Handgrip dynamometry

Male patients were in addition significantly stronger with MVC of 252.1 (±114.8) vs. 161.5 (±56.12) N, p=0.036), but did not exercise for longer (203(±159) vs. 163.2(±80.87) seconds, p=0.49) or perform more work (19283(±10584) vs. 14008(±6323) Ns, p=0.19), during handgrip exercise, (see table 6.5 for individual data).

Table 6.5 Individual handgrip dynamometry

	Hand Grip Dynamometry		
Patient No.	**MVC**	**Exercise time**	**Work done**
1	425.65	90.11	18268.12
2	130.09	127.91	9205.35
3	109.77	38.7	2109.28
4	155.71	145.73	12678.76
5	352.47	135.58	2342.5
6	222.79	334.76	34474.2
7	406.54	105.48	20593.45
8	218.72	166.66	21837.36
9	253.68	89.05	11715.78
10	143.92	185.36	13579.55
11	150.83	268.17	20914.6
12	186.2	240.83	21156.52
13	130.5	308.8	18021.06
14	46.35	20.11	824.42
15	282.95	202.91	28099.18
16	180.1	132.8	12163.05
17	182.94	268.59	28601.66
18	169.94	214.99	18896.14
19	321.98	97.89	15599.46
20	94.32	591.71	28324.27
21	223.19	99	12789.06

Overall MVC was significantly related to length of stay (r^2 = 0.39, P=0.0024) and significantly lower in those with complications (median (IQR) complications vs. no complications, 155.71 (130.09 – 218.72) vs. 222.99 (165.16 – 365.99), P=0.035.

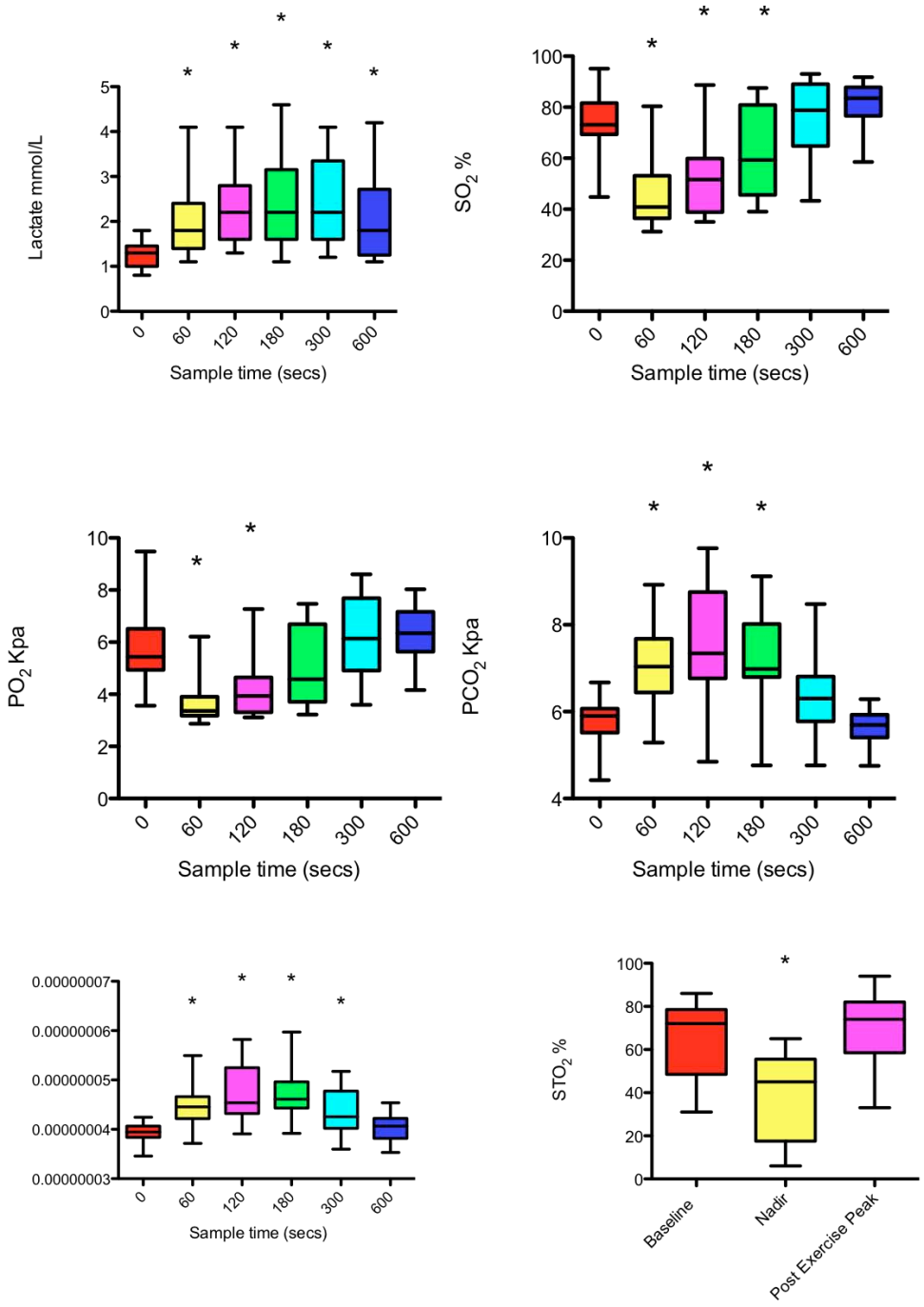
Table 6.10 in the Appendix shows individual exercise data and corresponding tissue oxygenation data for completeness.

6.2.3.1 Changes over time in fixed time point samples and tissue oxygenation

There were significant differences from baseline for all measured variables (see Figure 6.2). All variables demonstrated no statistical difference from baseline by 600 seconds except for lactate, which remained elevated.

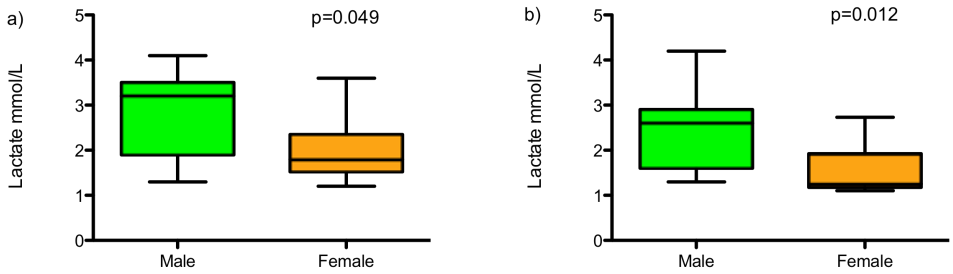
PO_2 was the earliest variable to return to near baseline values at 180 seconds. PCO_2 and SO_2 were near baseline values by 300 seconds, whilst hydrogen ion concentration took until 600 seconds to reach near baseline values (see Figure 6.2).

Figure 6.2 Box and whisker plots for fixed time point sampling for forearm lactate, SO_2, PO_2, PCO_2, Hydrogen ion concentration (mmol/L) and baseline pre and post exercise and nadir values for STO_2



There were no other significant differences in any measurable metabolic parameter between male and female subjects except for cumulative forearm lactate at 300 and 600 seconds, (see Figure 6.3)

Figure 6.3 Box and whisker plots for male and female groups for forearm lactate values at a) 300 and b) 600 seconds



6.2.3.2 Length of stay and complications

As already shown in section 6.2.1, over 50% (11/21) patients sustained postoperative morbidity. Those patients with postoperative morbidity also had a significantly longer length of stay than those without morbidity ($P<0.01$, log-rank test) as shown in Figure 6.4.

There was also a difference in peak lactate expression between the group with morbidity and the groups without morbidity. As shown in Figure 6.5 & 6.6 the group in which morbidity occurred had significantly lower peak lactate levels during exercise testing ($P<0.001$, unpaired t-test).

Figure 6.4 Impact of postoperative morbidity on length of stay.

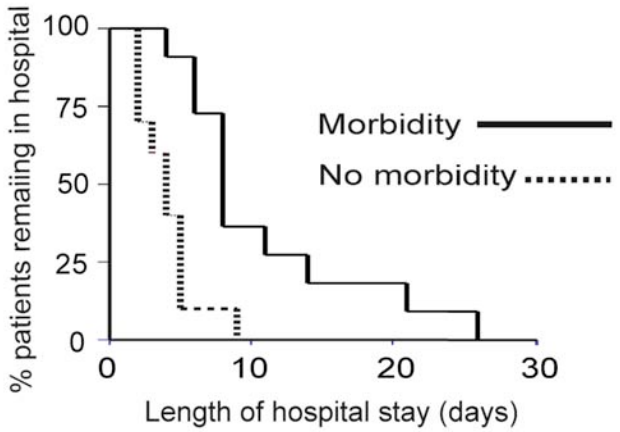
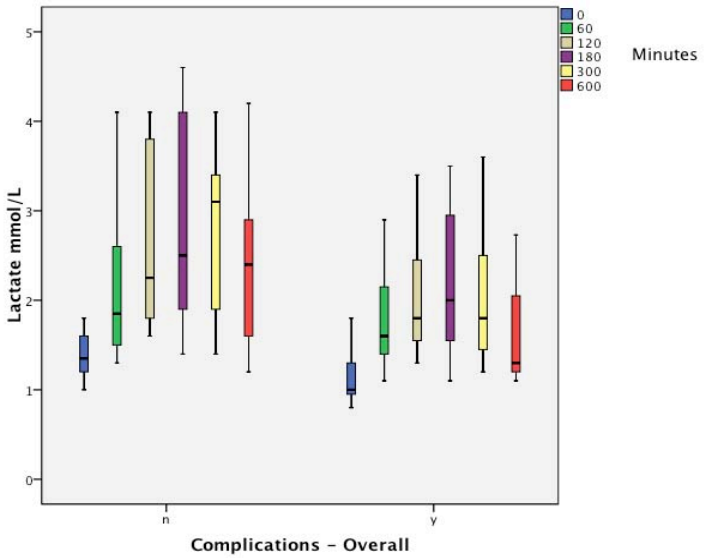


Figure 6.5 Difference in peak venous lactate levels between those with postoperative morbidity and those with no postoperative morbidity

Figure 6.6 Box and whisker plots for forearm lactate at all fixed time sample points against the presence or absence of complications.



In addition to the relationship with morbidity those patients who expressed lower levels of lactate, when split by the median of lactate expression for the whole group had a significantly longer length of stay (P=0.04, log-rank test), as shown in Figure 6.7

Figure 6.7 Prolonged length of hospital stay in patients with Lactate > median for the whole population

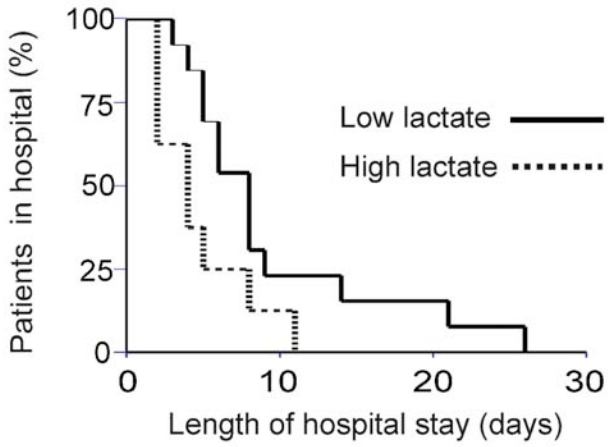


Table 6.11 in the Appendix shows details of all significant regression results against length of stay for completeness.

6.2.3.3 Relationship of MVC to forearm exercise model output

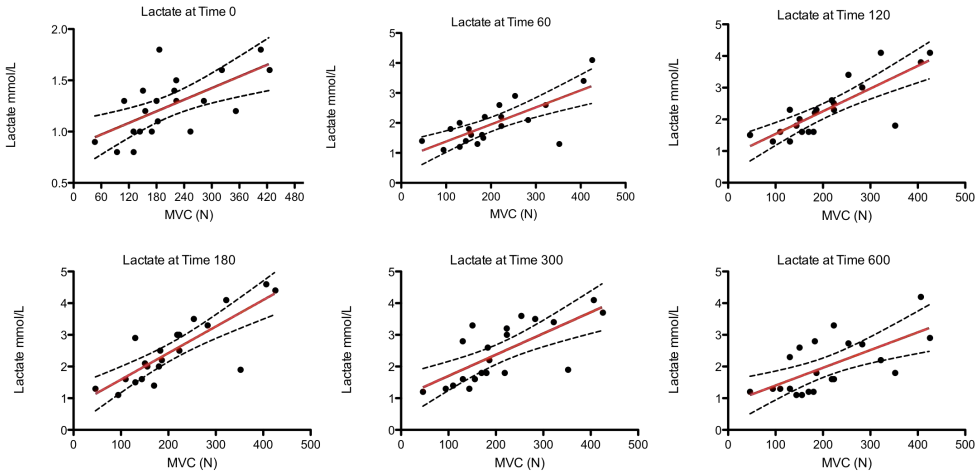
Tables 6.7 & Figure 6.8 show linear regression results for fixed time point forearm lactate sampling and endpoint summaries. There is a clear and strong association between these values and MVC for all points

Table 6.7 Linear regression vs. MVC

	Time point	r^2	p value	
Lactate	**0**	0.4085	0.0018	*
	60	0.558	< 0.0001	*
	120	0.6614	< 0.0001	*
	180	0.6717	< 0.0001	*
	300	0.5146	0.0003	*
	600	0.4272	0.0013	*
	Peak	0.589	< 0.0001	*
	Peak-baseline	0.4808	0.0005	*
	Peak % change over baseline	0.1994	0.0424	*
	Cumulative	0.6115	< 0.0001	*
	Cumulative-baseline	0.4572	0.0008	*
	Per sec	0.6115	< 0.0001	*

*=Significant result

Figure 6.8 Linear regression plots for forearm lactate at all time points against MVC, best fit line and 95% CI are shown



In addition there were significant relationships between MVC and SO_2, PO_2, PCO_2 and hydrogen ion concentration against MVC, (see table 6.8).

Table 6.8 Significant linear regression results vs. MVC

	Time point	r^2	P value	
SO_2	300	0.2008	0.0416	*
	Nadir-baseline	0.262	0.0177	*
	Peak % under baseline	0.3428	0.0053	*
PO_2	180	0.2358	0.0256	*
	300	0.212	0.0357	*
PCO_2	60	0.3102	0.0087	*
	120	0.4655	0.0007	*
	Peak	0.397	0.0022	*
	Peak-baseline	0.6146	< 0.0001	*
	Peak % change over baseline	0.6525	< 0.0001	*
$[H]^+$	60	0.5781	< 0.0001	*
	120	0.6608	< 0.0001	*
	180	0.2176	0.033	*
	Minimum	0.4568	0.0008	*
	Minimum-Baseline	0.4298	0.0013	*
	Peak % change under baseline	0.3974	0.0022	*

6.2.3.4 Relationship of work done to forearm exercise model output

There were fewer significant relationships between exercise test output variables and work done, but significant results are shown in Table 6.9.

Table 6.9 Significant linear regression results vs. Work done

	Time point	r^2	P value	
Lactate	600	0.2059	0.0388	*
SO_2	180	0.3549	0.0044	*
	Cumulative	0.2515	0.0206	*
	Per sec	0.2515	0.0206	*
PO_2	180	0.2863	0.0124	*
PCO_2	180	0.3215	0.0073	*
	300	0.4139	0.0017	*
	600	0.2179	0.0329	*
	Cumulative	0.4304	0.0012	*
	Cumulative-baseline	0.3843	0.0027	*
	Per sec	0.4304	0.0012	*

6.3 Discussion

Overall it was possible and relatively easy to conduct isometric forearm testing in this population of patients in a ward based setting. The test showed excellent correlation between handgrip dynamometry input (MVC and work done) and output of metabolic markers of metabolism but was no better than conventional risk scoring in predicting outcome.

The group was reasonably proportioned with 8 patients having hip and 14 patients having knee related prosthesis and evenly split between male and female. The cohort was well also matched for age and weight by sex but male patients were taller.

The group however showed a disproportionate number of female patients developing complications, with the relative risk of developing complications for male patients of 0.202 and female patients staying in hospital longer. It is difficult to explain this adequately because there was no significant difference in the risk scoring between males and females, including POSSUM morbidity and mortality scores or in their ASA status or operation time. There is also no consistent theme in the medical literature that demonstrates women have more complications than men and hence this study may represent a biased sample. Although strength (MVC) had a clear relationship to work done as shown in chapter 3 there was no clear relationship with lactate production, but strength alone has been sown to be an independent predictor of outcome. However men were significantly stronger in this study and may explain why the majority

of complications were seen in women as complications were clearly related to MVC.

The utility of POSSUM to predict surgical outcome was demonstrated in chapter 1 and the results of this study simply confirm its ability to do that. It did significantly under predict the morbidity rate in the complications group where over 50% developed a complication. This is most likely due to the fact that POMS was used to measure morbidity, which probably is more sensitive in identifying postoperative morbidity than the datasets in which POSSUM was validated, hence reports more complications.

The results of this study also add weight to the value of MVC to predict postoperative outcomes with it showing significant relationships between length of stay and being higher in the group with no complications. It is however possible in this study that MVC simply identified a male population. There was a significantly higher MVC (male vs. females 252.1 (±114.8) vs. 161.15(±56.12) in males than females and there were significantly more complications in females compared to males (F:M, 9:1), but there was no difference in exercise time or work done between the sexes. The disproportionate split of complications between male and females is a recurring theme in this study and probably explains many of the anomalies seen. MVC is a strength test and has been used to predict surgical outcome [153, 157, 161, 168], cognitive decline [172, 255], and recovery after stroke [256], amongst many other outcomes. As such in this study males were clearly stronger and it can be assumed had a better nutritional state, which may be beneficial in adding surgical recovery.

The nature of the isometric forearm exercise test is to stimulate high intensity exercise and challenge the anaerobic system, which it was clearly able to do, as there was a significant relationship between MVC and the metabolic output of the study, which was in many ways more consistent than in the healthy volunteers. There is a known effect of ageing by which aerobic capacity and strength decline and it is probable that an isometric test in an older and less fit population of surgical patients will stimulate a higher anaerobic response as evidenced by this study. It would in retrospect have been better to have studied this population in greater detail for the characteristics of forearm exercise performance and to establish a control population, which I plan to do in a future study to further understand that relationship.

There were a number of weak associations in this study including baseline values of STO_2 and forearm lactate. They may simply be to statistical error or may be due to a deficiency in the methodology of this study. An MVC was established prior to cannulation and the same rest periods given as in the isometric study in healthy volunteers. It is possible that my assumption that this would be adequate for surgical patients may be wrong. They appear to be more responsive to anaerobic exercise than the healthy volunteers and the initial MVC may have induce a lactate and STO_2 change that lasted longer than in healthy volunteers.

Of note however is the consistently significant association between low levels of lactate expression during exercise and its association with both postoperative complications and increased length of stay. The inability of individuals with lower anaerobic thresholds, including elective orthopaedic

patients, to generate lactate for optimal adaptive metabolic changes may be an important feature of dysregulated cellular function driven by perioperative inflammation and increased demands for oxygen delivery.

It can be seen in chapter 5 that those individuals with higher anaerobic thresholds produce statistically more lactate at any given point of exercise and a point particularly exaggerated in isometric testing. The small numbers of this study make speculation on trends fraught, and although we did not measure anaerobic threshold in the surgical patients it is possible that those with higher lactate responses and fewer complications have higher anaerobic thresholds, which is consistent with our original hypothesis.

6.4 Conclusions

I have shown that the use of isometric forearm handgrip exercise testing in an orthopaedic population undergoing joint replacement surgery is achievable as a preoperative test.

The test confirms work done by others that maximal voluntary contraction is a useful predictor of surgical outcome. In this population it was related to length of stay and the presence of postoperative complications.

The test also confirmed the utility of conventional risk scoring such as POSSUM to predict complications and length of stay.

The measurement of metabolic venous markers of metabolism during the test are consistent with it having stimulated anaerobic respiration in the exercising muscle and are in many ways a much clear and cleaner signal than those seen in the healthy volunteers during the development of this model. There was also a highly consistent and proportionate relationship between maximal voluntary contraction and the metabolic output of the test.

Overall there was a consistent and significant relationship with low levels of lactate expression, increased length of stay and postoperative complications. This is consistent with the hypothesis that fitter people and patients appear to be able to produce larger amounts of lactate during exercise than those that are less fit and likely to have a worse postoperative outcome, possibly due to dysregulated peripheral tissue metabolism that was detected by our test.

6.5 APPENDIX

Handgrip dynamometry and NIRS data for each patient

Table 6.10 Hand grip exercise and tissue oxygenation data

	Hand Grip Dynamometry			Tissue oxygenation				
Patient No.	**MVC**	**Exercise time**	**Work done**	**Baseline**	**Nadir**	**Peak**	**Baseline (PE)**	**NIRS VO_2**
1	425.65	90.11	18268.12	86	51	78	73	227
2	130.09	127.91	9205.35	38	6	65	63	472
3	109.77	38.7	2109.28	78	7	94	92	2908
4	155.71	145.73	12678.76	75	56	75	71	84
5	352.47	135.58	2342.5	54	18	63	44	134
6	222.79	334.76	34474.2	76	63	86	78	439
7	406.54	105.48	20593.45	42	24	43	32	110
8	218.72	166.66	21837.36	44	27	49	42	54
9	253.68	89.05	11715.78	82	60	76	71	179
10	143.92	185.36	13579.55	80	47	82	79	421
11	150.83	268.17	20914.6	72	45	74	69	219
12	186.2	240.83	21156.52	67	53	66	59	54
13	130.5	308.8	18021.06	74	65	73	66	201
14	46.35	20.11	824.42	31	17	33	28	127
15	282.95	202.91	28099.18	79	49	93	81	267
16	180.1	132.8	12163.05	46	11	48	42	167
17	182.94	268.59	28601.66	72	23	83	77	1655
18	169.94	214.99	18896.14	57	15	58	45	148
19	321.98	97.89	15599.46	81	55	82	75	270
20	94.32	591.71	28324.27	51	41	59	59	54
21	223.19	99	12789.06	72	62	78	73	137

MVC=Maximal Voluntary contraction, Baseline (pe) = post exercise baseline, NIRS VO_2=Near infra-red spectroscopy oxygen consumption

Significant regression results against length of stay

Table 6.11 Linear regression results for length of stay.

Demographics			
n=21	**r^2**	**p value**	
Weight	0.1405	0.094	*

Risk scoring & Surgery			
n=21	**r^2**	**p value**	
POSSUM morbidity	0.301	0.01	*
POSSUM mortality	0.318	0.0078	*
Operation time	0.2379	0.0249	*

Postoperative complications			
n=21	**r^2**	**p value**	
Day 3	0.3254	0.0069	*
Day 5	0.3889	0.0025	*
Day 8	0.541	0.0001	*
Day 15	0.4655	0.0007	*
Overall	0.3306	0.0064	*

Dynamometry			
n=21	**r^2**	**p value**	
MVC	0.277	0.0143	*

Venous blood gas & Tissue oxygenation			
n=21	**r^2**	**p value**	
Baseline lactate	0.3816	0.0028	*
Nadir SO_2-baseline	0.3785	0.003	*
Peak % change over baseline SO_2	0.3306	0.0064	*
Baseline STO_2	0.1988	0.0428	*

Chapter 7: CONCLUSIONS AND FUTURE WORK

Measuring, defining and predicating surgical outcome is a major challenge for healthcare and remains difficult. In the first chapter of this thesis I have explored the methods available by which to predict surgical outcome, which still largely predict the risk of a population rather than an individual, with the most recent guidelines encouraging a stepwise approach to assessing perioperative risk. The use of handgrip dynamometry to predict clinically important outcomes including perioperative outcome is discussed at length. I have also highlighted and discussed the evidence that as a preoperative test cardiopulmonary exercise testing has a unique ability to be able to help in predicting surgical outcome, but that the test can be expensive, require trained personnel and is not suitable for patients with severe musculoskeletal problems or those undergoing emergency surgery. Hence the need to develop a test that may be used instead of cardiopulmonary exercise testing for those unable to complete the test or as a replacement for cardiopulmonary exercise testing for the preoperative estimation of perioperative risk.

Chapter 1 also sets out my main hypotheses relating to this thesis.

1) There is a fundamental difference in the metabolic output i.e the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) of a rhythmic isometric (Cyclical) handgrip exercise model and a static isometric (Isometric) handgrip exercise model.

In chapters 2-4 I demonstrated that this hypothesis was true. There were significant differences both in the quantity and timing of release of the measurable venous markers of metabolism. In addition I showed that the isometric model of forearm exercise was a stronger stimulus of anaerobic respiration than the cyclical model. Chapters 2-4 also confirm that both tests were easy to do as preoperative bedside tests. Significant questions that came to light during these experiments were largely related to improvement in technique. For instance the use of a venous catheter that was capable of continuously analysing markers of respiration such as lactate and pH may have improved the sensitivity of the test in identifying inflections points. I intend to adapt the model in future work to incorporate this technology. I attempted to overcome this by constructing summary and cumulative measures of these test variables, but it has to be recognised that they are prone to error as a result. In addition the testing of each model in an elderly population with a number of comorbidities may have given us different results to that in a healthy volunteer group, but I wanted to keep the model as clean as possible by studying a population with as few confounding variables as possible.

2) The metabolic output from exercising forearm muscle i.e the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) or cumulative markers thereof of a standardised handgrip exercise model will have a direct relationship to the anaerobic threshold in the same individual as measured by cardiopulmonary exercise testing.

In chapter 5 I was able to demonstrate that the isometric forearm exercise model showed a consistently statistically significant relationship to anaerobic threshold as measured by cardiopulmonary exercise testing but not for the cyclical forearm exercise model. Thus this hypothesis was in part confirmed. Of interest was the novel finding that those with higher anaerobic thresholds tended to produce more lactate in the isometric forearm exercise model than those with lower anaerobic thresholds.

3) The metabolic output from exercising forearm muscle i.e. the measurable venous products of metabolism; forearm lactate, SO_2, PO_2, PCO_2, pH and tissue oxygenation (STO_2) or cumulative markers thereof of a standardised handgrip exercise model will be able to identify those patients at risk of a poor surgical outcome and thereby allow it to be used as a preoperative test instead of cardiopulmonary exercise testing, or for those patients unable to perform a cardiopulmonary exercise test.

Chapter 6 demonstrated the confirmation of this hypothesis. I was able to show that lactate was significantly higher in those patients who had fewer complications and shorter lengths of stay. I also confirmed the utility of conventional risk scoring with POSSUM and that the maximal voluntary contraction of handgrip dynamometry was predictive of complications and length of stay.

In summary the main findings of this thesis are:

- Both cyclical and isometric forearm exercise models are practical as preoperative tests
- The isometric forearm exercise model proved to be a much stronger stimulus to anaerobic respiration.
- The isometric forearm exercise model showed a statistically significant and consistent relationship with anaerobic threshold as measured by cardiopulmonary exercise testing.
- Maximal voluntary contraction as measured by handgrip dynamometry was significantly higher for patient with less complications and shorter lengths of stay.
- There was a significant association with forearm lactate to be higher in those with fewer complications and shorter lengths of stay.

PUBLICATIONS ARISING FROM THIS THESIS

MA Hamilton, J Pate, H Luery, MG Mythen, GL Ackland.

Metabolic changes following standardized handgrip exercise correlate with global anaerobic threshold.

ASA, Atlanta, October 2005, 1474

MA Hamilton, RM Grounds, MG Mythen, GL Ackland.

Standardized handgrip dynamometry as a measure of cardiopulmonary reserve: potential use in preoperative assessment

Currently in submission 2011

P Sultan, **MA Hamilton,** GL Ackland

Preoperative handgrip strength and postoperative outcomes: a systematic review

Currently in submission 2011

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