Stratification of perioperative risk in patients undergoing major hepato-pancreatico-biliary surgery using cardiopulmonary exercise testing

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ABBREVIATIONS

AAA	Abdominal aortic aneurysm
[a – b]	range
ACC/AHA	American College of Cardiology/ American Heart Association
ALT	Alkaline transaminase
ALP	Alkaline phosphatase
APACHE II	Acute physiology and chronic health evaluation II
ASA	American Society of Anaesthesiologists
AT	Anaerobic threshold
ATP	Adenosine triphosphate
AUC	Area under curve
BMI	Body mass index
BR	Breathing reserve
CI	Confidence Interval
CKD/CRF	Chronic kidney disease/ chronic renal failure
COPD	Chronic obstructive pulmonary disease
CO_2	Carbon dioxide
CPET/CPX	Cardiopulmonary exercise testing
CRP	C -reactive protein
CT/MDR-CT	Computed tomography/ multi-detector computed tomography
CVA	Cerebrovascular accident
DASI	Dukes activity status index
DBS	Demographic Batch Service
DGE	Delayed gastric emptying
D.o.H	Department of Health
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ERCP	Endoscopic retrograde cholangio-pancreatogram
et al	and others
EUS	Endoscopic ultrasound
FEV_1	Volume exhaled at end of first second of forced expiration
FVC	Forced vital capacity
$fvpO_2$	Femoral venous pressure of oxygen
GPS/mGPS	Glasgow Prognostic Score/ modified GPS
g/L- g/dl	Grams per litre – grams per decilitre
H^+	Proton
Hb	Haemoglobin
HCO_3^-	Bicarbonate
HDU	High dependency unit
HR	Hazard ratio
HTN	Hypertension
ICU/ITU	Intensive care unit/ intensive therapy unit
IDDM/NIDDM	Insulin dependent diabetes/ non-insulin dependant diabetes mellitus
IHD	Ischaemic heart disease
IPMN	Intraductal papillary mucinous neoplasm
IQR	Interquartile range
ISGPS	International study group on pancreatic surgery
kPa	Kilopascals
LAT/LT	Lactate threshold
L/P	Lactate/ Pyruvate ratio
MET	Metabolic equivalent

mg/dl	Miligrams per decilitre
mmol/l	Millimoles per litre
MRCP	Magnetic resonance cholangio-pancreatogram
MRI	Magnetic resonance imaging
NCEPOD	National confidential enquiry into patient outcome and death
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NYHA	New York Heart Association
O_2	Oxygen
O.f.N.S	Office for National Statistics
OR	Odds ratio
p	Statistical *p* value
PD	Pancreaticoduodenectomy
Peak $\dot{V}O_2$	Peak oxygen uptake
PET	Positron emission tomography
P_{ETO2}	End tidal oxygen
POBD	Preoperative biliary drainage
POMS	Post-operative morbidity score
POPF	Postoperative pancreatic fistula
POSSUM/VPOSSUM	Physiologic and operative severity score for the enumeration of mortality and morbidity/ vascular POSSUM
PPH	Postpancreatectomy haemorrhage
PPV/NPV	Positive predictor value/ negative predictor value
PT	Prothrombin time
PTBD	Percutaneuous transhepatic biliary drainage
PVE	Portal vein embolisation
RCRI	Revised cardiac risk index
RER	Respiratory exchange ratio
ROC	Receiver operating characteristics
RPM	Revolutions per minute
RR	Relative risk
SAPS	Simplified acute physiology score
SD	Standard deviation
$SfvCO_2$	Femoral venous saturation of carbon dioxide
$SfvO_2$	Femoral venous saturation of oxygen
SVT	Supraventricular tachycardia
TIA	Transient ischaemic attack
TNM	Staging based on tumour size, nodal status and metastasis
U/L	Units per litre
μmol/L	micromoles per litre
USS	Ultrasound scan
VASI	Veterans activity questionnaire index
$\dot{V}E$	Minute ventilation
$\dot{V}E/\dot{V}CO_2 - \dot{V}E/\dot{V}O_2$	Ventilatory equivalent of carbon dioxide – ventilatory equivalent of oxygen
VEGF	Vascular endothelial growth factor
$\dot{V}E/\dot{V}CO_2$	Oxygen uptake/ carbon dioxide output
$\dot{V}O_2/HR$	Oxygen uptake per heart rate
$\dot{V}O_2 max$	Maximal oxygen uptake
VT	Tidal volume
WHO	World Health Organisation
WR	Work rate

PREFACE

This study incorporates my work from conception to its completion from September 2007 to March 2011, at the department of surgery, Manchester Royal Infirmary. The following work was carried out at the Cardiopulmonary Exercise Testing clinic, Critical Care Unit and the department of Hepato-pancreatico-biliary Surgery.

All studies along with their findings reported in this thesis, represent my own original work. The work of other investigators is acknowledged where external data is used for discussion.

ABSTRACT

Contemporary hepatobiliary surgery practice must accurately assess operative risk in increasingly elderly populations with greater co-morbidity. Current methods fail to identify patients at high risk of postoperative complications. Cardiopulmonary exercise testing (CPET) derived anaerobic threshold (AT) and ventilatory equivalence of carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) are validated predictors of postoperative outcome in major intra-abdominal surgery and outperform contemporary tools of risk evaluation.

Despite evidence of improved in-hospital postoperative survival in large centres offering complex curative hepatobiliary surgery, morbidity remains high and long-term survival in the high-risk subset remains poor. This thesis investigated the role of validated CPET-derived markers in predicting perioperative outcomes for a high-risk hepatobiliary surgery population. It was also utilised to study the impact of malignant obstructive jaundice on peripheral oxygen extraction.

In a prospective cohort of high-risk patients undergoing liver resection, an AT of 9.9 ml O_2/kg/min predicted in-hospital mortality and long-term survival. Below this threshold, AT was 100% sensitive and 75.9% specific for in-hospital mortality (PPV 19%, NPV 100%). Long-term survival below the threshold of 9.9 was significantly worse when compared to those above (mortality HR 1.81). The $\dot{V}_E/\dot{V}_{CO_2}$ was the most significant predictor of postoperative complications and a threshold of 34.5 provided 84% specificity and 47% sensitivity (PPV 76%, NPV 60%). Amongst the high-risk pancreaticoduodenectomy patients, $\dot{V}_E/\dot{V}_{CO_2}$ was the single most predictive marker of in-hospital postoperative mortality with an AUC of 0.850 (p=0.020); a threshold value 41 was 75% sensitive and 94.6% specific (PPV 50%, NPV 98.1%). The $\dot{V}_E/\dot{V}_{CO_2}$ 41 was also the only predictor of poor long-term survival (HR 1.90). Notably, AT, Revised Cardiac Risk Index and Glasgow Prognostic Score did not predict outcome after pancreaticoduodenectomy.

Patients with malignant obstructive jaundice, evaluated for peripheral oxygen extraction using CPET, showed lower mean peak oxygen consumption (peak $\dot{V}_{O_2}$) at 63±17.4% of the predicted value. This was noted in absence of any significant pre-existing cardiopulmonary disease and normal respiratory reserve. Normal patterns of oxygen extraction were seen at rest, during incremental work rate and peak exercise levels. Levels of oxygen partial pressure and saturation exceeded baseline values after exercise signifying normal microcirculatory responses. Thus, aerobic capacity was limited by dysfunction in delivery (cardiac output) rather than oxygen extraction.

CPET provides useful prognostic adjuncts for early and long-term outcomes in the high-risk patients undergoing major hepatobiliary surgery. These findings provide useful tools for perioperative optimisation of the high-risk patient and plan appropriate level of postoperative care to address mortality and morbidity after surgery.

Key words:
Anaerobic threshold
Exercise testing
Hepatic resection
Obstructive jaundice
Pancreaticoduodenectomy
Postoperative complications
Survival

DECLARATION AND COPYRIGHT STATEMENT

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS WORK

Publications

1. *Original article:* Cardiopulmonary exercise testing for preoperative risk assessment prior to hepatic resection. Muneer A Junejo, James M Mason, Aali J Sheen et al. Br J Surg. 2012 Aug; 99(8):1097-104.

2. *Abstract:* Muneer Junejo, Aali J. Sheen, Ajith Siriwardena (2011). Cardiopulmonary exercise testing for preoperative risk assessment prior to hepatectomy. Gastroenterology Vol. 140, Issue 5, Supplement 1, Page S-595

3. *Abstract:* Muneer A Junejo, James M Mason, Aali J Sheen et al. CPET (cardiopulmonary exercise testing) as a means of preoperative risk assessment prior to pancreaticoduodenectomy (2011). International Hepato-Pancreato-Biliary Association, HPB, 13 (Suppl. 2), 1–145

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1. *Original article:* Role of cardiopulmonary exercise testing in predicting outcome in patients undergoing pancreaticoduodenectomy.

2. *Original article:* Evaluation of peripheral oxygen delivery and extraction in patients with malignant obstructive jaundice prior to pancreaticoduodenectomy using cardio-pulmonary exercise testing

Presentations

1. Towards a no-laparoscopy staging algorithm for patients undergoing pancreatic surgery. 8th European Hepato-Pancreato-Biliary Association (EHPBA), Athens. January 2009.

2. Role of Cardiopulmonary Exercise Testing in patients undergoing hepatic resection: a preliminary study. 9th International Hepato-Pancreato-Biliary (IHPBA) Congress. Buenos Aires. February 2010.

3. Peripheral oxygen extraction in obstructive jaundice. 3rd CPET Meeting, London. June 2010.

4. Role of cardiopulmonary exercise testing in pancreaticoduodenectomy: a preliminary study American Pancreatic Association (APA). Chicago, November 2010.

5. Perioperative risk assessment using cardiopulmonary exercise testing in patients undergoing pancreaticoduodenectomy. IAP Cochin, India. February 2011.

6. Cardiopulmonary exercise testing (CPET) for pre-operative risk assessment prior to hepatectomy. DDW, AGA Chicago, May 2011.

7. CPET (cardiopulmonary exercise testing) as a means of preoperative risk assessment prior to pancreaticoduodenectomy. 9th Congress of the European Hepato-Pancreato-Biliary Association (EHPBA), Cape Town, South Africa. April 2011.

8. Cardiopulmonary exercise testing for the preoperative risk assessment prior to hepatectomy. 9th Congress of the European Hepato-Pancreato-Biliary Association (EHPBA), Cape Town, South Africa. April 2011.

9. Cardiopulmonary exercise testing to evaluate high risk patients prior to hepatectomy. Digestive Disease Week, American Gastroenterological Association (AGA). San Diego, May 2012.

Dedicated to Katharina, Norah & Sophie

Chapter 1

INTRODUCTION

1.1   Overview

Changes in the last decade have seen the emergence of centralised cancer care in the UK National Health Service (D.o.H, 2001). This shift in paradigm, moving from often individual and disparate care of cancer patients in small volume centres resulting in poor outcome, has been informed by evidence of improved survival in large centres offering surgical cancer treatments (Birkmeyer et al., 2003a, Birkmeyer et al., 2003b). Apart from the "Volume-Outcome" relationship, improvement in surgical techniques, perioperative care and the advent of effective chemotherapy (Simmonds et al., 2006, Baize et al., 2006, Nordlinger et al., 2005, Neoptolemos et al., 2010, Nordlinger et al., 2008) have contributed to the continuing decline in early and late postoperative mortality following major hepato-pancreatico-biliary surgery.

However, despite apparent improvements related to high-volume surgeons and hospitals, a closer examination reveals different mechanisms active in determining postoperative outcomes. "Failure to rescue" a patient with a postoperative complication leading to death has been shown to be a stronger determinant of outcome than volume (Ghaferi et al., 2009, Ghaferi et al., 2011). In this context, accurate identification of the "high-risk" patient and early recognition with effective care of postoperative complications assume paramount importance.

The National Confidential Enquiry into Peri-Operative Deaths (NCEPOD) has played an instrumental role in investigating peri-operative practices and outcomes in surgical patients. Although, overall mortality from all surgical procedures remains low, pre-existing cardiopulmonary disease in the elderly is a major contributor towards higher peri-operative death (Lunn and Devlin, 1987). Pearse and colleagues (Pearse et al., 2006) in their evaluation of outcomes from general surgical procedures in England, Wales and Ireland over a 5 year period (1999 to 2004) evaluated high-risk procedures with a predicted mortality of 5% or more. Notably, these accounted for 12.5% of all hospital admissions for surgery (incorporating elective and emergency) but 83.8% of all

postoperative deaths. Furthermore, high-risk patients were seen to be discharged from intensive care units (ICU) to ward care prematurely. Readmission to ICU, after initial ward care, was also associated with higher rates of postoperative mortality.

This prevailing trend in postoperative mortality in the "high-risk" elective surgical population mirrors the findings reported in the landmark paper by Ghaferi et. al. (Ghaferi et al., 2009). The authors focused on outcomes in the high-risk surgical group of patient representing 23% of all patients were responsible for 68% of all 30-day postoperative deaths. A narrower focus on major gastrointestinal cancer procedures (gastrectomy, pancreatectomy, oesophagectomy) in 37,865 elderly patients, over the age of 65 years (Ghaferi et al., 2011), offers a more generalisable recognition of the role of predicting, recognising and effectively managing postoperative complications.

The value of preventing early postoperative complications is not limited to short-term outcomes alone. An evaluation of a prospective national database from North America in 105,951 patients reported on 30-day mortality and long-term survival following common surgical procedures (Khuri et al., 2005). Although the results may not be generalisable, as the procedures incorporated excluded hepatic and pancreatic resection surgery, they demonstrated the adverse effect of postoperative complications on 30-day and long-term postoperative survival. This relationship was the most important independent predictor of 30-day, 1 and 5 year post-operative survival than preoperative co-morbidities or intra-operative parameters with cardiopulmonary complications the dominant mechanism.

Historically, early postoperative survival (30-day mortality) has been the key determinant in defining procedure specific risk and outcomes. It has also been utilised as a marker of excellence attributed to surgical services in many centres. However, as demonstrated by the aforementioned national database-derived studies, low overall mortality rates in the postoperative cohort conceals a subgroup of high-risk category of patients representing disproportionally greater mortality. Furthermore,

improvements in critical care mean that patients experiencing major postoperative complications can be managed beyond the 30-day threshold and often leave hospital after a prolonged period of hospitalisation.

It is evident (Pearse et al., 2006) that current methods of assessing operative risk in the preoperative setting do not identify patients at risk of adverse outcome. Commonly, this evaluation relies on subjectively derived surrogates of cardiopulmonary function. Furthermore, wide variations in defining postoperative outcome make useful comparisons and extrapolation of the results from one centre to another difficult.

In this context, cardiopulmonary exercise testing (CPET) has emerged as a new tool, offering an objective, reliable and safe evaluation of peri-operative risk in patients undergoing major surgery (Older et al., 1999, Snowden et al., 2010). Although validated for major intra-abdominal surgery, the evaluation of its role in specific surgical populations has been limited (Smith et al., 2009, Hennis et al., 2011).

The aim of this thesis has been to investigate the utility of CPET in evaluating risk in patients undergoing major hepato-pancreatico-biliary surgery defined as hepatic resection or pancreaticoduodenectomy. The value of CPET-derived variables was compared to current preoperative prognostic tools to determine its accuracy and predictive potential for adverse postoperative outcomes. The low event rate of in-hospital mortality following surgery in large volume centres has meant that a prospective evaluation of death in many centres is limited in studies constrained by time. However, major and minor morbidity remain high and with its wider impact on short and long-term survival can be evaluated usefully in many centres. Predicting postoperative complications was the primary aim of the thesis with secondary attention to impact on critical care stay, hospital stay and survival.

Thus a tool that can offer an accurate, objective and reliable preoperative prognostication of adverse outcome following surgery, would inform risk-benefit arguments and improve decision making for patients and physician.

1.2 Peri-operative risk

1.2.1 Identifying surgical risk

It has been recognised that the majority of postoperative deaths following major surgery have tended to occur in elderly patients with cardiac and pulmonary disease (NCEPOD). Cardiac complications constitute a significant proportion of morbidity and mortality from major non-cardiac surgery. This underlying mechanism has led to the development of a string of 'criteria' and 'scores' to assess cardiac dysfunction and peri-operative risk of cardiac complications in non-cardiac surgery.

1.2.2 Intraoperative demands

Evidence in the last three decades has emerged to describe the attributes of survivors undergoing surgery. Whereas earlier investigation focused on preoperative patient characteristics in terms of age and co-morbidity and postoperative complications alone (Lunn and Devlin, 1987), Shoemaker et. al. (Shoemaker et al., 1988) demonstrated that physiological characteristics amongst survivors were consistent with the ability to meet increased demands of oxygen consumptions during and after surgery. This demand in oxygen consumption was met by supranormal values of cardiac output, and oxygen delivery.

The authors carried out a prospective evaluation of high-risk patients undergoing surgery with and without supranormal targets for cardiac output, oxygen delivery and oxygen consumption. This "high-risk" categorisation was based on age (>70 years), significant cardiopulmonary co-morbidity (myocardial infarction, chronic pulmonary obstructive disease, cerebrovascular accidents) or severe trauma involving >3 organs or >2 systems. Intra-operative features for high-risk category included major or prolonged surgery or massive blood loss. Postoperative shock, septicaemia, acute abdominal catastrophe (defined as acute pathology with haemodynamic instability) or organ failure (respiratory or renal) also categorised patients as high-risk. These criteria captured 7% of all patients

which represented 82% of overall mortality. Goal directed intraoperative and postoperative management of patients for supranormal oxygen delivery demonstrated improved morbidity and mortality benefit over therapy aiming for normal physiological parameters. More importantly, the authors demonstrated that no significant differences were noted amongst survivors and non-survivors in blood pressure, heart rate, central venous pressures, urine output and blood gas analysis.

In a later evaluation of haemodynamic patterns of survivors and non-survivors amongst high-risk patients during surgery (Shoemaker et al., 1999), the authors argued that poor oxygen delivery led to covert shock preceding development of organ dysfunction and death. Amongst 209 patients, oxygen debt of >140 mls/kg was associated with 100% mortality. Patients with low oxygen debt (<100 ml/kg) during surgery survived the postoperative course and debt of 100-140 ml/kg was associated with 50% mortality.

The evaluation of oxygen demands during major surgery suggests that it may lead to an increase in oxygen consumption irrespective of age. There could be as much as a 40% increase to 150 ml/min/m^2 of the body surface area or even greater requiring a similar increase in cardiac output (Older and Smith, 1988). Thus oxygen delivery, which is a product of cardiac output and arterial oxygen content during surgery, is the major determinant of outcome in terms of morbidity and survival.

1.2.3   Cardiac risk in non-cardiac surgery

1.2.3.1 Risk stratification criteria

One of the earliest attempts at identifying patients at high risk of adverse post surgical outcome was the development of the 'Classification of Physical Status' by the American Society of Anaesthesiologists, first published in 1963 (ASA, 1963). It described cardiac function based on

subjective assessment of symptoms described by the patient and this description ranged from a normal healthy person (ASA 1) to a moribund patient who is expected to die without surgery (ASA 5). Subject to patient and physician interpretation, it did not incorporate more predictive markers such as age and physical fitness. Progressing from this, the New York Heart Association (NYHA), produced their 'Classification of Functional Status' first published in 1973 (NYHA, 1973) describing different grades of heart failure based on functional status. Notably these were attempts at highlighting risk, and these criteria were not intended for preoperative screening.

A major limitation of these classifications, although simple and practical, is the subjective nature of the evaluation with bias from both the assessor and the patient. Furthermore, it is at best a surrogate evaluation of ventricular function and is not a reliable measure. By using exercise testing to compare functional status derived using NYHA criteria and exercise derived values, Dunselman (Dunselman et al., 1988) demonstrated a considerable overlap between classes I and II, and classes III and IV, showing that the NYHA based assessment is subjective and highly variable and unreliable.

One of the first screening tools to evaluate peri-operative cardiac risk in non-cardiac surgery was the Cardiac Risk Index by Goldman (Goldman et al., 1977). It identified congestive heart failure as a major risk for cardiac complications. A modified and validated version of this tool is currently employed in the form of the Revised Cardiac Risk Index (RCRI) (Lee et al., 1999). The RCRI incorporates the risk posed by major surgery with increased demands on ventricular function. Derived from a prospective evaluation of 4315 patients, providing internal validation, the RCRI provides a useful assessment of cardiac risk.

However, this tool is limited in its application as it relies on subjective derivation of functional capacity and is less reliable. Although a subsequent evaluation of these indices has shown a poor predictor value for postoperative cardiac events (Gilbert et al., 2000), it continues to be employed in the peri-operative setting.

1.2.3.2 Heart failure and myocardial ischaemia

Weber and colleagues (Weber and Janicki, 1985) defined the 'gold standard' for measuring heart failure using aerobic capacity by means of exercise testing. This functional classification of heart failure, proposed in 1985 using CPET, is derived by on an objectively derived measure of aerobic capacity in the form of maximal oxygen consumption ($\dot{V}O_2$ max in ml/kg/min). The authors proposed four classes based on $\dot{V}O_2$ max with class A representing little or no functional impairment ($\dot{V}O_2$ max >20 ml/kg/min), class B representing mild to moderate impairment ($\dot{V}O_2$ max 16 – 20 ml/kg/min), class C representing moderate to severe impairment ($\dot{V}O_2$ max 10 – 15 ml/kg/min) and class D representing severe impairment (<10 ml/kg/min). Thus the measure of aerobic capacity is applied to subjective criteria to allow more accurate measure of functional capacity where more reliable method of exercise testing may not be available (i.e. metabolic equivalents – MET, where 1 MET is defined as the equivalent of 3.5 ml/kg/min). The MET based evaluation of heart failure was endorsed by the by the American College of Cardiology and American Heart Association (ACC/AHA) (Eagle et al., 1996) in 2002, and was set at 4 METs (3.5 ml/kg/min x 4).

Where degree of heart failure has a direct bearing on oxygen delivery and consumption, presence of myocardial ischaemia has also undergone extensive scrutiny. Although the incidence of exercise induced abnormal electrocardiogram (ECG) changes in individual over the age of 65 years are significant (24%), with absence of cardiac dysfunction or a prior cardiac history, do not reflect a high risk of adverse outcome in patients undergoing surgery. Furthermore, myocardial ischaemia at high levels of exercise (greater than 85% of age predicted heart rate) is deemed to be a low risk for adverse postoperative cardiovascular outcome. Therefore, when these changes in ventricular function and myocardial ischaemia are seen to occur at an earlier stage, they are associated with a higher risk of cardiovascular morbidity and mortality.

Hernandez and colleagues (Hernandez et al., 2004), through their landmark study of the national Medicare data in the United States, demonstrated the greater importance of heart failure over the diagnosis of coronary artery disease. The study evaluated the impact of heart failure and coronary artery disease on in-hospital postoperative mortality, length of hospital and critical care stay, rate of readmissions and death within 30 days following discharge in patients over 65 years of age.

Despite the limitations inherent with the quality of national data and absence of adequate case mix, convincing arguments are made in the favour of heart failure as the major factor in adverse outcomes. Heart failure patients tended to be older with higher co-morbidities and tended to have a higher rate of emergency and urgent operative interventions with longer critical care and hospital stay. Although a reflection of current population trends, it could also point to an approach of a higher threshold for intervention in these patients when conservative approaches have failed. Heart failure patients demonstrated a 2-fold increase in 30-day postoperative mortality and early readmissions compared to patients with cardiac disease (controls) or patients with coronary disease only. The authors also noted that concomitant heart failure and coronary artery disease had similar survival outcomes compared to heart failure alone.

ECG based assessment of myocardial ischaemia alone, has a limited sensitivity and specificity of 66% and 84% respectively (Gianrossi et al., 1989). This accuracy varies widely from 40% in a single vessel disease, increasing to 90% in three-vessel disease. Compared to this, CPET allows a more accurate detection of myocardial ischaemia which is seen as a decline of cardiac output during exercise, lowering the rate of increase of oxygen consumption ($\dot{V}O_2$). In a prospective study of 202 patients with documented coronary artery disease, Belardinelli (Belardinelli et al., 2003) compared the accuracy of CPET with standard ECG based recognition of ischaemia, using myocardial scintigraphy to detect all true positive cases. CPET based detection was shown to offer a higher sensitivity (87% vs. 46%) and specificity (74% vs. 66%) compared to ECG.

1.2.4   Postoperative complications and outcome

Evaluating the variation in postoperative mortality amongst different hospitals, Ghaferi et. al supported the concept of "failure to rescue" as the cause of high mortality despite lack of variation in the rate of postoperative complications (Ghaferi et al., 2009).This analysis yielded robust data supporting the concept of recognising patients at risk of developing complications and an effective means of managing to reduce mortality. In this prospective, multicentre, risk adjusted evaluation of 186 centres, 130 patient and perioperative variables were recorded to evaluate 30-day postoperative morbidity and mortality following high-risk. 84,730 patients represented 23% of all patients undergoing surgery during this period but accounted for 68% of postoperative deaths. Although the study was limited due to incomplete capture of postoperative complications and selected centre involvement threatens generlisability, it underscores the point that complications will occur across the volume spectrum and early recognition and effective management holds the key to improving outcomes.

1.2.5   Measuring postoperative complications

A review of the literature relating to postoperative morbidity reveals a wide variation in describing outcomes following major hepato-pancreatico-biliary surgery. This makes the task of evaluating postoperative burden or prognostic value of preoperative tools difficult. Martin (Martin et al., 2002), evaluating complication reporting in the surgical literature, investigated data from 42 published randomized clinical trials and 77 retrospective series comprising 22,530 patients undergoing major surgery including pancreaticoduodenectomy and hepatic resection. The authors found only a small number of studies (2%) meeting their criteria in defining postoperative complications adequately. Thus, this failure to carry out adequate comparison of the outcomes prevents development of generally applicable criteria without any accurate evaluation or application of the tools proposed.

Major hepato-pancreatic-biliary surgery involves complex resectional surgery and is unique in its patient demographics (risk factors and prevalence of disease), peri-operative stress (obstructive jaundice) and postoperative course (anastomotic leaks, pancreatic fistula). Hence, an unadjusted comparison with other surgical procedures, using auditing tools such as the Physiological and Operative Severity Score in the enumeration of Mortality and morbidity (POSSUM) (Copeland et al., 1991), has not proved clinically useful (Lam et al., 2004, de Castro et al., 2009).

1.2.6   Role of cardiopulmonary exercise testing

In this context, cardiopulmonary exercise testing provides an objective, clinically useful, accurate and reliable assessment of both ventricular function and myocardial ischaemia, which is essential in recognising patients at high risk of cardiopulmonary complications.

1.3 Cardiopulmonary exercise testing (CPET)

CPET is a safe, non-invasive and an objective method of evaluating the patho-physiology of both the cardiovascular and respiratory systems. An extension of exercise testing, it allows a simultaneous and dynamic study of the responses of these systems and defines and quantifies specific dysfunction and limitation. By detecting oxygen consumption ($\dot{V}_{O_2}$) accurately, CPET evaluation is able to deliver reliable measure of cardiac output, ventilatory efficiency, circulation, peripheral oxygen extraction and intracellular metabolic changes.

1.3.1 CPET equipment

CPET apparatus consists of an ergometer to provide an exercise stimulus and the physiological response to it is measured using a 12 lead electrocardiogram (ECG) and a metabolic cart with a face mask for gas analyses. Oxygen and carbon dioxide analyses response time is less than 90 milliseconds to allow measurement of breath-by-breath changes. An electronically braked cycle is the preferred ergometer for exercise testing as it offers an accurate measurement of work rate and ease of measurements during testing (i.e blood gas analysis).

The test is carried out in an environment with regulated temperature and humidity and access to resuscitation equipment and services. Calibration is carried out before testing for flow measurements and gas analysers and adjusted for ambient barometric pressure, humidity and temperature. Non-invasive blood pressure monitoring continuous pulse oximetery measurements are also required.

1.3.2 Preparation for testing

The patient is advised loose comfortable clothing to allow free movement of limbs (figure 1.1). ECG leads are applied and face mask or mouth piece is attached with appropriate instructions for communication. The patient is seated on the cycle and height adjusted to ensure approximately 5-15

degrees of knee flexion when the foot is resting at the bottom of the pedal crank. Patients are guided through the test and asked to maintain their leg speed which is usually displayed on the ergometer.

The increment work rate for the test is set to allow the test to last 6 to 10 minutes. This is determined using he equations stated below:

1. $\dot{V}O_2$ unloaded (ml/min) = 150 + (6 x weight (kg)

2. Peak $\dot{V}O_2$ (ml/min) Men = height (cm) – age (years) x 20

   Peak $\dot{V}O_2$ (ml/min) Women = height (cm) – age (years) x 14

3. Work Rate increment (W/min) = (Peak $\dot{V}O_2 - \dot{V}O_2$ Unloaded) / 100

Figure 1.1: Study participant undertaking cardiopulmonary exercise testing at the clinical laboratory at the Manchester Royal Infirmary. Picture is produced following informed consent of the participant.

1.3.3   *Test protocol*

Clinical, laboratory based cardiopulmonary exercise testing for perioperative risk assessment is symptom-limited maximal testing, where patients are encouraged to give their "best effort". A national consensus based protocol is widely in use in the United Kingdom (Consensus Protocol for Preoperative CPX testing for York).

The test consists of four main phases. The first phase is the *Rest* phase which involves a two to five minute rest period to ensure a respiratory exchange rate (RER) of less than 1. RER is the ratio of volume of carbon dioxide elimination ($\dot{V}_{CO_2}$ L/min) to oxygen consumption ($\dot{V}_{O_2}$ L/min). Changes in its value from rest to peak exercise are utilized to assess accuracy and adequacy of the test. Patient is also allowed to become comfortable with the equipment and establish clear communication process. Baseline measurements are recorded. The second phase of *Unloaded Cycling* allows estimation of the oxygen consumption with peddling motion. The effect of hyperventilation from the physiological response to exercise settles during this phase stabilising gas exchange measurements.

The *Ramp* phase continues from unloaded cycling with incremental work rate which is determined prior to the start based on the patients predicted capacity. Data on gas exchange and ECG monitoring is carried out throughout. The patient is encouraged to maintain a good RPM and provided with feedback throughout the test. The test ends with the recovery phase to allow the ECG and heart rate to return to baseline levels.

The test is terminated if patients developed ECG changes (ST changes > 2.0 mm depression or > 3.0mm elevation, new dysrhythmia), near syncope or fail to maintain greater than 50 revolutions per minute as this is related to erratic effort and gas exchange measurements.

The focus of this thesis was to evaluate the relationship of validated CPET-derived variables and postoperative outcomes in patients following major hepato-pancreatico-biliary surgery. Anaerobic

threshold (AT), peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ (ventilatory equivalent of CO_2) have been the most studied of CPET variables in this setting, demonstrating a varying relationship and impact on postoperative outcomes in different surgical populations.

1.3.4 CPET derived data

Data derived from CPET is displayed in both tabular and graphical format. Directly recorded and derived values are displayed in a 9 panel graph (Figure 1.2) which includes oxygen consumption ($\dot{V}O_2$ in ml/kg/min), Carbon dioxide elimination ($\dot{V}CO_2$ in ml/kg/min), Respiratory Exchange Ratio (RER), minute ventilation ($\dot{V}E$ in litres/min), tidal volume (VT in litres), Heart Rate (HR – beats per minute), Work Rate (WR in Watts), End tidal oxygen ($P_{ET}O_2$), Ventilatory equivalent of oxygen ($\dot{V}E/\dot{V}O_2$) and carbon dioxide ($\dot{V}E/\dot{V}CO_2$) and $\dot{V}O_2$ – pulse ($\dot{V}O_2/HR$ – ml/heart rate).
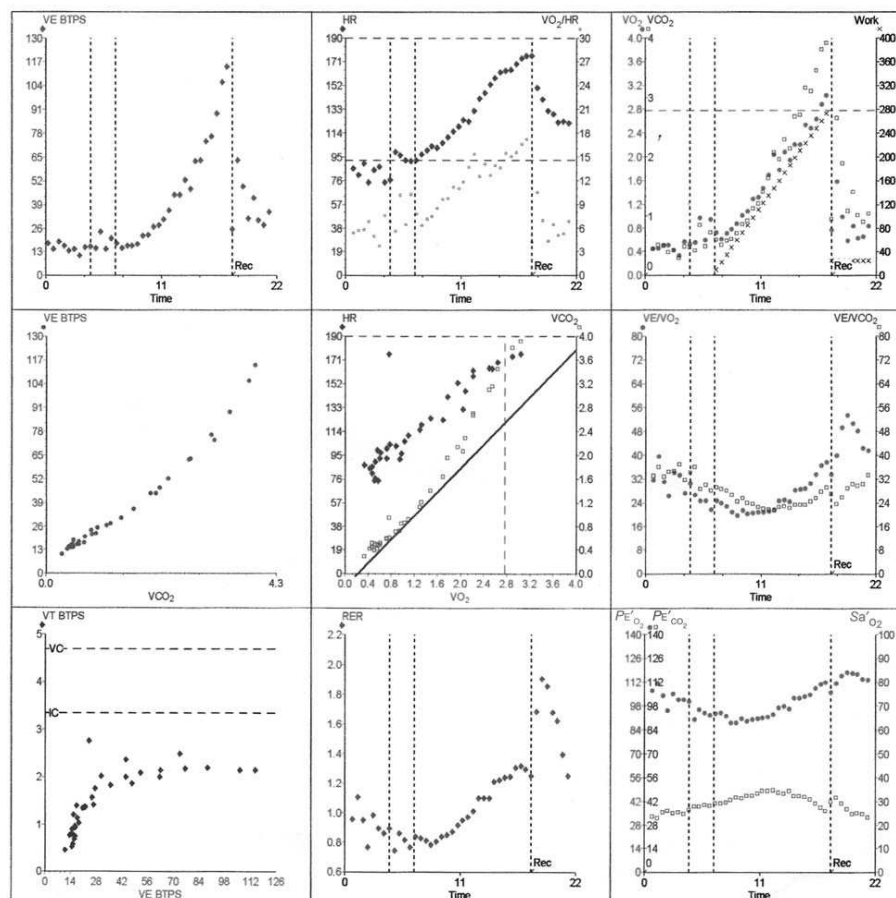
Figure 1.2: Nine-panel graph for the interpretation of CPET results.

1.3.5   CPET variables

1.3.5.1 $\dot{V}O_2$ – Oxygen uptake

Oxygen uptake represents the amount of energy expended as aerobic metabolism is the predominant source of ATP. $\dot{V}O_2$ represents the total amount of oxygen taken up and utilized. This measure can be reported in absolute terms (Liters/min) or relative to body mass (ml/kg/min). As alluded to earlier, overall oxygen consumption is dependent oxygen delivery and peripheral tissue extraction.

1.3.5.2 $\dot{V}O_2$ max and Peak $\dot{V}O_2$

Maximal oxygen consumption ($\dot{V}O_2$ max) is the highest $\dot{V}O_2$ value attained during maximal exercise. Although shown to be a good predictor of outcome, it is limited by patient effort. Additionally, increasingly older population with co-morbidity is unable to carry out sustained exercise to their "maximal" capacity which is often restricted by symptoms.

Peak oxygen consumption (peak $\dot{V}O_2$) is expressed as the highest mean oxygen consumption value obtained from 5 rolling breath-to-breath measures during the last part of the incremental ramp stage. Both measures can be reported in absolute terms (Liters/min) or relative to body mass (ml/kg/min).

1.3.5.3 $\dot{V}CO_2$ – Carbon dioxide output

Carbon dioxide (CO_2) is released as a by-product of cellular respiration. Rise in CO_2 production follows increase in O_2 consumption in steady state. During high intensity exercise, anaerobic metabolism and the resultant acidosis allows a greater quantity of CO_2 to be blown off as a consequence of buffering. It is measured in absolute terms (Liters/min) or relative to body mass (ml/kg/min).

1.3.5.4 RER – Respiratory Exchange Ratio

It is the ratio of carbon dioxide production to oxygen consumption ($\dot{V}CO_2$ / $\dot{V}O_2$). At rest and during low intensity exercise it reflects the fuel substrates and undergoes changes during high intensity exercise to represent changes in metabolically and non-metabolically derived CO_2. The value of RER is also useful in detecting hyperventilation in the unloaded cycling phase and adequate effort in the incremental ramp phase to attain anaerobic threshold.

1.3.5.5 $\dot{V}E$ – Pulmonary ventilation

Dependant on the frequency of breathing and tidal volume (VT in litres), it is the amount of air moving in and out of the lungs per minute. Resting value varies from 5-10L/min and during exercise represents a linear relationship to $\dot{V}O_2$ and workload until the development of lactic acidosis when the stimulation of chemoreceptor leads to increase in $\dot{V}E$ (litres/min).

1.3.5.6 BR – Breathing reserve

Representing the potential in increasing ventilation in response to exercise, breathing reserve is measured as a difference between maximum ventilation at rest (measured at the start of exercise testing) and minute ventilation at peak exercise.

1.3.5.7 HR – Heart rate

Heart rate or number of beats per minute is an integral measure of cardiac output (Stroke volume x HR). Maximal heart rate values are estimated based on age (220-age) and are used to derive other CPET variable.

1.3.5.8 WR – Work rate

Measured in Watts, it represents the rate at which work is performed. Associated with $\dot{V}O_2$, ($\dot{V}O_2$ – work rate relationship), it describes the amount of external energy expended with the utilization of oxygen.

1.3.5.9 $\dot{V}O_2$ /HR – Oxygen pulse

Oxygen uptake divided by heart rate is a surrogate marker of stroke volume. It represents the amount of oxygen carried to the tissues in each stroke volume. Earlier increase with exercise is largely dependent on increase in Stroke volume, whereas later in exercise it is the result of increased peripheral tissue oxygen extraction.

1.3.5.10   Myocardial ischaemia

Myocardial ischaemia resulting is wall motion abnormality leads haemodynamic changes reflected by reduced stroke volume and cardiac output during exercise. These changes precede onset of ECG abnormalities and angina. Thus gas exchange analysis in the presence of myocardial ischaemia demonstrate reduced stroke volume and cardiac output which can be evaluated using $\dot{V}O_2$ – pulse and the rate of increase of $\dot{V}O_2$ to work rate.

1.3.5.11 $P_{ET}O_2$ – End-tidal oxygen

$P_{ET}O_2$ is the percent of expired air that is oxygen at the end of exhalation. A rise in end-tidal concentration at high-intensity stage of exercise with onset of anaerobic metabolism heralds a reduction in uptake and is used as one of the indicators of anaerobic threshold.

1.3.5.12 $\dot{V}E/\dot{V}O_2$ & $\dot{V}E/\dot{V}CO_2$ - Ventilatory equivalent ratio for oxygen and carbon dioxide

The ventilatory equivalence of carbon dioxide ($\dot{V}E/\dot{V}CO_2$) is a measure of lung dead space, including the anatomic, e.g. trachea, and physiological and physiological dead space, e.g. non-perfusing

alveoli and represents lung efficiency. It is determined as the ratio of minute ventilation ($\dot{V}_E$) to carbon dioxide elimination ($\dot{V}_{CO_2}$ L/min). The ventilatory equivalence for oxygen ($\dot{V}_E/\dot{V}_{O_2}$) is equal to $\dot{V}_E$ divided by $\dot{V}_{O_2}$.

1.3.5.3 AT – Anaerobic threshold

Anaerobic threshold (AT) is the point where anaerobic metabolism starts to contribute to energy production and leads to an increase of lactic acid production. Before the onset of anaerobic threshold, $\dot{V}_{O_2}$ maintains a linear relationship with the metabolically derived $\dot{V}_{CO_2}$, which is below $\dot{V}_{O_2}$ (RER <1.0). Buffering of lactate leads an increase in the non-metabolically derived CO_2, which stimulates ventilation resulting in excess CO_2 elimination and a non-linear change in the $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ relationship (RER >1.0). AT is determined using the V-slope method, which describes the use of regression analysis to present the inflection point on a plot of $\dot{V}_{CO_2}$ vs. $\dot{V}_{O_2}$ (Beaver et al., 1986). It can be confirmed by changes in $\dot{V}_E/\dot{V}_{O_2}$ and $P_{ET\,O_2}$. (Figure 1.3)
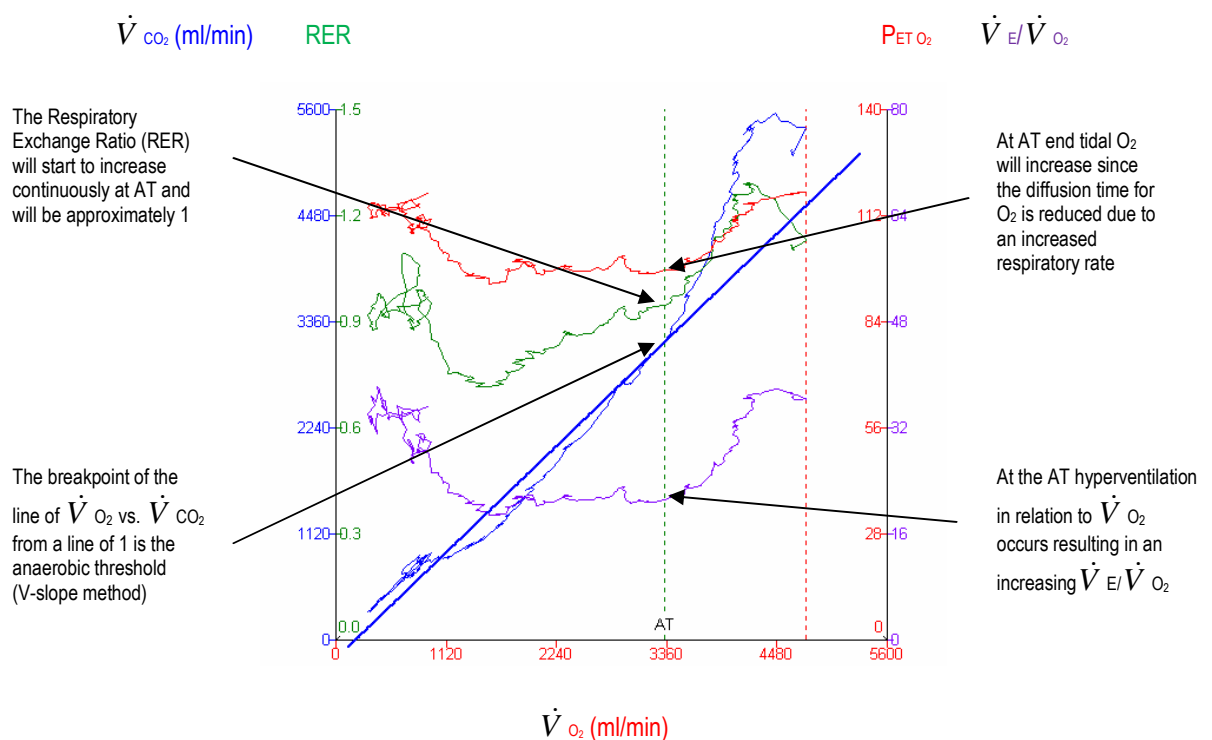
Figure 1.3: Detection of anaerobic threshold by gas exchange changes.

1.3.6 CPET and outcomes in surgery

The last two decades have seen the emergence of strong evidence of the prognostic value of CPET-derived variables in heart failure patients. In presence of heart failure, peak $\dot{V}O_2$ has been demonstrated to discriminate survival amongst patients undergoing heart transplant procedure (Mancini et al., 1991). As many elderly patients with heart failure present with other co-existing disease, the ability to sustain anaerobic exercise and achieve peak or maximal levels of oxygen consumption is limited. In this context, submaximal CPET-derived variables, such as AT and $\dot{V}E/\dot{V}CO_2$ at AT are better suited to be evaluated in this population as these are not affected by effort and have a greater chance of being evaluated successfully and safely. Gitt and colleagues (Gitt et al., 2002), evaluating survival in 223 consecutive heart failure patients demonstrated a greater value of these variables over peak $\dot{V}O_2$. Using a threshold of >34 for $\dot{V}E/\dot{V}CO_2$, and <11ml/kg/min for AT, the authors highlighted a value of combining these variables in achieving a greater accuracy of risk (Arena et al., 2004, Myers et al., 2009, Gitt et al., 2002).

As patients with cardiopulmonary disease are at greatest risk of postoperative complications, CPET has naturally assumed prominence as the potential source of providing the 'gold standard' in evaluating the peri-operative risk. An increasing number of studies have investigated CPET for postoperative mortality, morbidity and long-term survival in different surgical populations.

1.3.6.1 Intra-abdominal surgery

An early, prospective evaluation of CPET in major intra-abdominal surgery was reported by Older and colleagues (Older et al., 1993). In this single centre analysis of 187 patients aged over 60 years, AT of less than 11ml/kg/min was associated with 18% postoperative mortality with less than 1% in patients above this threshold. Presence of myocardial ischaemia below this threshold increased the

rate of mortality to 42%. This study further demonstrated that presence of myocardial ischaemia alone was not a significant marker of cardiovascular death.

In a subsequent larger prospective study of 548 patients over the age of 60 years, undergoing major intra-abdominal surgery (colorectal, vascular and gastric surgery – no hepatic or pancreatic resections) (Older et al., 1999), the authors categorised postoperative risk based on AT cut-off of 11 ml/kg/min and patients with values below this threshold (high-risk) received care on intensive care unit (ICU) postoperatively. Patients with myocardial ischaemia with AT >11 were designated moderate-risk and received high dependency unit (HDU) care postoperatively, whereas patients with no ischaemia received ward care (low-risk). Postoperative cardiovascular mortality was high in the ICU group (4.6%), with no deaths seen in the low risk group managed on the ward. The findings of these studies were limited by the bias produced from the CPET, informing postoperative care in the high-risk group.

This issue of bias was addressed in a recent, single centre, prospective study (Snowden et al., 2010), in which the CPET findings did not influence peri-operative care and the clinicians involved in care and data collection were blinded to CPET findings. Findings from 116 patients undergoing major elective surgery (including hepatic and pancreatic surgery) demonstrated a cut-off at 10.1 ml/kg/min for AT to be most optimum for predicting postoperative complications, utilising the postoperative morbidity survey (POMS). AT was also the best independent predictor of postoperative complications in a multivariate regression model, whereas RCRI failed to demonstrate any utility.

Similar findings have been reported in a more recent study. A retrospective analysis of preoperative CPET-derived AT and $\dot{V}_E/\dot{V}_{CO_2}$ in 843 patients undergoing elective abdominal surgery (Wilson et al., 2010) demonstrated similar cut-offs for AT (<11 ml/kg/min) for postoperative in-hospital and 90-

day mortality. $\dot{V}_E/\dot{V}_{CO_2}$ was also evaluated and demonstrated to be a strong predictor of postoperative in-hospital and 90-day mortality with the most optimal sensitivity and specificity at a threshold of 34. Limited by low event of postoperative deaths (2%), the study suggests the role of utilising two different CPET markers to act as useful adjuncts where RCRI failed to detect postoperative death.

The importance of identifying patients at high-risk of cardiac complications after major surgery was highlighted in a recent prospective, pragmatic trial (Swart and Carlisle, 2012), in which patients with the AT <11ml/kg/min were allocated to critical care or ward care following open colorectal surgery. Number of cardiac events were higher in the patients who received ward care with low AT (<AT), emphasizing the accuracy of this threshold in identifying patients at risk in this population. Outcomes of CPET evaluation in major surgery are shown in table 1.1.

1.3.6.2 Bariatric surgery

An inverse relationship between cardiopulmonary reserve as assessed by CPET and post-gastric bypass surgery was first reported by McCullough and colleagues (McCullough et al., 2006). Utilising treadmill for evaluation of capacity, postoperative complications were analysed with preoperatively derived CPET values. From 109 patients, peak $\dot{V}_{O_2}$ was shown to be associated with adverse outcome and a cut-off value of 15.8 ml/kg/min was derived.

A more recent prospective evaluation of outcomes following gastric bypass surgery was carried out using cycle ergometer to evaluate cardiopulmonary reserve (Hennis et al., 2012). Offering a more sensitive estimation of values with a cycle ergometer, the authors evaluated the prognostic utility of preoperative AT, peak $\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ for 5-day postoperative morbidity and length of hospital stay. Only AT was noted to be associated with higher morbidity and longer period of hospital stay yielding a cut-off predictive at 11 ml/kg/min. The differences in outcomes in these studies may be

due to different methodologies in deriving CPET values (treadmill vs. cycle ergometer) or defining

criteria for postoperative complications and adverse event. Regardless, CPET offers a more

accurate estimation of risk following surgery compared to conventional, subjective parameters in

use.

Author, year	Study design	Type of surgery	Population	CPET variables studied	Outcome
Older et al (1993)	Prospective, observational	Major intra-abdominal surgery	187 patients (aged >60 years)	AT	AT <11 ml/kg/min with myocardial ischaemia associated with higher cardiovascular postoperative mortality.
Older et al (1999)	Prospective, intervention	Major intra-abdominal surgery	548 patients (aged >60 year or <60 with cardiac disease)	AT	AT <11 ml/kg/min associated with cardiovascular postoperative death.
McCullough et al (2006)	Observational	Laparoscopic gastric bypass	109 patients (BMI >35 kg/m^2 with diabetes or >40 kg/m^2 without)	Peak $\dot{V}O_2$, BMI, AT, $\dot{V}E/\dot{V}CO_2$	Peak $\dot{V}O_2$ significant predictor of complications. No postoperative complications in patient with peak $\dot{V}O_2$ >15.8 ml/kg/min or BMI <45 kg/m^2.
Grocott et al (2012)	Prospective, observational	Gastric bypass	106 patients (<190 kgs)	AT, Peak $\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$, BMI, RCRI	Only AT associated with adverse postoperative outcomes with a lower value related to postoperative 5-day morbidity and increased length of hospital stay (> 3day). Cut-off at 11 ml/kg/min.
Snowden et al (2010)	Prospective, blinded observational	Major intra-abdominal surgery	116 patients (METS <7)	AT, RCRI, POSSUM, VASI	AT <10.1 ml/kg/min strongest independent predictor of postoperative complications.
Wilson et al (2010)	Retrospective, observational	Major intra-abdominal surgery	843 patients (age >55 years, <55 years with co-morbidities)	AT, $\dot{V}E/\dot{V}CO_2$, RCRI	AT ≤10.9 ml/kg/min and $\dot{V}E/\dot{V}CO_2$ >34 predictors of hospital and 90-day postoperative mortality.
Hightower et al (2010)	Prospective, blinded observational	Major intra-abdominal surgery	32 patients	HR at AT, AT % of predicted, ASA	HR at AT and % of AT more predictive of postoperative complication than ASA rank.
Swart et al (2012)	Prospective, pragmatic trial	Colorectal surgery	153 patients	AT, POSSUM, APACHE II	AT <11 ml/kg/min associated with postoperative cardiac events.

AT: anaerobic threshold in ml/kg/min, *BMI:* body mass index, *Peak $\dot{V}O_2$:* peak oxygen consumption, $\dot{V}E/\dot{V}CO_2$: ventilatory equivalent of carbon dioxide, *RCRI:* revised cardiac risk index, *VASI:* Veterans activity score index, *HR:* heart rate, *ASA:* American Association of Anaesthesiologists, *AAA:* abdominal aortic aneurysm, *SAPS II:* Simplified Acute Physiology Score, *APACHE II:* Acute Physiology And Chronic Health Evaluation score and *POSSUM:* Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity.

Table 1.1: Studies evaluating preoperative CPET in abdominal surgery

1.3.6.3 Thoracic surgery

Peak $\dot{V}O_2$ has proven to be a useful predictor of complications and survival in patients, following pulmonary resection surgery. Systematic review of 14 studies, incorporating 955 patients undergoing lung surgery, found maximal $\dot{V}O_2$ to be a strong predictor of postoperative morbidity (Benzo et al., 2007). This has seen CPET being incorporated in the European clinical guidelines for the assessment lung cancer prior to radical therapy (surgery and chemotherapy) (Brunelli et al., 2009). A preoperative peak $\dot{V}O_2$ of >75% of predicted or 20 ml/kg/min qualifies a patient to undergo pneumonectomy and a predicted value of <35% or <10 ml/kg/min is deemed high-risk for any resection.

A recent study of postoperative outcomes in 145 patients undergoing lung resection for cancer with chronic obstructive airway disease (COPD) (Torchio et al., 2010) found $\dot{V}E/\dot{V}CO_2$ to be the strongest independent predictor of postoperative morbidity and mortality, adding prognostic value to peak $\dot{V}O_2$.

Evaluation of CPET in oesophagectomy is limited by paucity of good studies. Reporting outcomes following oesophagectomy in 78 consecutive patients (Forshaw et al., 2008), the authors evaluated the predictive role of CPET-derived variables for postoperative morbidity, mortality, unplanned critical care stay, hospital stay and the effect of preoperative chemotherapy. Although the study was limited by sample size, it was further undermined by smaller proportion of patients undergoing two discrete surgical approaches (transthoracic 50%, transhiatal 50%). Although the authors suggest no prognostic utility of AT, their results cannot be generalised as further bias is introduced by lack of blinding which may underestimate the association with outcomes. The authors conceded that different postoperative procedures and specific patient populations may represent different demands and that the threshold of CPET-derived variables may vary in their accuracy. This may be an explanation for the lack of discrete cut-off as specific patient populations and procedures exert

specific demands on cardio-respiratory reserve and present with unique postoperative sequel of complications.

1.3.6.4 Vascular surgery

An early evaluation of CPET in patients undergoing abdominal aortic aneurysm (AAA) repair alluded to the usefulness of peak $\dot{V}O_2$ in identifying patients at high risk of postoperative complications (Nugent et al., 1998) (Table 1.2). Carlisle (Carlisle and Swart, 2007), in a prospective, observational study evaluated RCRI and CPET-derived AT, $\dot{V}E/\dot{V}CO_2$, $\dot{V}E/\dot{V}O_2$ and peak $\dot{V}O_2$ for mid-term survival in 130 patients following elective AAA repair. Although all the mentioned preoperative markers were associated with adverse outcome, $\dot{V}E/\dot{V}CO_2$ was the most significant independent predictor. As the clinicians involved in patient selection and peri-operative care were informed of the CPET results the findings may have been underestimated as patients identified at high risk in the process of preoperative evaluation may have received better care.

A retrospective assessment of 102 AAA patients was carried out by Thompson and colleagues (Thompson et al., 2011) to compare the prognostic potential of CPET derived factors with the Acute Physiology and Chronic Health Evaluation (APACHE) II score and Vascular Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (VPOSSUM). Although the authors found AT to be the only predictor of 30-day major morbidity and mortality and mid-term survival (30 months), the study was underpowered and the data was largely derived from older patients with significantly poor CPET parameters who were deemed unfit for surgery (36 patients). Although useful in predicting overall survival it cannot be generalised to postoperative predictor of survival. Additionally the study incorporated 63 patients undergoing open surgery, in the era of endovascular repair; patients undergoing open surgery represent a more complex group in terms of surgical complexity and postoperative morbidity (supra-renal clamping and renal impairment)

(Barshes et al., 2012). This prevents these findings from being applied usefully to the new cohorts of open AAA repair patients.

Author, year	Study design	Type of surgery	Population	CPET variables studied	Outcome
Carlisle et al (2007)	Prospective, observational	Open AAA surgery	130 patients	AT, Peak $\dot{V}$ O_2, $\dot{V}$ E/$\dot{V}$ CO_2, $\dot{V}$ E/$\dot{V}$ O_2, SAPS II, APCHE II, RCRI, POSSUM	All correlated with median 35-month survival, CPET-derived $\dot{V}$ E/$\dot{V}$ CO_2 was most predictive independent variable in multivariate regression analysis.
Thompson et al (2011)	Retrospective, observational	AAA patients (36 unfit and not operated, 63 open repair, 3 endovascular repair)	102 patients	AT, Peak $\dot{V}$ O_2, $\dot{V}$ E/$\dot{V}$ CO_2, $\dot{V}$ E/$\dot{V}$ O_2, APACHE II, VPOSSUM	AT only variable predicting 30-day major morbidity or mortality (postoperative) and 30-month (mid-term) survival.
Hartley et al (2012)	Prospective, observational	Elective AAA repairs (65% endovascular repair, 35% open repair)	415 patients	AT, AT 10.2 ml/kg/min, $\dot{V}$ O_2, $\dot{V}$ O_2 15 ml/kg/min, $\dot{V}$ E/$\dot{V}$ CO_2, $\dot{V}$ E/$\dot{V}$ CO_2 42	AT at 10.2 ml.kg/min only CPET predictor of 30-day death on multivariate model. $\dot{V}$ O_2 at 15 ml/kg/min only CPET predictor of 90-day mortality on multivariate regression analyses. Two or more subthreshold CPET values mean high risk of postoperative death.

AT: anaerobic threshold in ml/kg/min, $\dot{V}$ O_2: oxygen consumption, *Peak* $\dot{V}$ O_2: peak oxygen consumption, $\dot{V}$ E/$\dot{V}$ CO_2: ventilatory equivalent of carbon dioxide, *CPET:* cardiopulmonary exercise testing, *RCRI:* revised cardiac risk index, *AAA:* abdominal aortic aneurysm, *SAPS II:* Simplified Acute Physiology Score, *APACHE II:* Acute Physiology And Chronic Health Evaluation score and *POSSUM:* Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, *VPOSSUM:* vascular POSSUM.

Table 1.2: Studies evaluating preoperative CPET in abdominal aortic aneurysm surgery

A limited systematic review (Young et al., 2012), drawing on 7 articles, reported on the paucity of data to inform a preoperative prognostic role of CPET in stratifying risk of outcome following major vascular surgery. However, the evidence for the use of CPET is accumulating in favour of its prognostic value. A recent multicentre evaluation has reported on 30-day and 90-day of postoperative survival in 415 patients undergoing elective AAA repair (endovascular – 65%, open repair – 35%) (Hartley et al., 2012). Incorporating a large number of open repair patients, more

frequently associated with juxta-renal aneurysms and supra-renal clamping, demonstrates it to be

predictor of 90-day mortality. Using discriminating CPET variable thresholds, the authors report AT at

10.2 ml/kg/min to be the only CPET variable predicting 30-day mortality in a multivariable model,

whereas $\dot{V}$ O₂ at 15 ml/kg/min was the only CPET-derived predictor of 90-day death. The authors

also highlighted the higher predictive value when patients recorded two or more subthreshold CPET

values.

1.3.6.5 *Hepato-pancreatico-biliary surgery*

The evaluation of CPET in major hepato-pancreatico-biliary surgery was initially confined to hepatic

transplantation (Epstein et al., 2004, Prentis et al., 2012) (see Table 1.3). Although the findings

cannot be generalised to the hepatic resection populations, it provides some useful insights into the

application and utility of this tool. Epstein (Epstein et al., 2004) reported increased 100-day mortality

in patients with reduced peak $\dot{V}$ O₂ (<60% of predicted) and AT (<50% predicted) compared to

survivors following hepatic transplant. Overall mortality in the observation period was 10.2%. This

study was limited in its evaluation by the assumption that the patients with liver failure have normal

patterns of distribution of aerobic capacity and exercise limitation and a prolonged period of delay

occurring between preoperative CPET assessment and the time of surgery (mean delay 15 months).

In a more recent evaluation of preoperative CPET for elective hepatic transplantation (Prentis et al.,

2012), the authors highlighted the safety of the test in this subset of patients; however, successful

completion of assessment of submaximal parameters was limited to 91%. CPET testing was found to

detect myocardial dysfunction and ischaemia accurately when compared to stress echocardiogram

and coronary angiogram. Amongst CPET-derived variables, AT was the only marker associated with

adverse 90-day postoperative survival and demonstrated a high sensitivity and specificity (90.7%

and 83.3% respectively). The optimal cut-off shown was to be at 9.0 ml/kg/min, with patients showing

poor survival below this threshold. AT was also found to be useful in predicting critical care stay and was the only significant predictor of 90-day survival amongst the preoperative and intraoperative variables evaluated.

Early indications from the preliminary work on evaluation of CPET in post pancreaticoduodenectomy patients (Ausania et al., 2012), suggests its utility in identifying patients with low AT to be at high risk of developing pancreatic fistula, which remains a significant contributor of postoperative morbidity and mortality in these patients.

Author, year	*Study design*	*Type of surgery*	*Population*	*CPET variables studied*	*Outcome*
Epstein et al (2004)	Observational	Hepatic transplantation	59 patients	Peak $\dot{V}$ O$_2$ % of predicted, AT % of predicted	Peak $\dot{V}$ O$_2$ % of predicted and AT of <50% of predicted correlated with poor 100-day survival.
Prentis et al (2012)	Observational	Hepatic transplantation	60 patients	AT, Peak $\dot{V}$ O$_2$, $\dot{V}$ E/$\dot{V}$ CO$_2$, $\dot{V}$ O$_2$/HR	AT <9 ml/kg/min predicted 90-day postoperative survival. AT correlated with critical care and hospital stay.
Ausania et al (2012)	Prospective, observational	Pancreatic resection	124 patients	AT, Peak $\dot{V}$ O$_2$, $\dot{V}$ E/$\dot{V}$ CO$_2$	AT only amongst preoperative and intra-operative variables predictive of pacnreatic leak on multivariate analyses. Cut-off 10.2 ml/kg/min.
Chandrabalan et al (2013)	Retrospective, observational	Pancreatic resection	100 patients	AT 10 ml/kg/min, POSSUM, mGPS	AT only independant predictor of pancreatic fistula and length of hospital stay. No associtaion with cardiopulmonary complications or critical care stay. AT predicted failure to recieve adjuvant chemotherapy.

AT: anaerobic threshold in ml/kg/min, *BMI:* body mass index, *Peak $\dot{V}$ O$_2$:* peak oxygen consumption, $\dot{V}$ E/$\dot{V}$ CO$_2$: ventilatory equivalent of carbon dioxide, *METS:* metabolic equivalents, *RCRI:* revised cardiac risk index, *VASI:* Veterans activity score index, *HR:* heart rate, *ASA:* American Association of Anaesthesiologists, *AAA:* abdominal aortic aneurysm, *SAPS II:* Simplified Acute Physiology Score, *APACHE II:* Acute Physiology And Chronic Health Evaluation score and *POSSUM:* Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity.

Table 1.3: Studies evaluating preoperative CPET in hepato-pancreatic-biliary surgery

Another recent retrospective review of low AT demonstrates an adverse relationship with pancreatic fistula and length of hospital stay post-pancreatectomy (Chandrabalan et al., 2013). Using the threshold defined by Snowden and colleagues (Snowden et al., 2010), the authors evaluated the relationship of AT at 10.1 ml/kg/min with postpancreatectomy pancreatic fistula, cardiopulmonary complications, critical care and hospital stay, 30-day mortality and progression to receiving adjuvant chemotherapy where indicated on histo-pathological grounds. Comparing it to POSSUM and GPS, the authors found it to be the only predictor of fistula and postoperative length of hospital stay. Limited to a subgroup analysis of 55 patients in whom adjuvant chemotherapy was indicated, AT was shown to predict lack of receipt with low values.

Although the data on pancreatectomy patients remains limited to small cohorts, current evidence points to trends in uptake of CPET as a novel modality in stratifying risk and perioperative care of patients undergoing major hepato-pancreatico-biliary surgery.

1.4 Hepatic surgery

Liver or hepatic resection is also undertaken for a variety of reasons ranging from symptomatic benign to malignant conditions. The commonest indication for elective resection remains cancer and metastatic liver disease remains the commonest form of cancer affecting the liver. It is the most common indication for hepatic resection followed by primary malignancy of the liver (Poon et al., 2004, Jarnagin et al., 2002, Belghiti et al., 2000).

The development of liver resection as a viable treatment option has progressed with advances in surgical techniques, perioperative care and effective chemotherapy. Historically associated with high postoperative mortality, therapeutic liver resection can be undertaken with low postoperative mortality (<5% in large volume centres).

1.4.1 Major indications for hepatic resection

Amongst the high-risk group of patients, the risk of undertaking major resectional surgery can only be justified by achieving a potential cure and significant improvement in long-term outcomes. Large case series have reported a wide variation in indications for liver resection as they are impacted by local services, referral pathways, expertise and guidelines. The majority of resections continue to be undertaken for malignancy.

1.4.1.1 Primary malignancies

Hepatocellular carcinoma accounts for 90% of all primary liver malignancies and the incidence has seen a rise in the recent decades with increase in viral hepatitis (Perz et al., 2006). As the 5th most common cancer worldwide, it's the third most common cause of death after colorectal cancer (W.H.O., 2003). Liver resection is still considered to be the mainstay of a curative approach, with emphasis on patient selection and preoperative evaluation to achieve >40% future liver remnant

(Schindl et al., 2005) by use of portal vein embolisation (Ribero et al., 2007). Selective postoperative outcomes, in the form of 30-day and all in-hospital postoperative mortality are worse in patients with underlying cirrhosis (Farges et al., 1999). However, this risk is still small and outweighed by the overall benefit of a curative resection. Other hepatic parenchymal (cholangiocarcinoma) and extra-hepatic biliary (gall bladder, hilar cholangiocarcinoma) are less common but remain major indications for resection.

1.4.1.2 Colorectal liver metastases

Colorectal cancer is the second most common cause of death from cancer in the UK and accounted for 16,259 deaths in 2008 (O.f.N.S, 2010). Secondary metastases are the more prevalent form of cancer in the liver, with colorectal cancer metastases being the single most common indication for resection (Cancer UK). Liver resection offers the only treatment with the potential to cure patients with isolated metastatic disease (Simmonds et al., 2006) with 5-years survival exceeding 40%.

The main mode of spread of colorectal cancer to the liver occurs via portal circulation. Around 20 – 25% of patients with colorectal cancer present with synchronous liver metastases (Norstein and Silen, 1997). After resection of primary cancer, up to 50% develop liver metastases within 3 years (Stangl et al., 1994) which may be isolated in up to 30–40% (Weiss et al., 1986), amenable to curative resection. Up to 98% of these recurrences are within the 5-year follow-up period with 15% of patients developing recurrence after this disease-free period.

1.4.1.3 Other secondaries

The principal indication for hepatic resection in the high-risk surgical population in our hospital remains colorectal cancer metastases. Although outcomes following resection for other malignancies have been comparable in very selected groups of patients, overall outcomes remain poor.

Postoperative morbidity and mortality following resection for different primary and secondary malignancies of the liver remains comparable with no marked differences (Reddy et al., 2007). The true difference lies in the long-term benefit, as metastases represent generalised spread. Elias (Elias et al., 1998), in a retrospective analysis of 147 patients undergoing liver resection at a single centre for non-colorectal cancer reported 5-year survival rate of 74% for Neuroendocrine tumours, 46% for testicular tumours and 20% for breast cancer. Outcomes were less than 20% at 5-year follow-up period for gastric carcinomas and sarcomas. Similar findings have been reported by other authors (Yedibela et al., 2005).

The advent of novel therapies for treatment of advanced or recurrent breast cancer has demanded re-evaluation of risk-benefit ratio in patients undergoing hepatic resection for breast cancer metastases (Adam et al., 2006), as survival benefit may be significant in appropriately selected individuals.

1.4.2 Role of chemotherapy

Advent of effective adjuvant chemotherapy heralded a new era and has drastically changed long-term outcomes in patients with 'unresectable' or recurrent colorectal cancer metastatic disease. It has led to redefining the limits of resectability (Adam et al., 2004, Adam et al., 2010), and the application of surgery as a curative option is further broadened by the parallel development of other adjuncts (portal vein embolisation). This has resulted in greatly increasing the number of hepatic resections undertaken in the UK (Morris et al., 2010).

Morris and colleagues, using the National Cancer Data repository, evaluated 114,115 individuals undergoing hepatic resection for colorectal metastases from 1998 to 2004. The rate of resection was seen to increase from 1.7% in 1998 to 3.8% in 2004. Although variations were noted across cancer networks and hospitals, overall 5-year survival was greater than 40%.

A landmark randomised controlled trial, evaluating the role of neo-adjuvant chemotherapy prior to resection of operable colorectal liver disease (Nordlinger et al., 2008, Nordlinger et al., 2007) showed a 7.3% increase in progression-free survival of patients receiving neo-adjuvant chemotherapy. Although a higher incidence of postoperative complication was noted in this group (25% vs. 16% compared to patients receiving adjuvant chemotherapy alone), overall benefit was demonstrated with comparable long-term survival and increased disease-free period. This has seen a wider acceptance of preoperative chemotherapy in managing colorectal cancer involving the liver.

1.4.3   Role of surgery in colorectal metastasis: value of alternative therapy

In absence of surgery, palliative chemotherapy alone offers poor median survival of 6-8 months (Stangl et al., 1994). More importantly, neo-adjuvant chemotherapy renders a third of inoperable disease, resectable and improves overall survival (Neoptolemos et al., 2010). Comparing long-term outcomes in 39 patients with unresectable disease, Baize and colleagues (Baize et al., 2006) reported a conversion rate to resectable stage of 28% (11/39 patients). Following surgery, the overall median survival in these patients was significantly greater than those without surgery (60 vs. 18.5 months). Despite hepatic recurrence, repeat resections for colorectal liver metastasis offers no differences in postoperative mortality, morbidity and long-term survival (Antoniou et al., 2007) but suggesting greater benefit in surgery than palliative treatment alone.

Novel therapies, in the form of monoclonal antibodies against vascular endothelial growth factor (VEGF) and epidermal growth factor (EGFR) have been incorporated into treatment algorithms and guidelines for treating metastatic colorectal as they offer an added advantage in selected patients by enhancing the effect of chemotherapy and improving on disease free and overall long-term survival (Van Cutsem et al., 2010, Adam et al., 2010).

The precise role of ablative therapy, as a palliative or even a curative strategy, remains unclear as it has been reserved for patients unsuitable for surgical intervention (Garden et al., 2006). Randomisation of patients to different treatment modalities to evaluate prognostic benefit remains difficult as categorisation of "resectable" liver disease continues to evolve in the face of improved surgical techniques and effective chemotherapy agents. Presently, ablative therapy is offered to patients with resectable and unresectable hepatic metastatic disease, who are deemed unfit to undergo major hepatic resection due significant co-morbidities and high perioperative risk.

In this context, surgery continues to be the treatment of choice, in conjunction with chemotherapy and novel therapeutic agents (monoclonal antibodies), for patients with colorectal liver metastasis and is the only intervention that offers a potential for cure (Van Cutsem et al., 2006).

1.4.4   *Postoperative outcomes in hepatic resection*

Mortality from hepatic resection has been on the decline and is now accepted to be less than 5% in large centres. A systematic review comprising of 15 studies (Simmonds et al., 2006) with 103 patients undergoing hepatic resection reported liver failure, postoperative haemorrhage, generalised sepsis, cardiac failure, multi-organ failure, pulmonary embolism, bile leak and anastomotic leak to be the common causes of postoperative death. In-hospital postoperative mortality in the older population (>70 years of age) has also been low (<5%) with long-term survival benefit (de Liguori Carino et al., 2008). However, restricting the definition of early postoperative mortality hides the trend of postoperative deaths occurring from complications and prolonged critical care stay in the later period (Khuri et al., 2005).

Morbidity from liver resection has been reported to vary widely. This represents many factors, including studies from small centres which tend to experience more complications, impact of age and chemotherapy, patient selection and a wide variation in definitions of morbidity. Common

postoperative morbidity include: wound infection (5.4%), generalised sepsis (4.6%), pleural effusion (4.3%), bile leak (4.0%), peri-hepatic abscess (3.0%), hepatic failure (2.8%), arrhythmia (2.8%), postoperative haemorrhage (2.7%), cardiac failure (2.4%) and pneumonia (1.9%).

1.5   Pancreatic resection

1.5.1   *Pancreaticoduodenectomy for cancer*

Pancreatic cancer is the eleventh most common cancer in the UK (Cancer Research UK) with around 7,800 people diagnosed every year, with more than 80% of cases occurring in people aged 60 years and over.

Primary pancreatic malignancy is the single most common indication for pancreaticoduodenectomy (PD), as 80% of cases involve the head of the pancreas. Surgical resection is the only intervention associated with long-term survival (Yeo et al., 2002). However, resection is only beneficial in patients with disease confined to the pancreas (Adham et al., 2008).

1.5.2   *Survival with and without surgery*

In a national US database review of 100,313 patients with pancreatic cancer, majority presented with pathology in the head of pancreas (78%), whereas prevalence in the body and tail was 11% for both (Sener et al., 1999). Resection was undertaken only in 9% of patients and 58% of patients received no cancer treatment. 5-year survival was demonstrated to be significantly greater at 23% with surgery alone compared to 2.3% without surgery but receiving chemotherapy and/or radiotherapy.

Although, it is clear that surgical resection is the only intervention with the most favourable outcome, factors such as tumour size, differentiation, lymph node status, vessel invasion, location of tumour, resection margin, age of patient and the chemotherapy response all have a bearing on outcome (Adham et al., 2008). Unfortunately, the majority of the patients (>80 %) present late with advanced disease leaving less than 20% with the option of resection at the time of diagnosis. Palliative treatment of advanced pancreatic cancer or patients unfit to undergo surgery is limited to adjuvant chemotherapy as the role novel therapies is limited to clinical trials (Gastroenterology, 2005).

1.5.3 Postoperative mortality and morbidity

Complex pancreatic surgery undertaken at large volume centres has also seen an improvement in postoperative mortality and complications following pancreaticoduodenectomy (Birkmeyer et al., 1999, Gouma et al., 2000). The procedure can be undertaken safely with low postoperative in-hospital mortality (less than 5%) (McPhee et al., 2007). However, despite resectional surgery and adjuvant chemotherapy (Neoptolemos et al., 2001), 5-year survival following pancreaticoduodenectomy remains poor at 15 – 25%.

Postoperative 30-day mortality following pancreaticoduodenectomy has seen a progressive decline in the last few decades (Gouma et al., 2000, McPhee et al., 2007). Outcomes from small volume (<5 procedures/year) and medium volume centres (5 – 18 procedures/year) demonstrated higher postoperative mortality, leading to centralisation of services to create large centres (>18 procedures/year), where postoperative mortality remains <5%.

A large retrospective analysis of pancreaticoduodenectomy patients from a national in-patient sample from North America, from 1998 to 2003 (McPhee et al., 2007), showed that pre-existing cardiopulmonary disease (congestive heart failure, chronic lung disease) were the strongest preoperative predictors of postoperative in-hospital mortality.

Trends in postoperative complications over the last decades have also seen a decline, with high-volume centres performing better. This is largely the result of improvements in peri-operative critical, better prevention and early recognition and management of complications. However, postoperative morbidity remains high at 40 – 60% and difficult to define accurately due to variations in terminologies. Major complications following pancreaticoduodenectomy include pancreatic fistula (10%), biliary leakage (5%), delayed gastric emptying (40-50%), intra-abdominal abscess and sepsis (20%), pulmonary (10 – 20%) and cardiac complications (10%).

1.5.4   Obstructive jaundice

Malignant obstructive jaundice is a common result of pancreatic cancer and associated with adverse patho-physiological effects. The basis for the benefit of preoperative treatment of obstructive jaundice is based on experimental and clinical evidence of its detrimental effects (van der Gaag et al., 2009). The evidence from human studies has often been conflicted, providing no strong basis either for or against the correction of hyperbilirubinaemia prior to pancreaticoduodenectomy. As a result there is no consensus on discrete threshold of Bilirubin levels deemed detrimental or a preoperative treatment algorithm managing obstructive jaundice prior to pancreatic resection.

1.5.4.1 Adverse effects of obstructive jaundice

Obstructive jaundice resulting in absence of bile salts from the gut results in accumulation of endotoxin in the colon, which in turn results in portal and systemic endotoxaemia (Jiang and Puntis, 1997, Kimmings et al., 2000, Padillo et al., 2001a). Further bacterial translocation occurs with biliary infections and failure of the tight junctions in the biliary tract and altered mucosal permeability. The outcome of this is a significant immunological dysfunction (Ljungdahl et al., 2007), attributed to increased postoperative complications and death.

1.5.4.1.1   Impact on cardiovascular function

Adverse impact of malignant obstructive jaundice on the cardiovascular function is well established. It is associated with significant hypovolaemia and reduction in the extracellular fluid leading to renal impairment (Padillo et al., 2001b, Padillo et al., 2005). Padillo and colleagues, evaluating the effects of intravascular fluid resuscitation in patients with obstructive jaundice found, that reduced extracellular fluid volume was accompanied by elevated plasma renin and aldosterone levels in response to hypovolaemia, but paradoxically, elevated levels of atrial natriuretic peptide (ANP) were

noted. Furthermore, the authors found that volume replacement alone did not improve renal function, which occurred only after adequate biliary drainage.

This phenomenon was evaluated In an earlier study by Padillo and colleagues (Padillo et al., 2001b). The authors reported on the effects of malignant obstructive jaundice on cardiac function of 13 patients after undergoing biliary drainage. These patients were selected on the basis of no pre-existing cardiopulmonary or renal disease, and no intravenous fluid resuscitation was undertaken before biliary drainage. Biliary drainage was followed by significant improvements in global cardiac function and the levels of Bilirubin correlated with left ventricular systolic work.

1.5.4.1.2   *Impact on peripheral oxygen extraction*

Development of pancreatic cancer is associated with a hypermetabolic state demonstrating increased resting energy expenditure (Falconer et al., 1994). Coupled with an increase of up to 40% in demand for oxygen consumption in the postoperative phase of patients undergoing major surgery (Older and Smith, 1988), patients with cardiac dysfunction from obstructive jaundice may be at high risk of adverse outcome. This demand is met in large part by an increase in cardiac output and oxygen extraction is shown to play a smaller role in general surgical population. Although this ability to extract is affected in sepsis and diabetes (Baldi et al., 2003), the relationship between malignant obstructive jaundice and this extraction is not known (limited experimental data on cardiac and hepatic mitochondrial activity). Changes in central venous oxygen levels and extraction are well established in healthy individuals and patients with varying levels of congestive heart failure (Weber and Janicki, 1985, Stringer et al., 1994).

1.5.4.2   *Preoperative biliary drainage*

Contrary to the established notion of adverse effects of obstructive jaundice on postoperative outcomes, recent studies and systematic analyses have questioned the wisdom of this intervention,

reporting increased morbidity and longer hospital stay experienced in patients undergoing preoperative biliary drainage (Sewnath et al., 2002, van der Gaag et al., 2009).

Povoski and colleagues (Povoski et al., 1999), reporting outcomes from a prospectively collected database of 240 consecutive pancreaticoduodenectomies, showed significantly higher incidence of postoperative complications and death in patients undergoing preoperative biliary drainage. Other factors, such as age, history of jaundice, bilirubin level and underlying disease were not associated with outcomes. Although other similar studies have not reproduced these findings of high postoperative complications and mortality, they have demonstrated an association of increased infective complications following preoperative biliary intervention (Pisters et al., 2001).

In a multicentre, randomised trial, van der Gaag (van der Gaag et al., 2010) compared preoperative drainage with surgery alone in 196 patients undergoing pancreaticoduodenectomy. The authors reported higher rate of postoperative complications in the biliary drainage group, with no difference in hospital mortality or stay. This was consistent with the results of an earlier meta-analysis (Sewnath et al., 2002), of 5 randomised controlled studies and 18 cohort studies reporting increased complication rate with a longer hospital stay in patients undergoing preoperative drainage.

1.6   Summary statement

Addressing postoperative outcomes after major or high-risk surgery remain elusive. A low mortality rate in hepato-pancreatico-biliary surgery masks a subset of high-risk patients who represent the large proportion of adverse postoperative outcomes. Hidden in "overall" low mortality, these patients have historically escaped the rigorous attention to risk assessment and appropriate postoperative attention (Pearse et al., 2006). A closer look at the variability of postoperative mortality brings our attention to the early recognition of risk and adequate management of postoperative complications as complications following major surgery largely remain similar across many centres (Ghaferi et al., 2009). These complications not only translate in higher early mortality risk, but also impact on cost (critical care and hospital stay), failure to progress to further treatment (adjuvant chemotherapy) and adversely impact on long-term survival (Ghaferi et al., 2009, Chandrabalan et al., 2013, Khuri et al., 2005). Therefore, the current challenge in major surgery lies in recognition of the "high-risk" patient population which will experience adverse postoperative outcome.

There are several limitations in meeting these goals. Improvements in diagnostic methods, perioperative care and adjuvant therapies mean that curative hepatic and pancreatic resection is indicated in a larger population of patients with cancer. Coupled with population trends, older patients with higher co-morbidities will be facing a prospect of undergoing major hepato-pancreatic-biliary surgery. Relying on simple epidemiological determinants (age) and subjective risk assessment criteria (ASA, RCRI) will not be effective in stratifying risk in this complex patient population. Furthermore, a pressing need for individualising risk stratification and postoperative care would offer a promise of a more efficient use of scarce resources and offer a greater survival benefit to patients.

1.6.1   Study aims

In this context, CPET offers to provide the discriminating characteristics which identify patients at risk of developing adverse outcomes following surgery (Older et al., 1999, Snowden et al., 2010). The ability of the test in evaluating basic physiological responses of the cardiopulmonary unit and mechanisms of oxygen delivery, extraction and utilisation add to the clinical utility provided by the use of derived variables.

The aim of this work was to carry out the first evaluation of CPET in the "high-risk" surgical population undergoing treatment for hepato-pancreatico-biliary malignances. CPET in this patient population remains underutilised as evident from the paucity of literature which have limited this evaluation to a handful of outcome measures (Ausania et al., 2012, Chandrabalan et al., 2013). We aimed to evaluate the prognostic potential of preoperative CPET in defining patients at risk, stratifying perioperative risk, predicting postoperative morbidity and mortality and long-term survival.

As postoperative morbidity has been shown to impact greatly on all postoperative outcomes, the primary aim was to test the utility of CPET-derived variables in predicting postoperative complications. Secondary goals involved evaluating postoperative death, critical care and hospital stay and long-term survival in high-risk patients with hepato-pancreatico-biliary malignancies. Although, true prevalence of complications following surgery is an elusive figure owing to wide ranging definitions of complications (Martin et al., 2002), a high prevalence of postoperative morbidity means it can be adequately evaluated.

As the first CPET study in the hepato-pancreatico-biliary cancer population, it was also deemed useful to assess the prognostic value in predicting long-term outcomes as 5-year survival remains poor in patients with pancreatic cancer. This would give us useful insights in making informed decisions of complex care in patients confounded by major surgery. Thus CPET offers a prospect of replacing subjective, surrogate tests with a reliable, objective, safe and non-invasive means of assessing cardiopulmonary function to aid in improving outcomes after surgery.

Chapter 2

CARDIOPULMONARY EXERCISE TESTING FOR PREOPERATIVE RISK

ASSESSMENT PRIOR TO HEPATIC RESECTION

2.1 Abstract

Background: Contemporary liver surgery practice must accurately assess operative risk in increasingly elderly populations with greater co-morbidity. This study evaluates preoperative cardiopulmonary exercise testing (CPET) in high-risk patients undergoing hepatic resection.

Methods: In a prospective cohort of consecutive patients referred for liver resection, patients aged over 65 years (or younger with co-morbidity) were evaluated by preoperative CPET. Data were collected prospectively on functional status, postoperative complications and survival.

Results: Two hundred and four patients were assessed for hepatic resection of which 108 had preoperative CPET. An anaerobic threshold (AT) of 9.9 ml O_2/kg/min predicted in-hospital death and subsequent survival. Below this threshold, AT was 100% sensitive and 75.9% specific for in-hospital mortality with a positive predictive value (PPV) of 19% and a negative predictive value (NPV) of 100%: no deaths occurred above the threshold. Age and $\dot{V}_E/\dot{V}_{CO_2}$ at AT were statistically significant predictors of postoperative complications. Receiver operating characteristic (ROC) curve analysis showed a threshold of 34.5 for $\dot{V}_E/\dot{V}_{CO_2}$ at AT provided a specificity 84% and a sensitivity of 47%, PPV 76% (95% CI: 58% to 88%) and NPV 60% (95% CI: 48% to 72%) for postoperative complications. Long-term survival of those with an AT of less than 9.9 ml O_2/kg/min was significantly worse than that of patients with a higher AT (HR 1.81, 95% CI: 1.04 to 3.17, p=0.036).

Conclusions: CPET provides a useful prognostic adjunct in the preoperative assessment of patients undergoing hepatic resection.

2.2 Background

Hepatic resection is the standard of care for patients with resectable colorectal metastatic disease confined to the liver (Simmonds et al., 2006). Liver resection for malignancy is also undertaken in selected patients with primary liver tumours, biliary tract tumours (cholangiocarcinoma) and in some patients with non-colorectal hepatic metastases (Nordlinger et al., 2007, Weitz et al., 2005, Yedibela et al., 2005, Ercolani et al., 2005, Baize et al., 2006). Contemporary experience with techniques such as down-staging of tumour size by neoadjuvant chemotherapy (Nordlinger et al., 2009) and modification of the volume of the future remnant liver by selective portal vein embolisation (Wicherts et al., 2010) result in the ability to offer liver resection to an increasing number of patients. These changes, coupled with population trends resulting in a greater proportion of elderly patients, mean that in the 21st century, liver resection for cancer is often undertaken in older individuals and (in the setting of resection for colorectal hepatic metastases) in patients whose hepatic functional reserve may have been compromised by post-chemotherapy steatohepatitis (Nordlinger and Benoist, 2006).

Although a host of cohort reports outline the feasibility of undertaking liver resection with low perioperative mortality (Simmonds et al., 2006, Jarnagin et al., 2002, Imamura et al., 2003), optimum surgical practice must weigh the oncological benefits of resection against the potential risks in terms of morbidity and mortality. Despite the fact that postoperative mortality following hepatic resection continues to decline, morbidity remains high and varies from 20 to 50% (Jarnagin et al., 2002, Erdogan et al., 2009).

In this context, preoperative assessment of risk assumes an important role in patient management. Cardiopulmonary exercise testing is an established tool in the evaluation and management of a wide variety of clinical situations. Despite its provision of dynamic cardiopulmonary functional data, the place of this technique in preoperative risk assessment for specific intra-abdominal procedures remains unestablished (Smith et al., 2009).

To date there have been no studies of CPET in liver resection either in an exclusive cohort or as an independently reported subgroup of a broader cohort of surgical indications. Thus the aim of the present study was to evaluate the role of CPET in perioperative risk assessment in a prospective clinical cohort of patients undergoing hepatic resection.

2.3   Methods

2.3.1   Study design

This was a single-centre prospective cohort study assessing the prognostic value of preoperative

CPET with respect to outcome in patients referred for hepatic resection. The study was registered as

a prospective audit with the Research and Innovation Division of the Central Manchester University

Hospitals National Health Service (NHS) Foundation Trust (reference number 1476).

2.3.2   Study aims and population

The primary outcome studied was postoperative complications. Secondary outcomes included

postoperative mortality, defined as in-hospital mortality occurring beyond the 30th postoperative day

(all deaths in hospital, time unlimited), intensive therapy unit (ITU) stay, high dependency unit (HDU)

stay, overall hospital stay and longer term survival over a period of up to four years.

The study cohort was a consecutive series of patients undergoing assessment for liver resection at

the regional hepatobiliary surgery service of the Manchester Royal Infirmary during the period 1st

September 2007 through 31st December 2009. During this period the staging and assessment

protocol for liver resection comprised contrast enhanced magnetic resonance scanning of the liver

and 18fluoro-deoxyglucose positron emission tomography (PET) for patients with colorectal hepatic

metastases.

2.3.3   Patient-level data and disease descriptors

2.3.3.1 Baseline data on all patients

Baseline data recorded for all patients included age, sex, mode of surgery (laparoscopic or open),

type of liver resection (major resection classed as resection of ≥3 segments, minor resection <3

segments (Smoot et al., 2011, Erdogan et al., 2009), critical care stay (ITU, HDU), hospital stay, postoperative in-hospital mortality and long-term survival.

2.3.3.2 Low-risk patients

Patients under the age of 65 years with no significant co-morbidity were categorised as 'low-risk' for adverse post-operative outcome. This cut-off was drawn from studies providing evidence that adverse outcomes are largely associated in the older surgical patient population and have been evaluated at varying thresholds of 60 years (Older et al., 1999), 65 years (Hernandez et al., 2004, Ghaferi et al., 2011) and up to 75 years (Pearse et al., 2006). We decided to choose the middle value in order to utilize the available resources in capturing the highest proportion of patients at higher risk.

Apart from baseline characteristics, no other detailed data on co-morbidity or specific intra-operative or post-operative complications was noted. This evaluation was restricted to the 'high-risk' patient population providing preoperative CPET data.

2.3.3.3 High-risk patients

Patients over the age of 65 years, younger patients with co-morbidity and patients likely to require complex resection (synchronous liver and bowel resection, resection of liver plus extrahepatic biliary tree) additionally underwent CPET. Thus, these patients were categorised as high-risk on virtue of age (≥65 years), co-morbidities and operative stress.

An enhanced set of data obtained for patients undergoing CPET included self-reported history of smoking, body mass index, preoperative chemotherapy and prior liver resection. Preoperative co-morbidity was recorded at initial clinical assessment and included data on the following: cardiac – history of hypertension or ischaemic heart disease and New York Heart Association (NYHA)

functional class; diabetes mellitus (insulin dependent or otherwise); history of cerebro-vascular disease; chronic obstructive airways disease or renal impairment (defined according to the National Institute for Health and Clinical Excellence guidance on chronic kidney disease)(September 2008). In this subset, preoperative functional status assessment was carried out using the American Society of Anaesthesiologists (ASA) score and the six-point Revised Cardiac Risk Index (RCRI) including high-risk surgical procedure, history of ischaemic heart disease, history of heart failure, cerebrovascular disease, insulin dependent diabetes and preoperative serum creatinine concentration ≥177 μmol/L.

Cardiopulmonary and all postoperative complications were measured using the postoperative morbidity survey (POMS) (Bennett-Guerrero et al., 1999) which classifies morbidity as cardiovascular, pulmonary, renal, gastrointestinal, neurological, infectious, haematological, wound complications and pain. Complications were recorded for the whole postoperative in-hospital period. Liver failure (Balzan et al., 2005), biliary leak and radiological or surgical intervention (return to theatre) were recorded. Data were recorded prospectively and analysed at completion of the study. All-cause mortality was determined using the Demographics Batch Service (DBS) to access the national electronic database of the UK National Health Service (NHS), with follow-up data up to 4 years. Data was collected in a predesigned Case Report Form (CRF), given in the appendices (Appendix 1).

2.3.4   *Cardiopulmonary exercise testing protocol*

Patients undergoing surgery and meeting the inclusion criteria underwent cardiopulmonary exercise testing within a dedicated clinic. An defined study protocol was followed as described (Consensus Protocol for Preoperative CPX testing for York) was followed and interpreted by two observers (a clinical scientist and a consultant anaesthetist).

2.3.5 CPET variables

CPET variables collected included AT, $\dot{V}_E/\dot{V}_{CO_2}$, peak $\dot{V}_{O_2}$, peak $\dot{V}_{O_2}$-pulse and myocardial ischaemia during exercise testing.

2.3.6 Statistical methods

Per protocol analysis was performed using a statistical software package (SPSS 19.0, IBM® New York, USA) with appropriate statistical tests for each variable type. Data reported in the text include the median and range of values unless stated otherwise. Median values were compared using Mann-Whitney *U* non-parametric methods. As the purpose of the study was hypothesis generation, a value of *p* <0.050 was regarded as significant, without correction for multiple testing.

Simple logistic analyses were carried out for postoperative outcomes of morbidity and mortality. Variables with a *p* >0.100 in univariate analysis were excluded from a multiple regression model for postoperative outcomes. Models with multiple explanatory variables were assessed for interactions, which were reported if significant. Receiver operating characteristic (ROC) curves were plotted for continuous variables fitting regression models to estimate threshold values which discriminated between patient groups with differing clinical outcomes.

Preliminary survival analysis was carried out using the Kaplan Meier method to identify discrete groups with varying prognosis. Differences in survival curves were assessed using the log rank method as this gives equal weight to events at all points in time. Putative models were further evaluated using Cox simple and multiple regression. Cox models were tested for constant proportionality over time using the time covariate facility within SPSS, which were reported if significant.

2.4   Results

Of 204 patients assessed for perioperative risk, CPET was indicated preoperatively based on the predefined inclusion criteria in 131 patients. These patients were termed high-risk and the number that underwent resection in this category was 117 [Figure 2.1]. Protocol compliance was 82% with 108 patients undertaking preoperative CPET and 23 patients deviating from protocol by proceeding to surgery without CPET. Protocol non-compliance was because of a clinical decision to proceed to surgery without delay. These twenty-three 'high risk' resection patients were not included in subsequent analyses as no CPET-derived data were available.
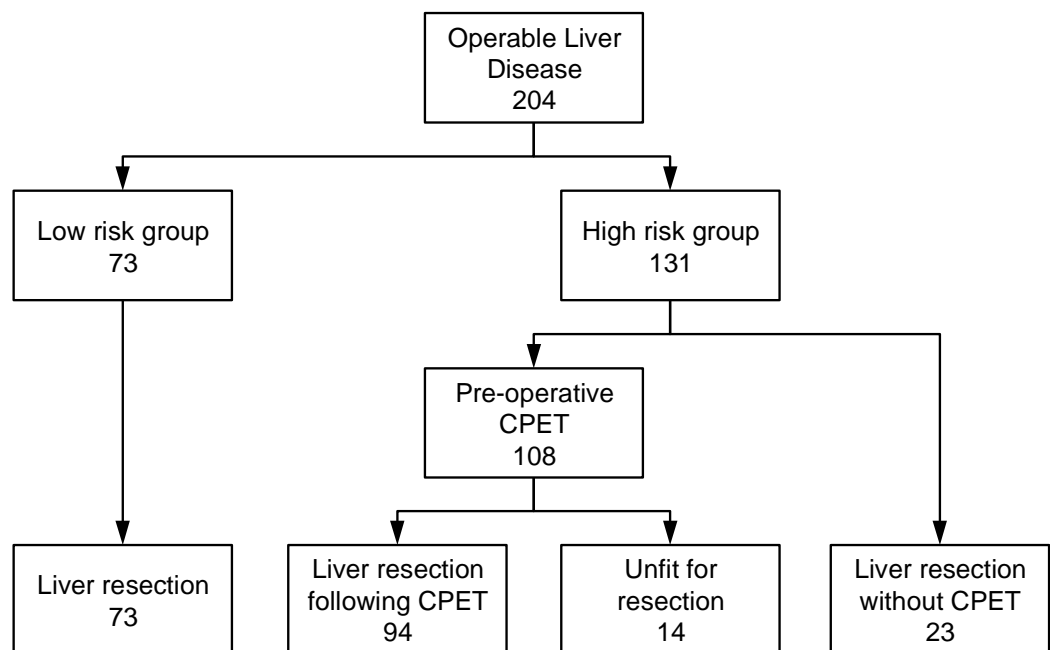
Figure 2.1: Flow diagram of patient inclusion. Patients older than 65 years or younger with co-morbidity formed the high risk group. Patients under 65 years of age without co-morbidity were classified as low risk; 23 patients deviating from protocol in the high risk group and undergoing liver resection without CPET were excluded from the analysis.

2.4.1 Outcomes in the study population

Following preoperative assessment, 190 patients underwent hepatic resection [Table 2.1].

Variables	All hepatic resections	High risk resections*	vs.	Low risk resections	p-value†
N	190	117		73	-
Age (years)	65 (23 – 85)	71 (24 – 85)		53 (23 – 65)	<0.001
Sex (M/F)	107/83	75/42		32/41	0.006 ‡
ITU stay (days)	0 (0-16)	0 (0-16)		0 (0-8)	0.019 #
HDU stay (days)	2 (0-20)	3 (0-15)		2 (0-20)	0.021
Hospital stay (days)	11 (2 – 57)	12 (2 – 57)		9 (2 – 38)	0.001
<30 day mortality	4 (2.1%)	4 (3.4%)		0 (0 %)	0.157 ‡
In-hospital mortality	8 (4.2%)	7 (5.9%)		1 (1.4 %)	0.139 ‡

Data presented as median (range) or count (%) unless otherwise indicated. The Mann-Whitney U test† was used for continuous- and Chi Square test‡ for categorical variables. *ITU,* Intensive care Unit; *HDU,* High dependency Unit. * Includes 94 patients with preoperative CPET and 23 patients qualifying for CPET but not undertaken. 14 patients assessed as unfit for surgery following are not included in this analyses.

Table 2.1: Outcome of liver resection by patient group. Comparing high and low-risk patient groups.

2.4.2 Low –risk resection patients

Cardiopulmonary exercise testing was not indicated according to protocol in 73 of the 204 patients and these individuals were designated the 'low-risk' group. The median age in the low risk group with no CPET was 53 (23 - 65) years. In overview, the high-risk patient population were older (by design) and characterised by longer critical care and hospital stay [Table 2.1].

2.4.3 High-risk resections without CPET

Twenty three high-risk patients underwent resent without pre-operative CPET. Compared to the high-risk patients with preoperative CPET, these patients were similar in age (p =0.491), critical care stay (ITU, p=0.742; HDU, p =0.086) and overall hospital stay (p =0.612). In non-CPET high risk

patients there was one death (1/23: 4.3%) within the 30 day postoperative period and two in-hospital deaths (2/23: 8.4%).

2.4.4   High-risk patients unfit for surgery

Fourteen of 108 CPET patients (13%) were categorised as unfit for surgery, based on functional and clinical status, and were not included in analyses of surgical complications and outcomes but contributed to longer-term survival analyses.

The decision not to offer surgery in these patients was based mainly on clinical (co-morbidity related) findings and the results of oncological staging tests although the CPET results were available to inform clinicians making these decisions. The median age of this 'unfit for surgery' group of patients was 76 (66 - 92 years). Also demonstrating significantly poorer CPET values compared to the resection cohort, the median AT was 8.9 vs.11.2 ml O_2/kg/min (p<0.001) and $\dot{V}_E/\dot{V}_{CO_2}$ was 38 vs. 32 (p<0.001) with a significantly higher age (median age of 76 vs. 71 years, p=0.002).

2.4.5   High –risk resections with CPET

Of 108 patients undergoing preoperative CPET, 94 (87%) proceeded to surgery and comprised the evaluated high-risk resection group. Of these, 44 (47%) patients underwent minor hepatic resection and 50 (53.2 %) had major resection. The median duration of surgery was 260 minutes (range 124 to 648) and median intraoperative blood transfusion was 0 units (range 0 to 10). The median age of these 94 high-risk resection patients was 71 (24 - 85) years.

Open hepatic resection was carried out in 86 (91.5%) patients with 8 (8.5%) undergoing laparoscopic resection which tended to be a minor resection (<3 segments) [Table 2.2]. No significant differences were noted in CPET derived variables between the two modes of surgery. However, duration of surgery (p=0.009) and postoperative hospital stay (p<0.001) were significantly shorter in the

laparoscopic population of patients. No difference was seen in postoperative morbidity (p=0.941) or

critical care stay (ITU p=0.526, HDU p=0.339).

Surgical and histological variables			
Open resection	86 (91%)	Liver resection only	82 (87.2%)
Laparoscopic	8 (9%)	Liver & bowel resection	11(11.7%)
Type of liver resection		Liver & pancreatic resection	1(1%)
Minor resection (<3 segments)	44 (47%)	*Histological diagnosis*	
Single segmentectomy	17 (18.1%)	Colorectal metastasis	74 (78%)
Metastasectomy	7 (7.4%)	Hepatocellular carcinoma	5 (5.3%)
Left lateral sectionectomy	9 (9.6%)	Haemangioma	3 (3.2%)
Right posterior sectionectomy	5 (5.3%)	Neuroendocrine tumour	2 (2.1%)
Other bisegmentectomies	6 (6.4%)	Polycystic liver disease	2 (2.1%)
Major resection (≥3 segments)	50 (53%)	Gall bladder carcinoma	1 (1.0%)
Right hemihepatectomy	27 (28.7%)	Renal cell carcinoma	1 (1.0%)
Left hemihepatectomy	12 (12.8%)	Cholangiocarcinoma	1 (1.0%)
Right trisectionectomy	6 (6.4%)	Inflammatory (benign)	5 (5.3%)
Left trisectionectomy	5 (5.3%)	Malignancies	84 (89.4%)
		Benign disease	10 (10.6%)

Table 2.2: Type of surgery and histological outcomes from CPET resection patients (94)

2.4.5.1 Patient characteristics in high-risk resections

An enhanced set of baseline data were recorded in patients undergoing CPET [Table 2.4]. Of the 94

patients undergoing preoperative CPET and hepatic resection, test findings were inadequate in 2

leaving 92 subjects providing data (the 2 excluded could not peddle the cycle ergometer and thus

could not attain AT; their results are excluded from outcome data relating to CPET variables).

2.4.5.2 High-risk under 65 years of age

Patients underwent preoperative CPET if they were deemed high-risk for surgery as per-protocol.

Characteristics of 22 patients under 65 years of age categorised as given in Table 2.3. Median ASA

score was 2 and prevalence of diabetes 28%, hypertension 52%, prior chemotherapy and liver

resection at 9%.

Variables	Age <65 years	Age ≥65 years	p-value†
N	22	72	-
Age (years)	58 (24 – 64)	74 (65 – 85)	<0.001
Sex (M/F)	12/10	48/24	0.321‡
BMI	29 (19-41)	26 (18-33)	0.069
AT	11.1 (7.7-14.8)	11.3 (7.4-21.0)	0.918
$\dot{V}E/\dot{V}CO_2$	29 (23-43)	33 (23-45)	0.001
Peak $\dot{V}O_2$	16.5 (10.8-28.1)	15.7 (9.5-25.5)	0.869
ITU stay (days)	0 (0-5)	0 (0-13)	0.363
HDU stay (days)	3 (0-11)	3 (0-15)	0.546
Hospital stay (days)	11 (7 – 25)	13 (3 – 57)	0.243
<30 day mortality	1 (4.5%)	2 (2.7%)	0.555‡
In-hospital mortality	2 (9%)	3 (4.2%)	0.333‡

Data presented as median (range) or count (%). The Mann-Whitney U test† was used for continuous- and Chi Square test‡ for categorical variables. *AT,* anaerobic threshold in ml O_2/kg/min; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent for carbon dioxide; peak $\dot{V}O_2$, peak oxygen uptake; *ITU,* Intensive care Unit; *HDU,* High dependency Unit.

Table 2.3: Outcomes in high-risk patients above and below the age of 65 years

2.4.5.3 CPET variables in high-risk resections

The median AT value was 11.2 ml O_2/kg/min (7.4 – 21.0); $\dot{V}E/\dot{V}CO_2$ at AT was 32.0 (23.0 – 45.0);

peak $\dot{V}O_2$ was 16.1 ml O_2/kg/min (9.5 - 28.1); and, peak $\dot{V}O_2$-pulse was 9 ml O_2/HR (3.0 – 17.0).

Exercise induced myocardial ischaemia was seen in 12% of patients using CPET

Age in years	71 (24 – 85)	Pulmonary complications	38 (40.4%)
Sex (M/F)	60/34	Cardiopulmonary complications	39 (41.5%)
CPET to operation (days)	14 (1 – 350)	Renal complications	5 (5.3%)
BMI kg/m^2	26 (18 – 41)	Neurological complications	14 (14.9%)
ASA	2 (1 – 4)	Infectious complications	20 (21.3%)
RCRI	1 (1 – 4)	Haematological complications	11 (11.7%)
Preoperative chemotherapy	39 (41.5%)	Wound complications	2 (2.1%)
History of smoking	34 (36.2%)	Major bleeding	1 (1.1%)
COPD	7 (7.4 %)	Bile leak/fistula	10 (10.6%)
IHD	25 (26.6%)	Liver failure	4 (4.3%)
HTN	50 (53.2%)	All complications	48 (51.1%)
Diabetes	20 (21.3%)	Return to theatre	5 (5.3%)
CVA	5 (5.3%)	*Length of stay*	
CRF	5 (5.3%)	ITU stay	0 (0 – 13)
Previous liver resection	10 (10.6%)	HDU stay	3 (0 – 15)
Postoperative outcomes		Hospital stay	12 (3 – 57)
Cardiovascular complications	10 (10.6%)		

Data are presented as median (range), or count (%) unless otherwise indicated. *CPET,* cardiopulmonary exercise testing; *BMI*, Body Mass Index; *ASA*, American Society of Anaesthesiologists; *RCRI,* Revised Cardiac Risk Index; *COPD,* chronic obstructive pulmonary disease; *IHD,* ischaemic heart disease; *HTN,* hypertension; *CVA,* cerebro-vascular accident; *CRF,* chronic renal failure; *ITU,* Intensive care Unit; *HDU,* High dependency Unit.

Table 2.4: Detailed characteristics in patients (94) undergoing resection following CPET

2.4.5.4 CPET and postoperative complications

Postoperative complications of any type occurred in 51% of patients after undergoing hepatic resection with preoperative CPET. 41.5% experienced cardiopulmonary complications [see Table 2.4] representing the bulk of postoperative morbidity.

Simple logistic regression analysis found that cardiopulmonary morbidity was associated with age and $\dot{V}_E/\dot{V}_{CO_2}$ at AT, but not BMI, RCRI, AT or ASA [table 2.5].

Variables	B	S.E.	p	OR	95% C.I.
Cardiopulmonary morbidity					
Age	0.085	0.031	0.006	1.089	1.025 to 1.158
BMI	-0.039	0.48	0.413	0.961	0.875 to 1.056
RCRI	0.087	0.295	0.767	1.091	0.612 to 1.945
$\dot{V}E/\dot{V}CO_2$	0.125	0.049	0.011	1.133	1.029 to 1.247
AT	-0.110	0.102	0.285	0.896	0.733 to 1.095
All postoperative morbidity					
Age	0.061	0.027	0.022	1.063	1.009 to 1.120
BMI	-0.062	0.048	0.192	0.940	0.856 to 1.032
RCRI	0.128	0.293	0.662	1.137	0.640 to 2.020
$\dot{V}E/\dot{V}CO_2$	0.147	0.051	0.004	1.159	1.049 to 1.280
AT	-0.046	0.096	0.633	0.955	0.791 to 1.153

Variables presented as a continuous and categorical data ([1]). Significance at $p < 0.05$, *BMI,* Body Mass Index; *RCRI,* Revised Cardiac Risk Index; *AT,* Anaerobic threshold in ml O_2/kg/min; $\dot{V}E/\dot{V}CO_2$, Ventilatory equivalent for carbon dioxide.

Table 2.5: Simple logistic regression analyses of preoperative variables and postoperative complications

ROC analysis of $\dot{V}E/\dot{V}CO_2$ provided an AUC of 0.65 (95% CI: 0.53 to 0.77, p=0.018). A threshold of 34.5 provided moderately high specificity (81%): a reasonable rule-in test, (i.e. cardiopulmonary complications occurred in 66% of patients with $\dot{V}E/\dot{V}CO_2 \geq 34.5$ at AT); a sensitivity of 50%, a specificity of 81%, a PPV of 66% (95% CI: 47% to 80%) and a NPV of 70% (95% CI: 58% to 80%), [Figure 2.2]. The relative risk (RR) of cardiopulmonary morbidity with $\dot{V}E/\dot{V}CO_2 \geq 34.5$ at AT was 2.17 (95% CI: 1.36 to 3.44).

ROC analysis of age for cardiopulmonary complications provided an AUC of 0.68 (95% CI: 0.57 to 0.79, p=0.003) [Figure 2.3]. A cut-off at 75.5 years provided modest specificity at 83.3%, whereas sensitivity was improved at a cut-off of 70.5 years.

Threshold	Sens.	Spec.
Cardiop. ≥34.5	50.0%	81.5%
AUC: 0.65 ≥36.5	39.5%	90.7%
All ≥34.5	46.8%	84.2%
AUC 0.67 ≥36.5	36.2%	93.3%
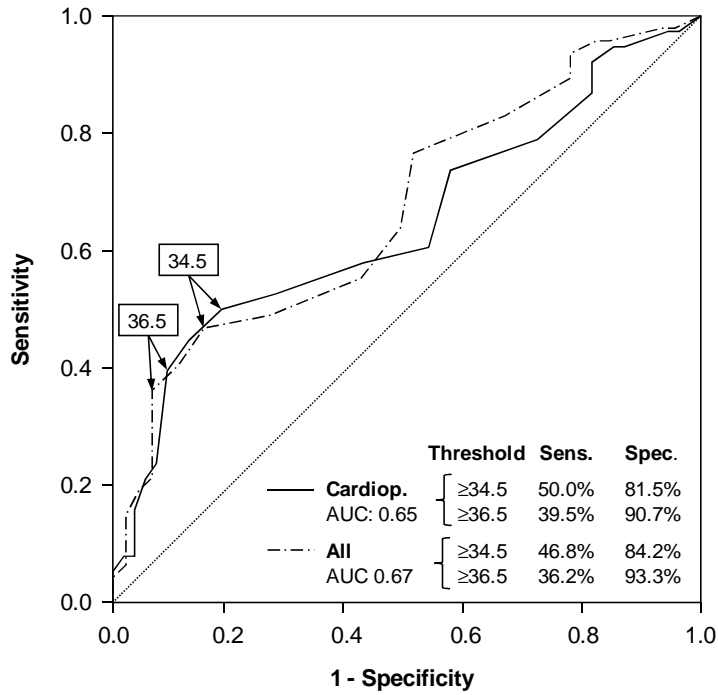
Figure 2.2: Receiver Operating Characteristic curves for $\dot{V}E/\dot{V}CO_2$ at AT as a predictor of postoperative cardiopulmonary and all complications.

Threshold	Sens.	Spec.
Age ≥70.5	74.4%	55.5%
AUC: 0.68 ≥75.5	46.2%	83.3%
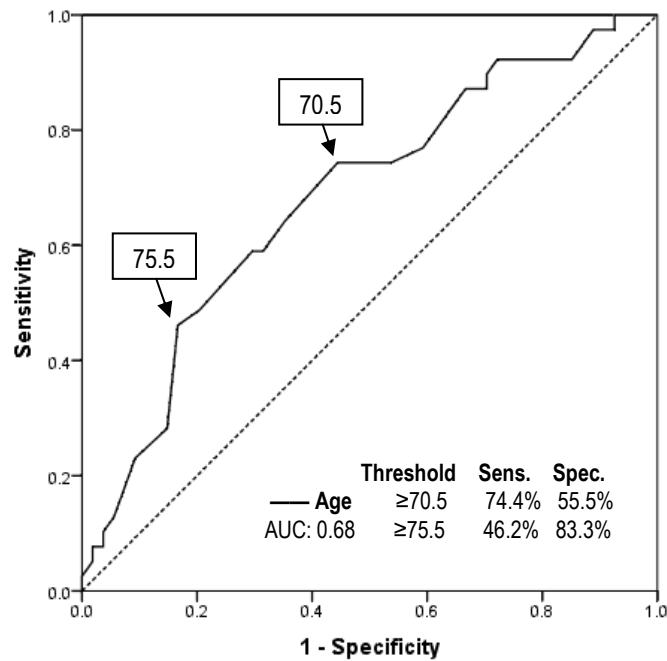
Figure 2.3: Receiver Operating Characteristic curve for age as a predictor of postoperative cardiopulmonary complications.

A multiple variable predictive regression analysis for cardiopulmonary complications and preoperative variables (p<0.1) was carried out. Both age (OR 1.07, 95% CI: 1.01 to 1.14, p=0.027) and $\dot{V}$E/$\dot{V}$CO$_2$≥34.5 at AT (OR 3.45 (95% CI: 1.31 to 9.14, p=0.013) were significant independent predictors with estimates similar to simple models [Table 2.6].

Variables	B	S.E.	p	OR	95% CI
Cardiopulmonary complications					
Age	0.070	0.031	0.027	1.072	1.008 to 1.140
$\dot{V}$E/$\dot{V}$CO$_2$≥34.5	-1.239	0.496	0.013	0.290	0.109 to 0.766
Constant	-4.444	2.325	0.056	0.012	
All complications					
Age	0.046	0.027	0.090	1.047	0.993 to 1.103
$\dot{V}$E/$\dot{V}$CO$_2$≥34.5	-1.379	0.518	0.008	0.252	0.091 to 0.695
Constant	-2.171	1.995	0.277	0.114	

Variables presented as a continuous and categorical data. Significance at $p < 0.05$, $\dot{V}$E / $\dot{V}$CO$_2$: Ventilatory equivalent for CO$_2$.

Table 2.6: Multiple regression analysis of factors for postoperative complications
(Preoperative variables with a predetermined statistical significance of >0.1 excluded)

When predicting the risk of any postoperative complication, age and $\dot{V}$E/$\dot{V}$CO$_2$ were statistically significant [Table 2.5]. ROC analysis showed that a threshold of 34.5 for $\dot{V}$E/$\dot{V}$CO$_2$ provided moderately high specificity (84%) and a reasonable rule-in test, (i.e. complications occurred in 76% of patients with $\dot{V}$E/$\dot{V}$CO$_2$≥34.5 at AT) with a sensitivity of 47%, a specificity of 84%, a PPV of 76% (95% CI: 58% to 88%) and a NPV of 60% (95% CI: 48% to 72%), (Figure 2.2). The RR of any complication with $\dot{V}$E/$\dot{V}$CO$_2$≥34.5 was 1.91 (95%CI: 1.31 to 2.77). ROC analysis for age and any complication provided an AUC of 0.65 (95% CI: 0.54 to 0.76, p=0.012). The optimal cut-off was seen at 69.5 years providing a sensitivity of 75% and specificity of 55.6%.

Multiple regression including predictive variables for any complication found $\dot{V}_E/\dot{V}_{CO_2} \geq 34.5$ at AT to be the only independent predictor (OR 3.97, 95% CI: 1.44 to 10.96, p=0.008), Table 2.6.

2.4.5.5 CPET and postoperative mortality

Postoperative mortality in the high risk (including the 94 CPET and 23 non-CPET resection patients) and low risk groups are given in Table 2.1.

In 94 high-risk CPET resection patients, in-hospital and 30-day postoperative mortality was 5.3% (5) and 3.2% (3) respectively. All deaths occurred from complications related to surgery. No preoperative marker was associated with 30 day postoperative mortality at the prescribed level of statistical significance (p <0.05).

AT was the only preoperative marker associated with postoperative in-hospital mortality (odds ratio OR =0.48, 95%CI: 0.25 to 0.94, p=0.032) on univariate logistic regression (table 2.7). The median (IQR [range]) value of AT amongst postoperative survivors was 11.3 ml O_2/kg/min (10.1-12.7 [7.4-21.0]) compared to 9.5 ml O_2/kg/min (8.1-9.8 [7.7-9.8) amongst patients with postoperative in-hospital deaths (figure 2.4).

Variables	B	S.E.	p	OR	95% C.I.
In-hospital postoperative mortality					
Age	-0.032	0.039	0.414	0.969	0.898 to 1.045
BMI	0.076	0.090	0.399	1.079	0.904 to 1.288
RCRI	0.805	0.529	0.128	2.238	0.794 to 6.305
$\dot{V}_E/\dot{V}_{CO_2}$	-0.044	0.099	0.657	0.957	0.789 to 1.161
AT	-0.732	0.342	0.032	0.481	0.246 to 0.939

Variables presented as a continuous and categorical data[1]. Significance at *p* < 0.05, *BMI,* Body Mass Index; *RCRI,* Revised Cardiac Risk Index; *AT,* Anaerobic threshold in ml O_2/kg/min; $\dot{V}_E/\dot{V}_{CO_2}$, Ventilatory equivalent for carbon dioxide.

Table 2.7: Simple logistic regression analyses of preoperative variables and postoperative mortality
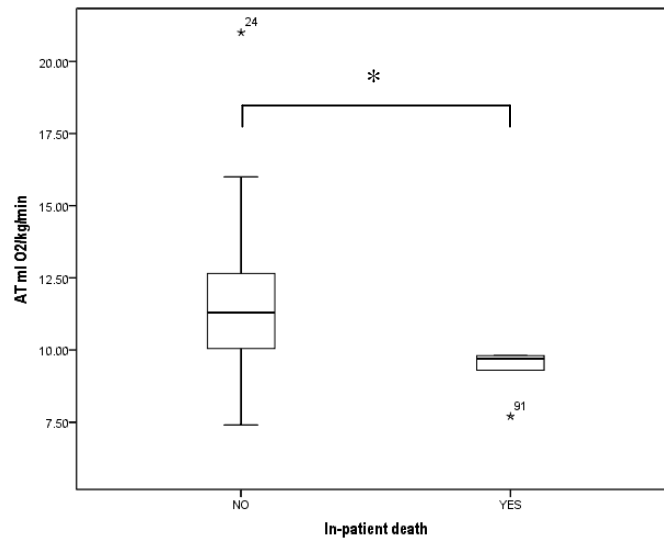
Figure 2.4: Box plot for anaerobic threshold (AT) and in-hospital postoperative mortality
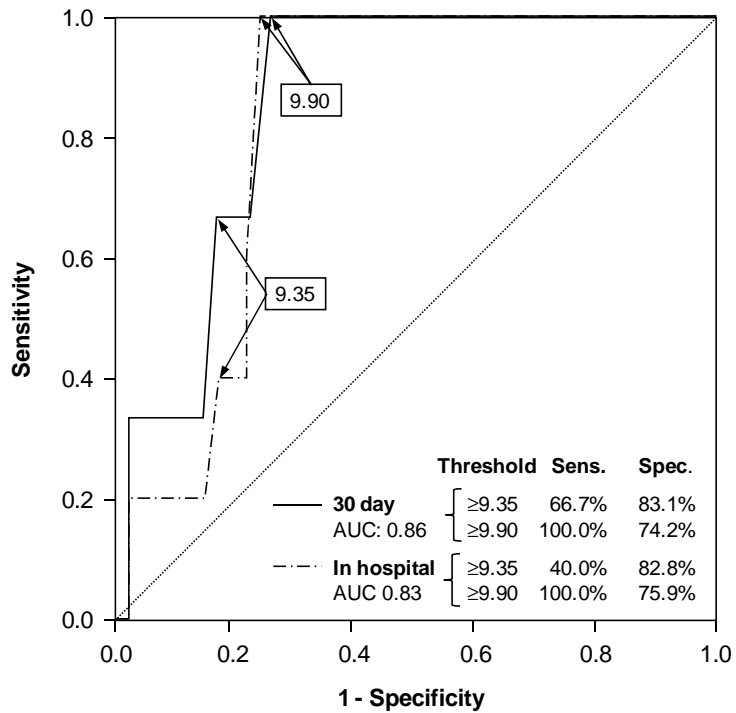
Figure 2.5: Receiver Operating Characteristic curves for anaerobic threshold demonstrating cut-offs for 30 day and all in-hospital postoperatively mortality in patients undergoing resection following CPET.

ROC analysis identified a cut-off at 9.9 ml O_2/kg/min providing 100% sensitivity and 75.9% specificity: positive predictor value (PPV) 19% (95%CI: 8.5% to 37.8%) and negative predictor value (NPV) 100% (95%CI: 94.4% to 100%) as all deaths occurred in patients with AT <9.9 ml O_2/kg/min (figure 2.5).

2.4.5.6 *Length of critical care and hospital stay*

The duration of critical care and length of hospital stay in the two risk groups is given in Table 2.2. Amongst patients undergoing resection following CPET, there was a significant negative correlation between AT and ITU stay (Spearman's rho = -0.261, p=0.012), but not overall length of hospital stay. AT below 9.9 ml O_2/kg/min was associated with increased unplanned ITU stay (1.2 vs. 0.3 days, Mann-Whitney U, p=0.002).

2.4.6 *Survival*

Patients were followed up postoperatively for a mean duration of 1067 days (range 633 to 1508). Kaplan Meier survival analysis demonstrated discrete patterns of survival [Figure 2.6]. Patients who had CPET with an AT ≥9.9ml O_2/kg/min had substantially improved survival compared with patients with a lower value (log rank, p=0.038), but worse survival than low-risk patients who did not undergo CPET (log rank, p=0.038).

Using Cox regression for the study cohort, we compared survival characteristics amongst low-risk (non-CPET) and high-risk (CPET) patients. Comparing high-risk patients below threshold with those above (AT 9.9) showed a hazard ratio (HR) of 1.81 (95%CI: 1.04 to 3.17, p=0.036). Comparison of this subset of high-risk population showing improved survival (AT ≥9.9) with low-risk non-CPET patients provided a hazard ratio of 1.86 (95%CI: 1.02 to 3.42, p=0.045).

No. at risk					
Low risk	73	66	51	29	2
AT≥9.9	67	59	40	18	1
AT<9.9	39	28	19	10	1

Key	Group	Log rank test
———	(1) Lower risk	(1) vs. (2), p=0.038
— · — ·	(2) Higher risk: CPET, AT≥9.9	(2) vs. (3), p=0.038
— ·· —	(3) Higher risk: CPET, AT<9.9	(3) vs. (1), p<0.001
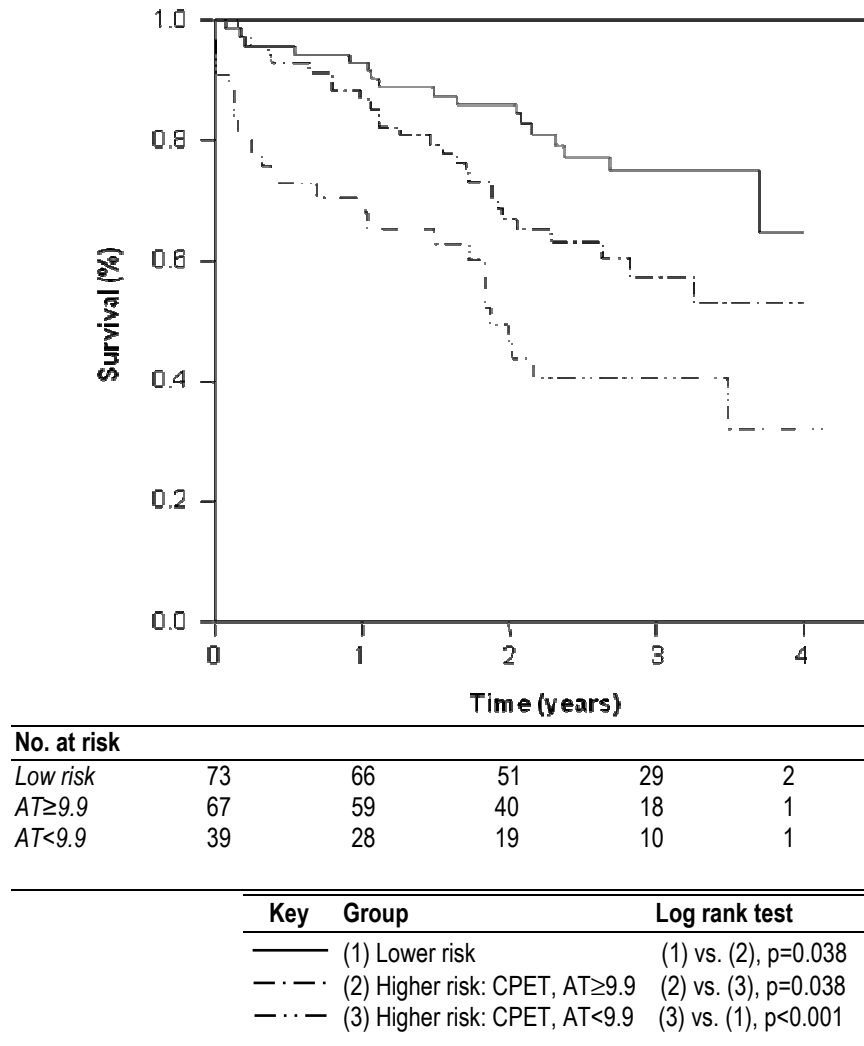
Figure 2.6: Kaplan Meier survival characteristics of high risk CPET patients (106) and low risk patients (73) undergoing liver resection. 2 patients were excluded from the cohort of 108 CPET patients for survival analyses as variables were not determined due to inadequate tests. 14 unfit patients not undergoing liver resection after CPET were included in the high risk CPET group.

Adjusting for age, we carried out Cox regression to evaluate the independent value of the AT threshold (figure 2.7). Enhancing the pool of patients providing CPET data, survival was analysed in all patients undertaking preoperative risk evaluation (108 patients incorporating 94 patients undergoing surgery and 14 unfit patients). AT provided a significant predictive benefit of survival and higher risk of death in patients with subthreshold AT value (HR 1.92 (95% CI: 1.01 to 3.39, p=0.024).
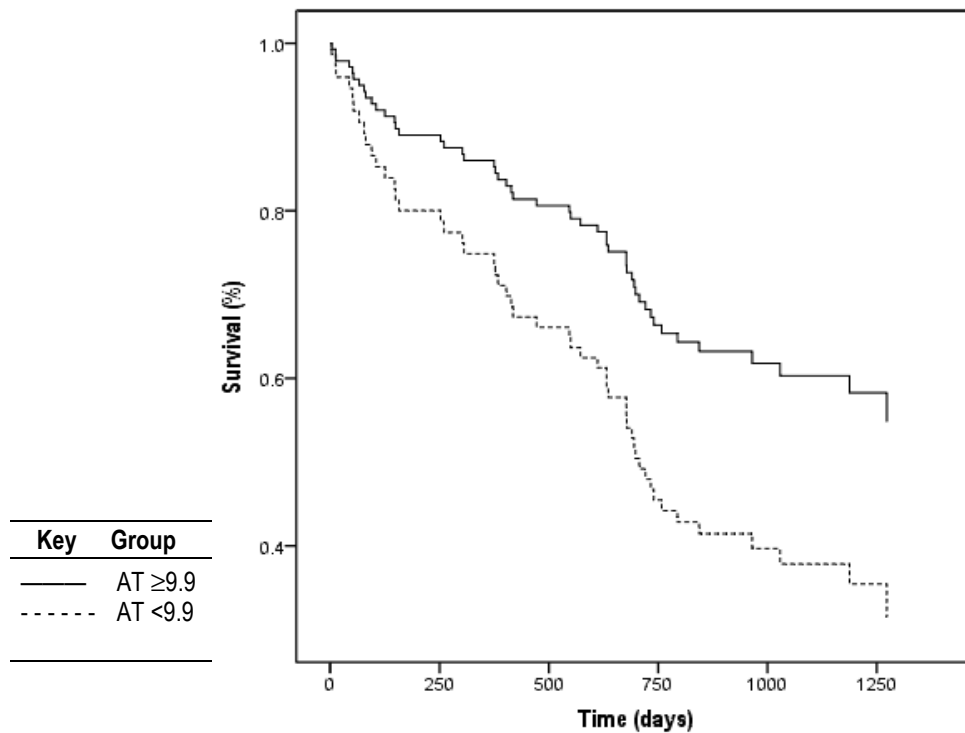
Figure 2.7: Cox regression survival curve for AT at 9.9 ml O$_2$/kg/min adjusted for age. Data from 108 high-risk patients with preoperative CPET.

Assessing survival trends after adjusting for all postoperative in-hospital and 90-day deaths, the AT threshold of 9.9 did not demonstrate significance (log rank, p=0.231) in predicting survival amongst patients undergoing preoperative CPET.

2.5   Discussion

This study reports a prospective evaluation of CPET in a consecutive series of high risk patients, aged over 65 years or with significant pre-existing co-morbidity, undergoing hepatic resection. The findings of the study support the potential usefulness of CPET in hepatic resection. The best prognostic marker of cardiopulmonary or any postoperative complication was $\dot{V}E/\dot{V}CO_2$ ratio at AT with a cut-off at 34.5. This identified patients at approximately double the risk of complication. An anaerobic threshold at 9.9 ml O_2/kg/min provided an optimally sensitive (100%) rule-out test for in-hospital mortality and significantly differentiated longer-term survival.

Major abdominal surgery induces a marked systemic inflammatory response (Shoemaker et al., 1988). This is related to increase in oxygen demand which provides the rationale for cardiopulmonary assessment prior to surgery. This rise in demand for oxygen consumption, which may amount to as much as 44% (Older and Smith, 1988), is met largely by increased cardiac output as it cannot normally be met by increased oxygen extraction alone. This reserve function can be assessed preoperatively by exercise testing simulating surgical demands. The utility of the $\dot{V}E/\dot{V}CO_2$ ratio and AT lies in their being unaffected by patient effort. With an increasingly older population the presence of underlying co-morbidity and exercise limitation precludes reliance on effort based parameters such as maximal $\dot{V}O_2$.

An earlier prospective study (Older et al., 1993) of preoperative CPET in 187 patients undergoing major intra-abdominal surgery demonstrated an association of AT<11 ml O_2/kg/min with postoperative cardiovascular mortality. Postoperative mortality in that study was reported at 0.8% in patients with AT ≥11 and 18% in those with AT <11 ml O_2/kg/min.

AT has been found to be prognostic of postoperative complications in several recent studies (Snowden et al., 2010, Older et al., 1999). Despite this, adoption of CPET based risk assessment

has lagged in practice and guidelines, although prognostic superiority has been shown over the RCRI, incremental shuttle walk test and the Duke Activity Status Index (DASI) questionnaire (Snowden et al., 2010, Struthers et al., 2008).

In this first study of evaluating CPET in long-term outcomes in hepatic resection, we established discrete prognostic value of AT threshold in predicting early postoperative deaths. There was a demonstration of a survival benefit in high-risk patients with AT ≥9.9 over patient with subthreshold values. This benefit persisted regardless of age. However, removing 90-day mortality patients from the analysis did not reveal significance. This may be attributed to the fact that most early deaths are the result of surgery and the effects may level out to limit the long-term risk of major surgery.

There are some limitations when interpreting these findings. First, the design of the study selected patients who were above the age of 65 years incorporating bias from old age. This selection bias by excluded patients of all ages undermines its significance for predicting adverse outcomes. Furthermore, as a result, an optimal representative cut-off for outcomes could not be derived. Although, it is a strong epidemiological predictor, using age alone as a discriminator of adverse outcome may be of limited value. Offering an evaluation within this subset of high-risk groups, the findings support a stronger relationship of CPET-derived variable with postoperative outcome than age. With an increasing number of older patients presenting with treatable disease, CPET offers a quantifiable risk-evaluation beyond a predicted outcome for age.

Second, as in any hypothesis-generating study, the AT cut-off was derived from the high-risk group and the discriminate power is potentially limited by the small number of in-hospital deaths after surgery. Therefore, the results should be considered in this context and further evaluation in a wider cohort is needed to validate the findings. Third, the CPET findings were not purely observational: in the small group found unfit for surgery, CPET results were available to clinicians to support their decisions. Fourth, 23 patients did not undergo CPET despite meeting criteria for the test (protocol

violations). Reasons for failure to undergo CPET were varied but mainly related to individual clinicians' and patients' decisions to proceed directly to surgery. Finally, although representative, the cohort was heterogeneous in terms of the type of resection and tumour histopathology: a much larger study would be required to explore these covariates.

While CPET provides useful prognostic information for patients and clinicians, its clinical bearing upon surgical decision-making is less clear. Older patients performing well under CPET may gain reassurance of a relatively good survival prognosis. High risk patients performing poorly with CPET face an uncertain response to surgery, but will be better informed about perioperative risk. Thus, the clinical utility of CPET in liver resection may lie in providing additional prognostic information to help inform patient and doctor decision-making rather than in providing simple contraindications for surgery.

CHAPTER 3

ROLE OF CARDIOPULMONARY EXERCISE TESTING IN PREDICTING OUTCOME IN PATIENTS UNDERGOING PANCREATICODUODENECTOMY

3.1   Abstract

Background: Pancreaticoduodenectomy is the standard of care for tumours confined to the head of pancreas and can be undertaken with low operative mortality. However, the procedure has a high morbidity, particularly in older patient populations with pre-existing co-morbidities. This study evaluates the potential role of cardiopulmonary exercise testing as a means of predicting post-operative morbidity and outcome in high-risk patients undergoing pancreaticoduodenectomy.

Methods: In a prospective cohort of consecutive patients undergoing pancreaticoduodenectomy, those aged over 65 years (or younger with co-morbidity) were categorized as high-risk and underwent preoperative assessment by CPET according to a pre-defined protocol. Data were collected on functional status, postoperative complications and survival. Predictive potential of CPET derived markers was compared to other predictors including the Revised Cardiac Risk Index (RCRI) and the Glasgow Prognostic Score (GPS).

Results: 143 patients underwent preoperative assessment of whom 50 were deemed low-risk for surgery per protocol. Of 93 high-risk patients 64 proceeded to surgery after preoperative CPET. CPET-derived ventilatory equivalent of carbon dioxide ($\dot{V}_E/\dot{V}_{CO_2}$) at anaerobic threshold (AT) was a predictive marker of postoperative mortality with an AUC of 0.85 (95% CI 0.63 to 1.07, p=0.020); a threshold of 41 was 75% sensitive and 94.6% specific (PPV 50%, NPV 98.1%). Above this threshold, raised $\dot{V}_E/\dot{V}_{CO_2}$ was a predictor of poor long-term survival (HR 1.90, 95%CI: 1.02 to 3.57, p=0.045). CPET-derived AT, the RCRI and the GPS did not predict postoperative outcome.

Conclusions: CPET is a useful adjunctive test for predicting postoperative outcome in patients being assessed for pancreaticoduodenectomy. CPET-derived $\dot{V}_E/\dot{V}_{CO_2}$ above a threshold of 41 predicts early postoperative death and poor long-term survival.

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3.2 Background

Surgical resection is the standard of care for patients with tumours confined to the head of the pancreas (Adham et al., 2008, Yeo et al., 2002, Neoptolemos et al., 2001, Singh et al., 1990). An increasing number of reports attest that pancreaticoduodenectomy can be performed with low operative mortality (McPhee et al., 2007). However, perioperative morbidity remains high and the risk-benefit ratio of complex resectional surgery in a disease which has a poor prognosis for the majority remains small. Thus one of the principal thrusts of current pancreatic oncological surgery is towards optimal patient selection.

Detailed oncological staging can be undertaken with a combination of high-resolution cross-sectional imaging combined with endoscopic ultrasonography and laparoscopy with laparoscopic ultrasonography providing further intra-operative detail. Compared to this sophistication in oncological staging, there are less objectively validated systems in place for assessment of risk in terms of cardio-respiratory co-morbidity. This need is particularly pressing when it is considered that pancreatic ductal adenocarcinoma is predominantly a disease of later life and that patients coming for assessment for resection may be quite high risk for postoperative cardiac or pulmonary complications. Furthermore, postoperative complications affect timing and suitability of adjuvant chemotherapy leading to adverse outcome (Neoptolemos et al., 2010, Chandrabalan et al., 2013).

A feature of pancreatic malignancy is its presentation with obstructive jaundice (Sener et al., 1999). Although the role of preoperative biliary drainage is clear in selected hepatic resections, prior to surgery (cholangiocarcinomas), the use of routine preoperative biliary drainage for operable pancreatic cancers remains controversial (van der Gaag et al., 2010, Sewnath et al., 2002). Despite demonstrable association of hyperbilirubinaemia and adverse cardiac function (Padillo et al., 2001b), clinical benefit of routine preoperative drainage remains unproven and there are no validated discrete thresholds for preoperative treatment. Despite a plethora of experimental and human

literature evaluating the impact of obstructive jaundice (van der Gaag et al., 2009), its role in peripheral oxygen delivery and consumption is limited to cardiac function and intravascular volume, the interaction with tissue oxygen extraction characteristics remains unexplored.

Current methods of evaluating perioperative risk rely on tools comprising subjectively derived assessment of functional capacity, such as the Revised Cardiac Risk Index or the Physiological and Operative Severity Score for Enumeration of Morbidity and Mortality. These measures along with other forms of functional assessments (shuttle walk test, Duke's score) have been shown to be poor surrogates for cardiopulmonary functional assessment (Snowden et al., 2010, Struthers et al., 2008).

Cardiopulmonary exercise testing provides an accurate and a reliable non-invasive assessment of cardiopulmonary function. CPET derived variables have been demonstrated to provide prognostic information relating to outcome following major intra-abdominal surgery (Older et al., 1999, Snowden et al., 2010). Despite validation in a heterogeneous general surgical population, its evaluation in pancreatic resectional surgery has been limited.

Thus the aim of the present study was utilise CPET to evaluate its prognostic potential for postoperative outcomes in patients undergoing pancreaticoduodenectomy. A further study was carried out to assess the physiological changes in oxygen delivery and consumption characteristics in patients with obstructive jaundice prior to pancreaticoduodenectomy (chapter 4).

3.3   Methods

3.3.1   Study design

This was a single-centre prospective cohort study evaluating outcome in patients undergoing pancreaticoduodenectomy with preoperative risk assessment in protocol-defined high-risk patients using cardiopulmonary exercise testing. The study was registered as a prospective audit with the Research and Innovation Division of the Central Manchester University Hospitals National Health Service (NHS) Foundation Trust (reference number 1840).

3.3.2   Study aims and population

The primary outcome studied was postoperative complications. Secondary outcomes included postoperative mortality, defined as in-hospital mortality occurring beyond the 30th postoperative day (all deaths in hospital, time unlimited), intensive therapy unit stay, high dependency unit stay, overall hospital stay and longer term survival over a period of up to four years. Long-term survival was also evaluated in patients who underwent preoperative assessment with CPET, but failed to undergo pancreatic resection either from advanced disease or after being deemed unfit for major surgery.

The study cohort comprised a consecutive series of patients undergoing pancreaticoduodenectomy at a tertiary hepatobiliary surgery referral centre. The study was undertaken over a 39-month period from 1st September 2007 to 31st December 2010. Staging of primary disease was undertaken using high-resolution, contrast-enhanced computed tomography with endoscopic ultrasound (EUS) (and EUS-guided fine needle aspiration) in patients with cystic lesions. Patients presenting with obstructive jaundice routinely underwent endoscopic retrograde cholangiopancreatography (ERCP) with placement of an endobiliary stent or means of percutaneous transhepatic biliary drainage (PTBD).

3.3.3   Patient risk categorisation for CPET

The evidence from large database studies has highlighted age as a good marker of identifying patients at risk of developing adverse postoperative outcome (Older and Smith, 1988, Older et al., 1999, Shoemaker et al., 1988, Hernandez et al., 2004). In addition to this, a wider criterion for inclusion of patients with pre-existing comorbidity was utilised.

Following clinical assessment, individuals with pre-existing co-morbidity (history of cardiovascular disease, emphysema, diabetes, renal impairment, major surgery, significant deterioration in health or at clinicians discretion – see detail in section 3.3.4) or aged over 65 years were further assessed by preoperative CPET in compliance with a pre-defined hepato-pancreato-biliary unit protocol. These patients were classified as 'high-risk'.

Younger individuals (<65 years) with no significant pre-existing co-morbidity, proceeded to surgery without preoperative CPET, classified as the 'low-risk' group.

3.3.4   Patient-level data and disease descriptors

3.3.4.1 Baseline data on all patients

Baseline data were recorded for all patients including age, sex, preoperative haematological and biochemical profile, which included full blood count, liver function tests, renal function tests and C-reactive protein. Operative detail (duration of surgery and intra-operative blood transfusion) was also recorded.

3.3.4.2 Enhanced characteristics in high-risk patients

An enhanced set of data were obtained for patients undergoing CPET including self-reported history of smoking and preoperative co-morbidities. Preoperative co-morbidity was recorded at initial clinical

assessment and included data on the following: cardiac – history of hypertension or ischaemic heart disease; diabetes mellitus (insulin dependent or otherwise); history of cerebrovascular disease; chronic obstructive airways disease or renal impairment (defined according to the National Institute for Health and Clinical Excellence guidance on chronic kidney disease). In this subset, preoperative functional status was assessed using the American Society of Anaesthesiologists (ASA) score and the six-point Revised Cardiac Risk Index (RCRI); including high-risk surgical procedure, history of ischaemic heart disease, history of heart failure, cerebrovascular disease, insulin dependent diabetes and preoperative serum creatinine concentration ≥177 µmol/L. Other predictors of postoperative risk including body mass index (BMI) and Glasgow Prognostic Score (GPS) (Knight et al., 2010) were collected prospectively to permit comparison with CPET data.

Postoperative morbidity was defined using the International Study Group for Pancreatic Surgery (ISGPS) classification for postpancreatectomy complications of postoperative pancreatic fistula (POPF) (Bassi et al., 2005), delayed gastric emptying (DGE) (Wente et al., 2007a) and postpancreatectomy haemorrhage (PPH) (Wente et al., 2007b). Cardiac complications included Acute Myocardial infarction (detection of rise of serum troponin, symptoms of ischaemia, electrocardiogram (ECG) changes indicative of new ischaemia (new ST-T changes or new left bundle branch block) and development of pathological Q waves in the ECG); Congestive Cardiac Failure: clinical and radiological diagnosis with evidence of pulmonary oedema on a plain chest X-ray along with the presence of clinical signs and symptoms consistent with the diagnosis; Serious dysrhythmia (including ventricular fibrillation, ventricular tachycardia); asystole: complete heart block or a supraventricular tachycardia resulting in compromised tissue perfusion and primary cardiac arrest. Pulmonary complications included pneumonia, defined as the presence of a new or progressive pulmonary infiltrate on chest radiography and at least two of the following clinical features: fever (temperature > 38 °C), leukocytosis or leukopaenia, purulent sputum; respiratory

failure requiring ventilatory support (invasive and/or non-invasive); pneumothorax requiring percutaneous intervention and pleural effusion requiring percutaneous intervention. Renal complications included acute kidney injury defined as an increase in baseline creatinine of x 1.5 and requirement for renal replacement therapy. Other recorded complications included confusion, cerebrovascular accidents, wound infections, thromboembolic events (deep vein thrombosis and pulmonary embolism), sepsis and interventions (radiological, endoscopic or surgical) which included return to theatre. Complications were recorded for the whole postoperative in-hospital period. Data was collected in a predesigned Case Report Form (CRF), given in the appendices (Appendix 1).

Data were recorded prospectively and analysed at completion of the study. All cause mortality was determined using the Demographics Batch Service (DBS) to access the national electronic database of the UK NHS.

3.3.5 Cardiopulmonary exercise testing protocol

Preoperative cardiopulmonary exercise testing was carried out once the decision to undertake pancreaticoduodenectomy was made and patients met the inclusion criteria as per protocol. An established study protocol (Association) was followed and the test was carried out and interpreted by two observers (a clinical scientist and a consultant anaesthetist). AT was determined as described earlier (chapter 1).

3.3.6 Statistical methods

Per protocol analysis was performed using SPSS (16.0, full-version Chicago, IL.), with appropriate statistical tests for each variable type. Data reported in the text include the median and range of values unless stated otherwise. Median values were compared using Mann Whitney U non-parametric methods. As the purpose of the study was hypothesis generation, a value of $p < 0.050$ was regarded as significant, without correction for multiple testing.

Simple logistic analyses were carried out for postoperative outcomes of morbidity and mortality. Variables with a p >0.100 in simple regression were excluded from a multiple regression model for postoperative outcomes. Models with multiple explanatory variables were assessed for interactions, which were reported if significant. Receiver operating characteristic curves were plotted to identify threshold values which discriminated between patient groups with differing clinical outcomes.

Preliminary survival analysis was carried out using the Kaplan Meier method to identify discrete groups with varying prognosis. Differences in survival curves were assessed using the log rank method as this gives equal weight to events at all points in time. Putative models were further evaluated using Cox simple and multiple regression. Cox models were tested for constant proportionality over time using the time covariate facility within SPSS, which were reported if significant.

3.4   Results

Over a 36-month period from 1st September 2007 to 31st December 2010, 134 pancreatectomies were carried out [Figure 3.1]. Patients undergoing distal pancreatectomy (16) during the study period were excluded. One hundred eighteen consecutive patients undergoing pancreaticoduodenectomy constituted the study population. Total pancreatectomy was included in the study cohort as the procedure was seen to involve surgical and postoperative demands.   Per protocol, of 118 consecutive resections, 68 patients were designated high-risk for preoperative assessment with CPET. Four of these patients were unable to undergo CPET (reasons included: a history of recent pulmonary embolism, recurrent hip dislocation and a clinical decision to undertake surgery early based on satisfactory routine preoperative assessment alone). The low-risk patient group comprised 50 patients.
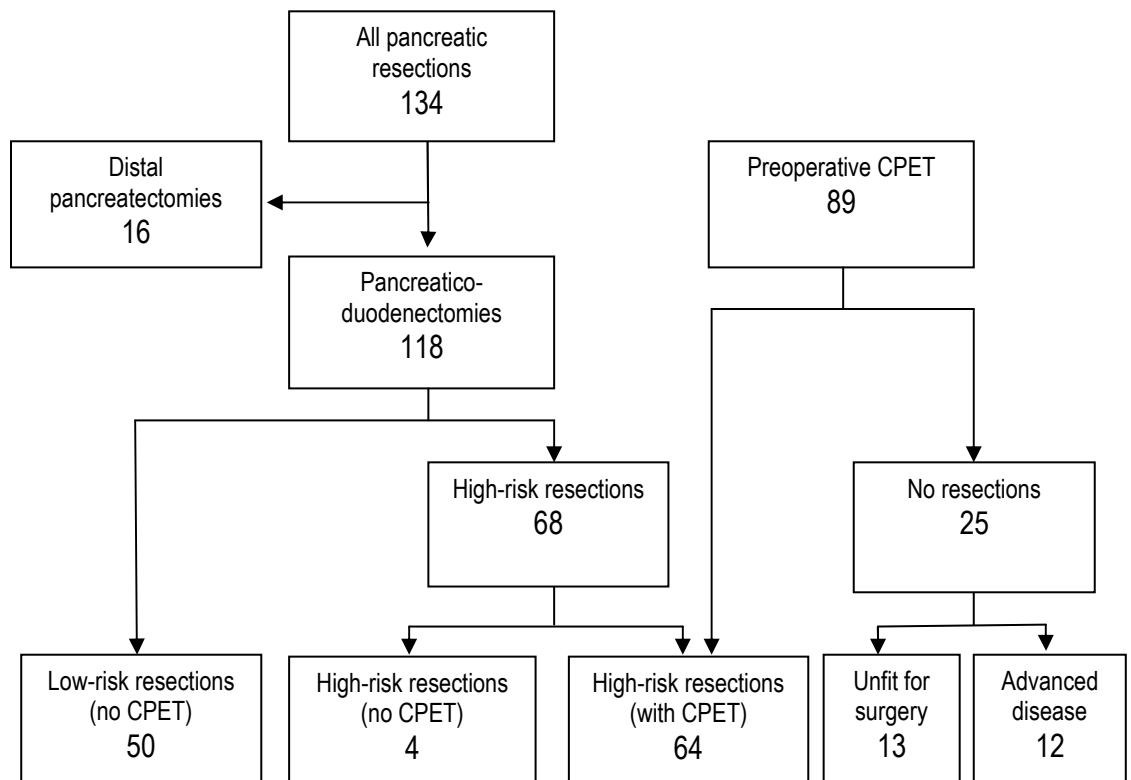
Figure 3.1: Flow diagram of patients undergoing pancreatic resection which included pancreaticoduodenectomies and total pancreatectomies. 89 patients undergoing preoperative CPET are also shown of whom only 64 proceeded to curative resection.

25 patients did not proceed to resection after preoperative CPET evaluation, either because of advanced disease (13) or deemed unfit for surgery (12) on the basis of significantly perioperative mortality [note that the CPET results were available to clinicians making these decisions].

Baseline characteristics and postoperative outcomes in all patients are described in Table 3.1. No significant difference was noted between the low and high-risk groups in the incidence of preoperative obstructive jaundice, preoperative biliary drainage, preoperative Bilirubin levels, Glasgow Prognostic Score (GPS) or postoperative ITU stay. HDU and hospital stay were significantly longer in the high-risk group.

Variables	All patients	High risk group*	vs.	Low risk group	p-value†
n	118	68		50	-
Age in years	61 (36 – 80)	68 (45 – 80)		53 (36 – 65)	<0.001
Sex (male/female)	67/51	41/27		26/24	0.371 ‡
Obstructive jaundice	71 (60%)	44 (65%)		27 (54%)	0.242 ‡
Preoperative biliary drainage	70/71 (99%)	44/44 (100%)		26/27 (96%)	0.167 ‡
Preoperative Bilirubin (µmol/L)	10 (2 – 323)	10.5 (2 – 216)		9.5 (2 – 323)	0.867
GPS	0 (0 – 2)	0 (0 – 2)		0 (0 – 2)	0.902
ITU stay in days	0 (0 – 194)	0 (0 – 194)		0 (0 – 24)	0.097
HDU stay in days	5 (0 – 32)	5 (0 – 32)		4 (1 – 19)	0.003
Hospital stay in days	16 (3 – 194)	18 (3 – 194)		13.5 (9 – 53)	0.005
<30 day post-op mortality	2 (1.7%)	2 (2.9%)		0 (0%)	0.223 ‡
In-hospital mortality	5 (4.2%)	5 (7.4%)		0 (0%)	0.051 ‡

* High risk patient group includes 4 patients meeting CPET criteria but proceeding to surgery without preoperative CPET. Values are presented as medians (range) and numbers (%) unless otherwise indicated. *POBD*, preoperative biliary drainage; *GPS,* Glasgow Prognostic Score; *ITU*, Intensive care Unit; *HDU*, High dependency Unit. Mann-Whitney *U* test †used for continuous and Chi Square test ‡ for categorical variables.

Table 3.1: Outcome from 118 pancreaticoduodenectomies

3.4.1 *Preoperative obstructive jaundice*

In the study population of 118, obstructive jaundice was the presenting feature in 71 patients (60%), of which 27/50 patients (54%) were in the low-risk, and 44/68 (65%) were in the high-risk group. Preoperative biliary drainage was undertaken in 70, with ERCP being the commonest modality (64/70 - 91%) followed by PTBD (5/70 – 7%). One patient underwent biliary drainage via t-tube placed at laparotomy for suspected ductal stone where there was an incidental finding of pancreatic mass before being referred for definitive resectional surgery.

All patients undergoing preoperative biliary drainage for obstructive jaundice had higher levels of Bilirubin at the time of surgery compared to those without obstructive jaundice on presentation (p<0.001).

The median duration of time between preoperative biliary drainage and pancreaticoduodenectomy in 70 patients was 37 days (4 – 118). Amongst patients undergoing preoperative CPET assessment, the median delay from presentation to surgery was 38 days (4 – 118). CPET assessment was carried out at a median of 27 days (1 – 82) after preoperative biliary drainage and the level of Bilirubin had remained significantly higher during assessment of functional capacity with CPET (mean 22.7 µmol/L, 95% CI: 15.8 to 32.7) than the preoperative values on the day of surgery (mean 15.2 µmol/L, 95% CI: 10.9 to 21.2) (p <0.001, paired t-test).

The oxygen carrying capacity as determined by oxygen saturation and haemoglobin values were identical at both time points (p=0.769).

3.4.2   High-risk resections after CPET

3.4.2.1 Preoperative and CPET characteristics

An enhanced set of preoperative data collected in the high-risk CPET group of 64 patients is detailed in Table 3.2.

Number	64*	ASA	3 (1 – 3)
Age (years)	67 (45 – 80)	RCRI	1 (1 – 3)
Gender (males/females)	38/26	GPS	0 (0 – 2)
BMI (kg/m^2)	26 (15 – 44)	CPET to operation in days	13 (1 – 209)
History of smoking	34 (57%)	*Preoperative variables*	
COPD	7 (12%)	Haemoglobin (g/dl)	12.7 (9.6 – 15.5)
Ischaemic heart disease	11 (18%)	White cell count (x10^9 /L)	7.2 (3.1 – 14.6)
Hypertension	30 (50%)	C-reactive protein (mg/dl)	7 (3 – 184)
Diabetes	14 (23%)	Bilirubin (µmol/L)	10.5 (2 – 166)
Cerebrovascular disease	6 (10%)	Albumin (g/L)	41.5 (25 – 49)
Obstructive jaundice	43 (67%)	Alkaline Phosphatase (U/L)	146.5 (48 – 1121)
POBD	43/43 (100%)	Alanine Transaminase (U/L)	31 (11 – 169)

* This excludes data from 4 high risk patients proceeding to surgery without preoperative CPET. Data presented as median (range) or number (%) unless otherwise indicated. *BMI*, Body Mass Index; *COPD,* chronic obstructive pulmonary disease; *POBD*, preoperative biliary drainage; *ASA*, American Society of Anaesthesiologists; *RCRI,* Revised Cardiac Risk Index; *GPS,* Glasgow prognostic Score; *CPET*, cardiopulmonary exercise testing; All variables were recorded on admission prior to surgery.

Table 3.2: Detailed preoperative characteristics of CPET pancreaticoduodenectomy patients

Of the 64 patients undergoing preoperative CPET, the test was inadequate in 4 individuals leaving 60 patients contributing to analyses. The reasons for failure to complete the test included supraventricular tachycardia with exercise in one which settled with cessation of exercise and started on prophylactic treatment, anxiety leading to hyperventilation and two cases of inability to cycle adequately with failure to maintain RPM >50.

The median AT in these 60 patients was 11.0 ml O_2/kg/min (7.5 – 18.7) with a peak $\dot{V}O_2$ of 15.5 ml O_2/kg/min (9.7 – 25.8). The median $\dot{V}E/\dot{V}CO_2$ was 33 (24 – 52) and myocardial ischaemia occurred in 3 patients (5%) during CPET.

3.4.2.2 Postoperative morbidity and CPET

Operative and postoperative outcomes in 64 high-risk patients undergoing resection after CPET are given in Table 3.3

Number	64*	DGE (ISGPS grade, A=4,B=11,C=5)	20 (31.2%)
		PF (ISGPS grade, A=3,B=12,C=1)	16 (25%)
Intraoperative variables		PPH (ISGPS grade, A=0,B=5,C=0)	5 (7.8%)
Pancreaticoduodenectomy	61 (95.3%)	Cardiac complications	15 (23%)
Total pancreatectomy	3 (4.7%)	Pulmonary complications	24 (37.5%)
Duration of surgery	452 (210-780)	Cardiopulmonary complications	32 (50%)
Postoperative outcome		All complications	41 (64%)
ITU stay in days	0 (0-194)	Return to theatre	3 (4.7%)
HDU stay in days	5 (2-23)	< 30 day deaths	2 (3.1%)
Hospital stay in days	18 (3-194)	All in-hospital deaths	4 (6.3%)

Data presented as median (range) or number (%) unless otherwise indicated. *ITU*, Intensive care Unit; *HDU*, High dependency Unit; ISGPS, International Study Group for Pancreatic Surgery; *DGE,* Delayed Gastric Emptying; *PF,* post-pancreatectomy fistula; *PPH,* Post-pancreatectomy haemorrhage.

Table 3.3: Operative and postoperative characteristics in high-risk resections after CPET

Preoperative variables analysed for postoperative morbidity included age, ASA, RCRI, BMI, GPS, AT, $\dot{V}E/\dot{V}CO_2$, peak $\dot{V}O_2$, and myocardial ischaemia. No preoperative variable was a significant predictor (p<0.050) of cardiac complications using simple logistic regression (Table 3.4). Similarly, none of the preoperative variables assessed were significant predictors of pulmonary or 'any' complication.

Variables	B	S.E.	p	OR	95% CI
Cardiac complications					
Age	0.078	0.046	0.088	1.082	0.988 to1.184
AT	0.242	0.147	0.100	1.274	0.955 to 1.700
$\dot{V}E/\dot{V}CO_2$	0.031	0.052	0.555	1.031	0.931 to 1.142
Peak $\dot{V}O_2$	0.049	0.099	0.619	1.051	0.865 to 1.276
Ischaemia	1.992	1.267	0.116	7.333	0.612 to 87.909
ASA	0.652	0.572	0.255	1.919	0.625 to 5.891
RCRI	0.109	0.449	0.808	1.115	0.463 to 2.687
BMI	-0.081	0.064	0.208	0.922	0.813 to 1.046
GPS	-0.458	0.586	0.434	0.633	0.201 to 1.994
Pulmonary complications					
Age	-0.036	0.036	0.322	0.965	0.900 to 1.035
AT	-0.058	0.132	0.658	0.943	0.729 to 1.221
$\dot{V}E/\dot{V}CO_2$	-0.021	0.048	0.657	0.979	0.891 to 1.075
Peak $\dot{V}O_2$	-0.076	0.094	0.418	0.927	0.772 to 1.114
ASA	0.286	0.464	0.537	1.331	0.537 to 3.303
RCRI	0.677	0.406	0.095	1.967	0.889 to 4.355
BMI	0.082	0.048	0.089	1.085	0.988 to 1.193
GPS	-0.174	0.448	0.698	0.841	0.349 to 2.022
Any complication					
Age	0.045	0.036	0.218	1.046	0.974 to 1.123
AT	0.069	0.133	0.604	1.071	0.826 to 1.389
$\dot{V}E/\dot{V}CO_2$	-0.014	0.047	0.759	0.986	0.900 to 1.080
Peak $\dot{V}O_2$	-0.024	0.085	0.780	0.977	0.828 to 1.153
ASA	0.332	0.451	0.461	1.394	0.576 to 3.372
RCRI	0.651	0.445	0.143	1.918	0.802 to 4.584
BMI	0.025	0.047	0.605	1.025	0.934 to 1.125
GPS	-0.004	0.430	0.993	0.996	0.429 to 2.317

AT, anaerobic threshold in O_2 ml/kg/min , $\dot{V}E/\dot{V}CO_2$, Ventilatory equivalence for CO_2; *Peak* $\dot{V}O_2$, peak oxygen consumption; *ASA,* American Society of Anaesthesiologists; *RCRI,* Revised Cardiac Risk Index; *BMI*, Body Mass Index ; *GPS,* Glasgow Prognostic Score.

Table 3.4: Simple logistic regression analyses of preoperative variables and postoperative morbidity

3.4.2.3 Postoperative mortality and CPET

Early (30-day) and late (all in-hospital) postoperative deaths are reported in Table 3.1. Postoperative

mortality was generally low with no significant difference between low and high-risk groups at 30

days (p=0.223). All post-operative deaths resulted from surgical complications. In high-risk patients,

simple logistic regression analyses identified $\dot{V}E/\dot{V}CO_2$ to correlate with 30-day mortality (OR: 1.35,

95%CI: 1.04 to 1.75, p=0.026). Other markers that showed no correlation (p<0.100), included age, AT, $\dot{V}E/\dot{V}CO_2$, Peak $\dot{V}O_2$, $\dot{V}O_2$/HR, ASA, RCRI and GPS (data not shown).

For in-hospital mortality, simple logistic regression fitted $\dot{V}E/\dot{V}CO_2$ (OR 1.27, 95% CI: 1.06 to 1.53, p=0.011) and RCRI (OR 4.37, 95% CI: 1.01 to 18.88, p=0.049) [table 3.5]. In a multiple logistic regression model included these preoperative variables only $\dot{V}E/\dot{V}CO_2$ remained statistically significant with a similar estimate to the simple regression model (OR 1.34, 95% CI: 1.07 to 1.69, p=0.012).

Variables	B	S.E.	p	OR	95% CI
In-hospital mortality					
Age	0.002	0.069	0.982	1.002	0.875 to 1.146
AT	-0.110	0.273	0.687	0.896	0.525 to 1.529
$\dot{V}E/\dot{V}CO_2$	0.241	0.095	0.011	1.273	1.057 to 1.533
Peak $\dot{V}O_2$	0.017	0.154	0.913	1.017	0.753 to 1.374
$\dot{V}O_2$ /HR	-0.035	0.163	0.831	0.966	0.702 to 1.329
ASA	18.969	6960.181	0.998	1.730E8	0.000 to 0.
RCRI	1.473	0.747	0.049	4.364	1.009 to 18.880
GPS	-18.834	7099.735	0.998	0.000	0.000 to 0.

AT, anaerobic threshold in O_2 ml/kg/min , $\dot{V}E/\dot{V}CO_2$, Ventilatory equivalence for carbon dioxide; *Peak $\dot{V}O_2$*, peak oxygen consumption in ml/kg/min; *ASA,* American Society of Anaesthesiologists; *RCRI,* Revised Cardiac Risk Index; *BMI*, Body Mass Index in kg/m^2 ; *GPS,* Glasgow Prognostic Score.

Table 3.5: Simple logistic regression analyses of preoperative variable and in-hospital postoperative mortality

Postoperative mortality was low and distribution of high $\dot{V}E/\dot{V}CO_2$ ratio was seen to relate to in-hospital mortality (figure 3.2). The Receiver Operating Characteristic (ROC) curve of $\dot{V}E/\dot{V}CO_2$ for in-hospital postoperative mortality provided an AUC of 0.85 (95% CI: 0.63 to 1.07, p=0.020) [Figure 3.3]. A cut-off at 41.0 provided test sensitivity of 75% (95% CI: 0.30 to 0.95), specificity of 94.6% (95% CI: 0.85 to 0.98), PPV of 50% (95% CI: 0.19 to 0.81) and NPV of 98.1% (95% CI: 0.90 to 0.99).

Thus a negative result effectively ruled out in-hospital mortality, while one in two patients above threshold died before discharge.
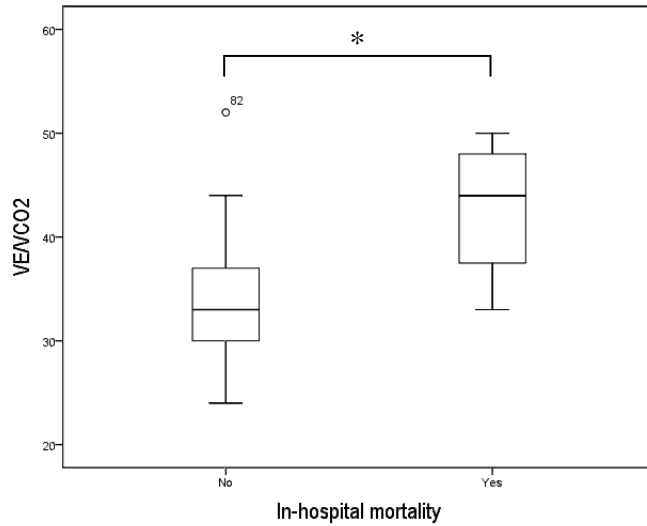
Figure 3.2: Box plot for $\dot{V}_E/\dot{V}_{CO_2}$ and in-hospital postoperative mortality.

	AUC	Threshold	Sens.	Spec.
30 day	0.95	≥41	100%	92%
In hospital	0.84	≥41	75%%	93%
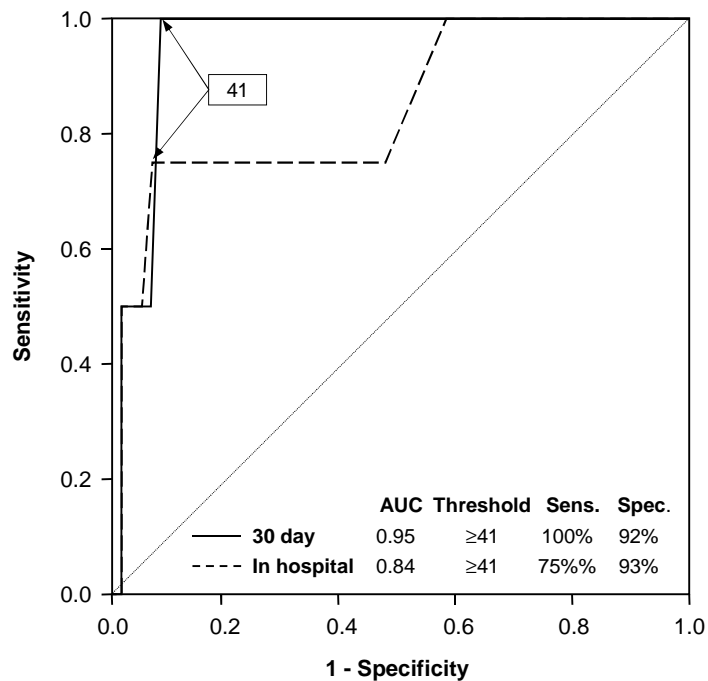
Figure 3.3: Receiver Operating Characteristic curve for $\dot{V}_E/\dot{V}_{CO_2}$ as a predictor of postoperative 30-day and in-hospital mortality.

3.4.2.4 ISGPS defined post-pancreatectomy complications

ISGPS defined complications of postoperative pancreatic fistula (POPF), postpancreatectomy haemorrhage (PPH) and delayed gastric emptying (DGE) are reported in Table 3.3. CPET derived variables (AT, $\dot{V}_E/\dot{V}_{CO_2}$, peak $\dot{V}_{O_2}$) and other preoperative variables (age, ASA, RCRI, GPS, BMI and myocardial ischaemia) did not predict ISGPS defined complications.

3.4.2.5 Length of critical care and hospital stay

CPET derived variables did not predict unplanned ITU stay or HDU stay postoperatively. Overall hospital stay correlated with higher age (p=0.027) and low peak $\dot{V}_{O_2}$ (p=0.038). Other preoperative variables including age, ASA, RCRI and GPS, did not demonstrate any correlation with postoperative critical care stay or overall hospital stay.

3.4.3 High-risk patients who did not have surgery after CPET

Data were available from patients who underwent preoperative CPET assessment but failed to undergo surgery either due to high operative risk (13/89 – 15%) or advanced malignancy (12/89 – 14%) (Figure 3.1). The median age in unfit patients was 72 years (61 – 82), BMI 23 kg/m^2 (20 – 31), AT 8.8 ml O_2/kg/min (5.6 – 13.1), $\dot{V}_E/\dot{V}_{CO_2}$ 39 (31 – 61) and peak $\dot{V}_{O_2}$ 12.8 ml O_2/min (7.8 – 17.6). Twelve patients with advanced disease were referred for palliative chemotherapy. Median age in this group was 66 years (60 – 84), BMI of 24 kg/m^2 (18 – 38), AT of 10.5 ml O_2/kg/min (8.1 – 15.5), $\dot{V}_E/\dot{V}_{CO_2}$ of 36.5 (27 – 45) and peak $\dot{V}_{O_2}$ of 16.6 ml O_2/min (10.9 – 24.9).

3.4.4 Survival

The majority of resections in the high-risk patients were subsequently confirmed malignant on histology (Table 3.6).

Number	64
Pancreatic ductal adenocarcinoma	27 (42.2%)
Ampullary adenocarcinoma	13 (20.3%)
IPMN	5 (7.8%)
Cholangiocarcinoma	3 (4.7%)
Duodenal adenocarcinoma	3 (4.7%)
Neuroendocrine tumour	2 (3.1%)
Metastatic seminoma	1 (1.6%)
Metastatic Renal Cell carcinoma	1 (1.6%)
Autoimmune pancreatitis	2 (3.3%)
Chronic pancreatitis	3 (4.7%)
Benign adenoma	3 (4.7%)
Benign distal bile duct stricture	1 (1.6%)

Data presented as number (%). *IPMN,* Intraductal papillary mucinous neoplasms.

Table 3.6: Histological diagnosis after resection in high-risk CPET patients.

Overall, the median period of follow-up for all 143 patients undergoing assessment for resection was 1057 days (424 to 1657). For the 118 patients undergoing pancreaticoduodenectomy the median follow-up period was 997 days (424 to 1596).

Discrete patterns of survival were demonstrated on Kaplan Meier analyses amongst different patient groups [Figure 3.4]. CPET patients with $\dot{V}$E/$\dot{V}$CO$_2$ less than 41 had a substantially better survival than patients above this threshold (HR 2.95, 95% CI: 1.17 to 7.42, p=0.022). This predictive potential of $\dot{V}$E/$\dot{V}$CO$_2$ threshold was retained when the survival model was adjusted for age using Cox regression analysis (HR 1.95, 95% CI: 1.03 to 3.71, p=0.040).

Postoperative complications (cardiopulmonary or all) and AT were not shown to predict long-term survival following resection. Adjusted for 90-day and in-hospital mortality, $\dot{V}$E/$\dot{V}$CO$_2$ threshold failed to demonstrate predictive characteristics for long-term survival in high-risk patients (log rank, p=0.291).
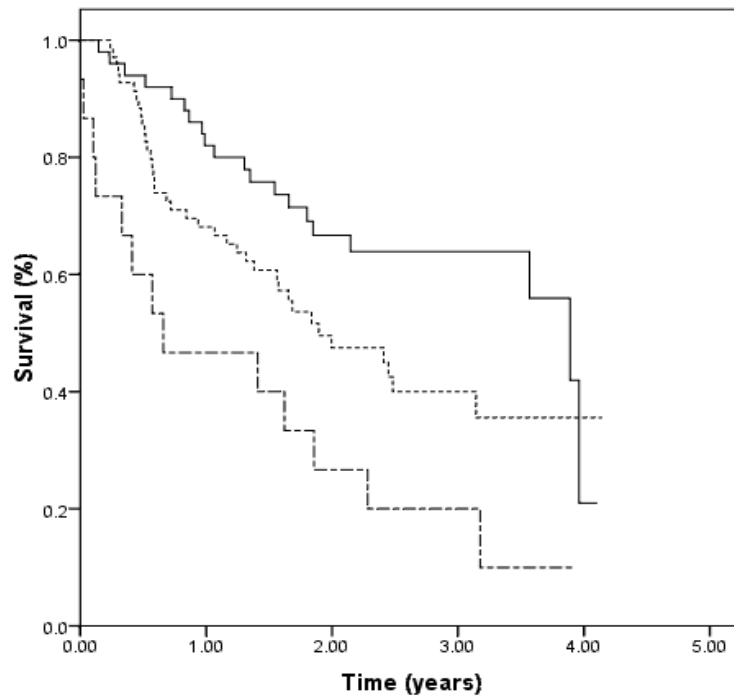
Number at risk

Low risk	50	41	27	16	1
High-risk $\dot{V}E/\dot{V}CO_2$ <41	69	47	23	10	1
High-risk $\dot{V}E/\dot{V}CO_2$ ≥41	15	7	4	2	0

Group	Log rank test
——— 1. Low risk	(1) vs. (2), p=0.033
- - - - - - 2. High-risk $\dot{V}E/\dot{V}CO_2$ <41	(2) vs. (3), p=0.022
— - — - 3. High-risk $\dot{V}E/\dot{V}CO_2$ ≥41	(3) vs. (1), p=0.000

Figure 3.4: Kaplan Meier survival characteristics of all patients groups. 50 low-risk patients underwent resection. 89 high-risk patients underwent preoperative CPET evaluation with 64 proceeding to resection. The remaining 25 patients were deemed inoperable. CPET was inadequate in 4 patients undergoing resection and one patient with advanced disease. 84 patients contributed CPET data for survival analyses.

3.5   Discussion

This study reports an exploratory prospective cohort of high-risk patients undergoing pancreaticoduodenectomy with preoperative CPET. CPET-derived $\dot{V}_E/\dot{V}_{CO_2}$ ratio at AT with a cut-off at 41 was the best predictor of postoperative in-hospital mortality and long-term survival in this high-risk pancreaticoduodenectomy population. Commonly used risk markers, including RCRI, BMI and GPS were not predictive of adverse outcome in this cohort.

A CPET-derived variable provided an adequate predictor of mortality-related outcomes to augment the decision-making process, by predicting early and long-term survival. A $\dot{V}_E/\dot{V}_{CO_2}$ threshold of 41 as a predictor of postoperative and long-term survival is similar to the finding of Carlisle and colleagues (Carlisle and Swart, 2007), reporting $\dot{V}_E/\dot{V}_{CO_2}$ above 42 as the strongest predictor of 30 day and mid-term survival following elective abdominal aortic aneurysm repair. This threshold value has not been consistent across different surgical populations. In a retrospective study of elective colorectal and urology surgical procedures in 843 patients, Wilson and colleagues (Wilson et al., 2010) reported a cut-off of 34 for $\dot{V}_E/\dot{V}_{CO_2}$ to be the optimal predictor of postoperative hospital mortality (RR 4.6, 95% CI: 1.4 to 14.8) with a sensitivity of 88% and a specificity of 47%.

The AT failed to demonstrate significant utility in our study. This stands in contrast to finding by Older et. al (Older et al., 1993). Their prospective study of preoperative CPET in 187 patients undergoing major intra-abdominal surgery demonstrated an association of AT<11 ml O_2/kg/min with postoperative cardiovascular mortality. This discriminatory benefit has been further validated by subsequent studies evaluating its role in major intra-abdominal surgical procedures, albeit with a lower cut-off (Snowden et al., 2010). Such variations in the sensitivity and specificity suggest that the applicable CPET measure and threshold may be specific to patient population and surgical procedure (Forshaw et al., 2008, Hennis et al., 2011).

The failure of AT to demonstrate any utility in our study may be explained by the potential confounding role played by obstructive jaundice during CPET. This is likely to be a relevant factor, as CPET assessment is carried out in the period when patients are jaundiced or in the awaiting biliary drainage before surgery. This can be further affected if complications occur resulting in undermining functional capacity.

Our findings suggest that functional capacity as assessed by $\dot{V}E/\dot{V}CO_2$ is a strong predictor of early and late postoperative outcome and may have a greater role to play than primary pancreatic pathology or respectability of cancer alone. Although it is clear that CPET-derived functional assessment outperforms other methods as a predictor of post-operative and long-term survival, its clinical utility in pancreaticoduodenectomy lies in acting as an adjunct to other forms of assessment and in allowing clinician and patient to make a more informed decision about the relative risks and benefits of surgery.

There are a number of potential limitations when interpreting these findings. As in any hypothesis generating study, the findings should undergo external validation by other investigators in a similar patient cohort. The $\dot{V}E/\dot{V}CO_2$ threshold was determined for a high-risk cohort of pancreaticoduodenectomy patients and was limited by a low event-rate in postoperative mortality: further evaluation in a larger cohort would be required to validate the utility of this marker in postoperative mortality. Another limitation is the lack of blinding of CPET results to clinicians: the availability of results to inform decision making undermines the strength of association between variables and outcome measures. Intra-operative parameters (duration of surgery, blood loss, transfusion requirement) and postoperative surgical complications (pancreatic fistula) are probably more predictive of early postoperative survival than CPET-derived markers, although this study was underpowered to establish this conclusively. Finally, although representative, the cohort was

heterogeneous in terms of the type of tumour histopathology: a much larger study would be required to explore these covariates.

An important bias in accurate preoperative evaluation of cardiopulmonary function is introduced by the presence of malignant obstructive jaundice. Obstructive jaundice is known to adversely affect global cardiac function (Padillo et al., 2001b). As increase in cardiac output remains the predominant mechanism of meeting increased oxygen demands following major abdominal surgery (Older and Smith, 1988), the clinical impact of obstructive jaundice on postoperative outcomes in the context of pancreatic surgery remains unclear (Sewnath et al., 2002, van der Gaag et al., 2010).

CHAPTER 4

EVALUATION OF PERIPHERAL OXYGEN DELIVERY AND EXTRACTION IN

PATIENTS WITH MALIGNANT OBSTRUCTIVE JAUNDICE PRIOR TO

PANCREATICODUODENECTOMY USING CARDIO-PULMONARY EXERCISE

TESTING

4.1   Abstract

Background: Malignant obstructive jaundice is associated with adverse effect on cardiovascular system resulting in poor aerobic capacity. This capacity is largely dependent on cardiac output and oxygen extraction plays a smaller role. The aim of this study was to explore the changes seen in peripheral oxygen extraction from malignant obstructive jaundice.

Methods: Patients with malignant obstructive jaundice underwent cardiopulmonary exercise testing (CPET) for assessment of oxygen consumption and perioperative risk prior to pancreaticoduodenectomy. Peripheral oxygen extraction was calculated by measuring femoral venous blood levels of oxygen during exercise.

Results: Nine patients with malignant obstructive jaundice underwent evaluation of changes in oxygen consumption, oxygen delivery and extraction during different stages of exercise. No significant pre-existing cardiopulmonary pathology was noted in any patient with normal breathing reserve and renal function. No significant complication was noted from obstructive jaundice or biliary drainage during the course of the study. Median (IQR [range]) peak oxygen consumption was low at 67.0 (49.5-76.5 [32.0-84.0]) % of predicted. Resting levels of femoral venous oxygen pressure ($fvpO_2$) and saturation ($SfvO_2$) were comparable to levels reported in fit young individuals. Normal patterns of oxygen extraction were seen with increasing work rate towards lactate threshold (LAT). Near maximal oxygen extraction occurred at peak exercise. Levels of $fvpO_2$ and $SfvO_2$ exceeded baseline values during recovery after the end of exercise.

Conclusions: These findings suggest that peripheral oxygen extraction remains normal at rest and peak exercise with normal microcirculatory responses in patients with malignant obstructive jaundice. The primary limitation in oxygen consumption is the result of reduced oxygen delivery (cardiac output).

4.2   Background

We observed that patients presenting for major hepato-pancreatico-biliary surgery with obstructive jaundice frequently demonstrated poor aerobic capacity on preoperative cardiopulmonary exercise testing. This was noted in absence of a recorded history of heart disease and normal systolic function on resting trans-thoracic echocardiogram. This is in keeping with the association of left ventricular dysfunction with obstructive jaundice (Padillo et al., 2001b). This observation led us to formally investigate the mechanisms leading to poor exercise tolerance with obstructive jaundice.

Clinical studies have demonstrated that raised Bilirubin secondary to malignant obstruction is associated with raised endotoxin and inflammatory cytokine levels as a result of increased intestinal translocation in the absence of bile and an underlying malignancy (Falconer et al., 1994, Kimmings et al., 2000, Padillo et al., 2002). Others have demonstrated a significant cardiovascular dysfunction arising from hypovolaemia and/or reduced left ventricular systolic work function (Padillo et al., 2005).

It is well recognised that a systemic inflammatory response triggered by infection, trauma or major surgery induces cardiovascular changes in resuscitated patients, characterised by increased cardiac output, increased oxygen delivery and increased oxygen consumption (Shoemaker et al., 1988, Older and Smith, 1988, Older et al., 1993). The increase in oxygen delivery (product of cardiac output and arterial oxygen content) exceeds the increase in oxygen consumption (product of cardiac output and arterial – venous oxygen difference) which results in decreased arterial – venous difference in oxygen content.

Following the seminal work of Older and colleagues (Older et al., 1999), cardiopulmonary exercise testing is gaining importance as a preoperative investigation for patients undergoing major surgery in the United Kingdom (Simpson et al., 2009, Huddart et al., 2013). CPET-derived lactate threshold (LT) is the point at which aerobic respiration is supplemented by anaerobic metabolism. Low overall

oxygen consumption at lactate threshold or a raised equivalence for exhaled carbon dioxide is associated with an increase in relative risk of peri-operative complications and death. O_2 consumption is measured non-invasively by assessment of gas changes during CPET. In order to measure cardiac output, oxygen content or peripheral oxygen extraction additional investigation is required.

Weber and Janicki (Weber and Janicki, 1985) demonstrated maximal peripheral oxygen extraction (>70%) in patients with varying degrees of heart failure during exercise. The authors demonstrated that reduced cardiac output was the primary cause of reduced aerobic capacity rather than impaired oxygen extraction. Stringer (Stringer et al., 1994) showed that beyond lactate threshold, an additional fall in femoral venous O_2 saturation occurred without significant additional fall in femoral venous oxygen pressure due to right shift of the haemoglobin dissociation curve in response to metabolic acidosis. These changes represent normal microcirculatory responses to reduced oxygen delivery.

We hypothesised that poor exercise capacity in association with obstructive jaundice was secondary to a cardiovascular disorder characterised by low O_2 extraction and a normal or raised cardiac output. In order to assess O_2 extraction we elected to invasively measure femoral venous blood gases during CPET.

4.3   Methods

After Institutional (R00809) and regional ethics committee approval (NW5-09/H1010/51), patients presenting with obstructive jaundice to a tertiary hepato-pancreatico-biliary surgical unit were recruited. Written informed consent was obtained from all participants.

4.3.1   Study design and sample size

This study was carried out as an explorative pilot evaluation of the impact of malignant obstructive jaundice on peripheral oxygen extraction during exercise. Due to the invasive nature of the study, a minimal number of ten patients were approached for participation to test our hypothesis that peripheral oxygen extraction was impaired in malignant obstructive jaundice.

4.3.2   Study population

Patients with an abnormally elevated serum Bilirubin (>50 umol/L), radiological evidence suggestive of malignant biliary obstruction without metastasis, potential for pancreaticoduodenectomy and hospital admission for biliary drainage were considered for participation. Endoscopic retrograde cholangiography (ERCP) with deployment of a plastic stent was used where possible. Percutaneous trans-hepatic biliary drainage (PTBD) was used if ERCP was unsuitable or unsuccessful.

Study exclusion criteria included age of <18 years, history of cardiopulmonary disease (congestive heart failure, ischaemic heart disease, myocardial infarction, chronic obstruction airway disease or restrictive lung disease as assessed by pulmonary function test), history of diabetes, chronic renal impairment, sepsis in association with the current episode of obstructive jaundice or biliary drainage, history of thromboembolism or coagulopathy, complication secondary to biliary drainage (e.g. bleeding, perforation, pancreatitis).

4.3.3   Cardiopulmonary exercise testing

A nationally recognised CPET protocol was used as described earlier. Calibration was undertaken before each test for gas flow and gas analysis. A symptom-limited CPET was supervised and interpreted by two observers.

$\dot{V}$ O2 was continuously recorded from rest to peak exercise. Peak $\dot{V}$ O2 was expressed as the highest mean $\dot{V}$ O2 obtained from five rolling breath to breath measures. The LT was detected by gas exchange analysis. During the CPET, rising ventilator equivalence for oxygen ($\dot{V}$ E/$\dot{V}$ O2), a rising end-tidal pressure of O2, a respiratory exchange ratio rising above one suggested that LT had taken place. The $\dot{V}$ O2 at LT was measured post-CPET using the modified V-slope method. The $\dot{V}$ O2 at which femoral venous lactate concentration increased by 1 mmol/L was used as a non-gas exchange measure of LT.

4.3.4   Femoral venous blood sampling

Prior to CPET a 10cm 18 gauge polyethylene catheter (Vygon, UK Ltd.) was inserted into a femoral vein using strict asepsis, local anaesthesia and ultrasound guidance.

Femoral venous blood gas analysis was performed at rest, after three minutes of unloaded cycling, at one minute intervals during the continuous incremental ramp phase, at peak exercise and after one minute of recovery. All samples were collected into a heparinised syringe and analysed (Radiometer ABL 835 Flex, Copenhagen) immediately following CPET with an appropriately maintained blood gas analyser.

4.3.5 Data analysis

Baseline patient characteristics including age, sex, body mass index, duration of jaundice and mode of biliary drainage were recorded. Measurement of haemoglobin, white cell count, C-reactive protein, renal profile and liver function was performed before start of CPET.

Femoral venous lactate concentration was plotted against time. The $\dot{V}_{O_2}$ which corresponded with a 1 mmol/L rise in femoral venous lactate was used as a blood lactate measure of lactate threshold. $\dot{V}_{O_2}$ at Lactate threshold derived by the modified V-slope method was compared with femoral venous blood lactate method for correlation and agreement. The Bland Altman plot was utilised as a test of agreement using Medcalc version 11.6, Medcalc Software, Belgium.

CPET and femoral venous blood derived parameters in the study sample were collected for all stages of the exercise and analysed using non-parametric tests for variance all parameters (Friedman two-way analyses) and between two subsequent stages in exercise (Wilcoxon signed rank test for matched pairs). A p value of <0.05 was considered significant.

4.4 Results

One patient was excluded from the study as a result of developing acute renal failure on the day of CPET. Nine patients (5 male, 4 female) completed the study. All patients completed symptom-limited CPET with no adverse outcome. Median (IQR [range]) values for RER at peak effort was 1.15 (1.09-1.23 [1.03-1.42]) and the predicted peak HR was 84 (74-95 [64-97]) %. Successful operative resection was undertaken in three patients. The remaining six patients were referred for palliative treatment.

The baseline characteristics of the participants are given in table 4.1.

Variables	Median (IQR [range])
Age (years)	71 (59-78 [50-80])
Mass (kg)	70.0 (65.5-73.0 [61.0-83.0])
Height (cm)	165.0 (158.5-176.0 [157.0-183.0])
Haemoglobin (gm/dl)	12.6 (10.6-14.1 [9.4-14.4])
White cell count ($\times 10^9$/L)	8.7 (6.8-10.5 [5.2-12.8])
Platelets ($\times 10^9$/L)	281.0 (269.0-379.5 [255.0-482.0])
Prothrombin time (seconds)	13.2 (12.7-13.9 [12.1-15.3])
Alkaline phosphatase (U/L)	263.0 (222.0-673.0 [166.0-1443.0])
Alanine transaminase (U/L)	113.0 (65.5-225.0 [34.0-396.0])
Albumin (gm/L)	39.0 (34.0-42.5 [31.0-45.0])
Bilirubin (μmol/L)	166 (116-299 [51-600])
C-reactive protein (mg/L)	13.0 (9.5-46.5 [6.0-59.0])
Sodium (mmol/L)	136.0 (135.0-137.5 [135.0-142.0])
Potassium (mmol/L)	4.2 (3.4-4.5 [2.8-4.6])
Urea (mmol/L)	5.2 (4.2-6.1 [3.6-11.6])
Creatinine (mmol/L)	61.5 (50.3-65.5 [48.0-69.0])
Glucose (mmol/L)	6.7 (5.5-8.7 [4.9-10.2])

Table 4.1: Detailed pre-exercise results for all participants

The duration of obstructive jaundice ranged from 2 to 5 weeks. All patients underwent successful

biliary stent placement with the median delay from drainage to CPET at 6.0 (2.0-7.5 [2.0-14.0]) days.

All patients were jaundiced at the time of the test as specified in the protocol. No complications were

noted following biliary drainage prior to CPET. No patient suffered a complication as a result of

femoral venous cannulation with the median duration of femoral cannula placement was 75.0 (50.0-

87.5 [30.0-100.0]) minutes.

4.4.1   *CPET and femoral venous blood results*

The value of lactate threshold derived from CPET generated V-slope method and femoral venous

samples correlated strongly (r=0.85, 95% CI 0.45 to 0.97, p=0.003). The mean (SD) difference in

lactate threshold derived by two methods was 0.19 (0.83) O_2 ml/kg/min (Figure 4.1). This method

allowed harmonising of discrete physiological points during exercise from all study participants.
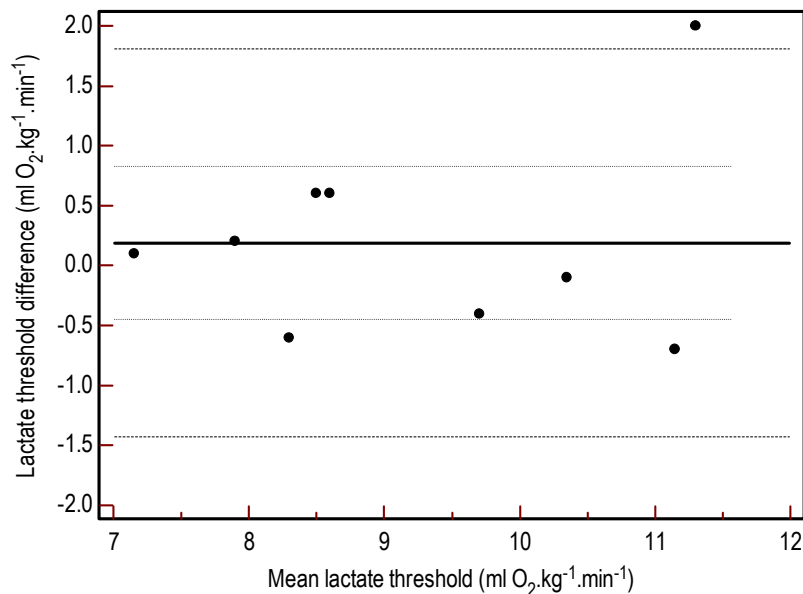
Figure 4.1: Bland-Altman Plot for lactate threshold derivation using femoral venous blood sampling and exercise testing.

Peripheral O_2 saturation assessed with pulse oximetery was 96% or higher in all participants throughout CPET. Participants exercised to a median peak of 74 (59-90 [45-109]) Watts. Median minute-by-minute changes in $\dot{V}O_2$, $\dot{V}O_2$/HR and peripheral O_2 extraction are given in figure 4.2.
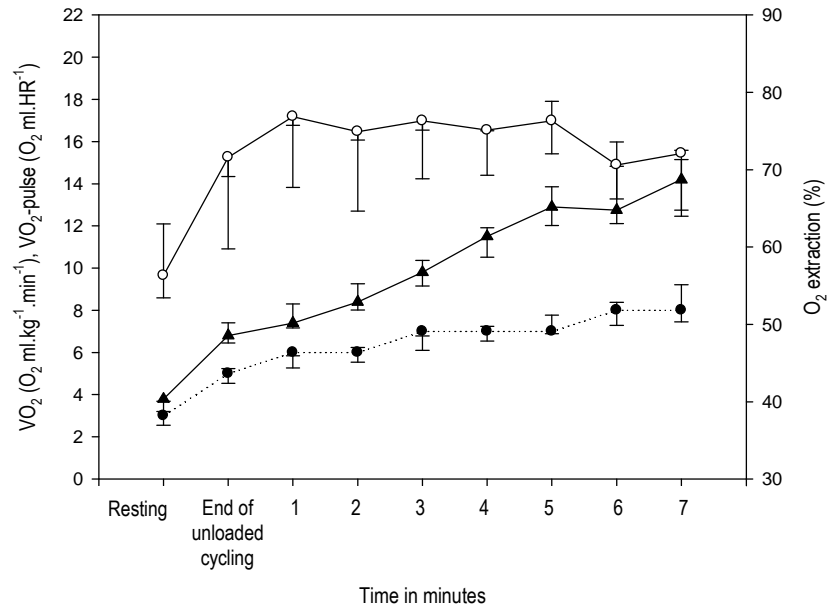
Figure 4.2: Minute-by-minute changes in oxygen consumption ($\dot{V}O_2$, ▲), $\dot{V}O_2$– pulse (●) and oxygen extraction (○) are represented as median values during different stages of exercise. Resting values represent baseline measurements before the start of exercise. Values at the end of 3-minute unloaded cycling are given followed by minute-by-minute measurements with the start of incremental loaded cycling.

Median $\dot{V}O_2$ changes from rest to LT to peak exercise (shown in Figure 4.3) was 3.80 (2.80-3.95 [2.10-4.20]), 8.90 (8.00-10.55 [7.20-12.30]) and 14.20 (12.25-16.60 [10.80-19.40]) O2 ml/kg/min respectively. Changes in overall $\dot{V}O_2$ were significant throughout all stages of the exercise test (Friedman p <0.001).
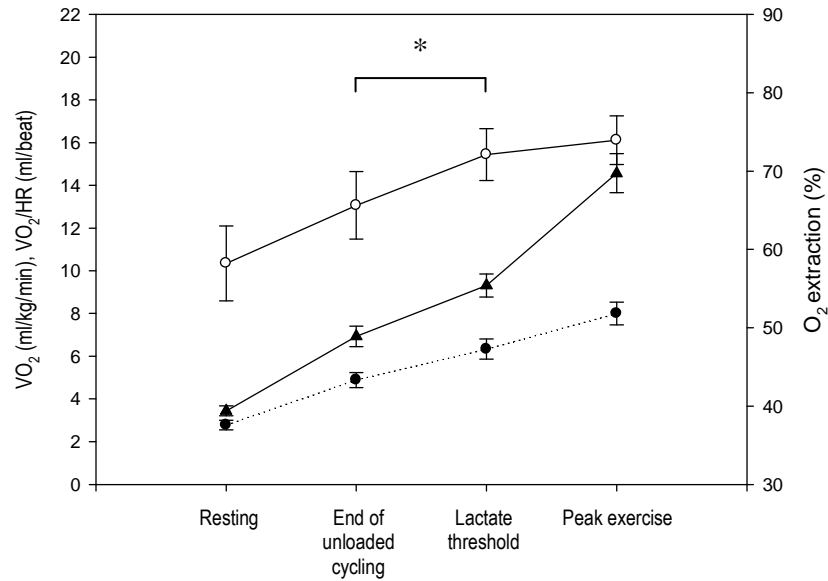
Figure 4.3: Changes in oxygen consumption ($\dot{V}O_2$, ▲), $\dot{V}O_2$– pulse ($\dot{V}O_2/HR$, ●) and oxygen extraction (○), during different stages of exercise. Oxygen extraction is seen to rise significantly from rest and unloaded cycling to lactate threshold (p=0.012), after which extraction remains insignificant (p=0.214). Resting values represent baseline measurements before the start of exercise. Values at the end of 3-minute unloaded cycling are given followed by minute-by-minute measurements with the start of incremental loaded cycling.*

Median peak $\dot{V}O_2$ was 67.0 (49.0-76.5 [32.0-84.0]) % predicted for age and gender. No patient had significantly abnormal spirometry and median breathing reserve at peak exercise was 59.4 (55.0-65.5 [28.3-66.9]) %. All patients reached their peak effort between 8 and 10 minutes of symptom-limited incremental exercise testing.

Median $\dot{V}E/\dot{V}O_2$ at LT was raised at 35.0 (30.0-39.5 [29.0-48.0]), where predicted median value for men was 30.1 (28.8-30.6 [27.9-30.8]) and for women was 29.9 (29.0-31.7 [28.2-31.9]).

Median $\dot{V}O_2/HR$ response was 6.0 (5.0-7.5 [5.0-9.0]) and 8.0 (6.5-9.5 [6.0-10.0]) ml/beat at LT and peak exercise respectively with 77% of predicted response at peak level.

Results for femoral venous blood gas analysis demonstrated progressive changes during exercise (Figure 4.4). Changes at peak effort varied from 8 to 10 minutes of exercise testing in different participants. Discrete physiological points (i.e. lactate threshold cannot displayed in a minute-by-minute representation as it occurred at variable points during exercise in each participant).
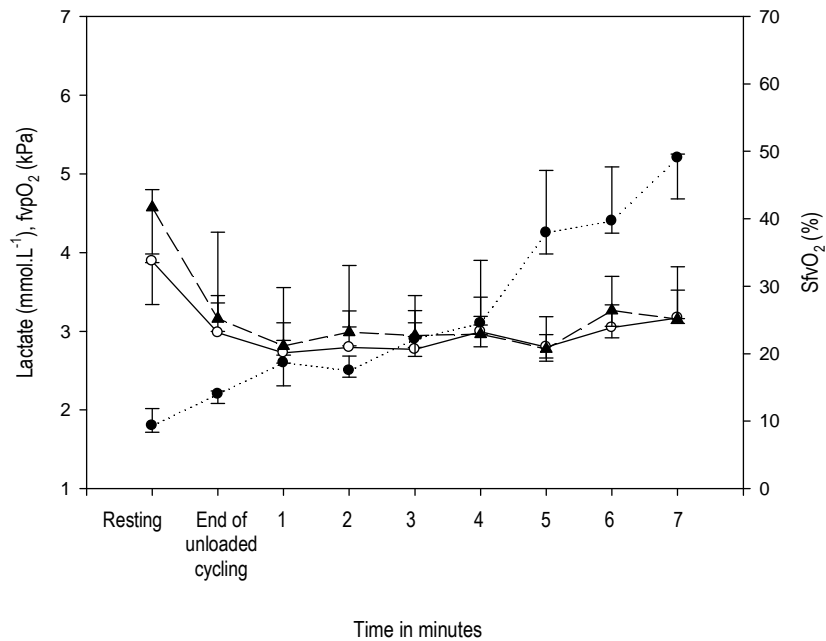
Figure 4.4: Minute-by-minute changes in femoral venous blood variables from start to end of exercise. Values represent median femoral venous O_2 pressure (fvpO$_2$, ○), O_2 saturation (SfvO$_2$, ▲) and lactate levels (●). Resting values represent baseline measurements before the start of exercise. Values at the end of 3-minute unloaded cycling are given followed by minute-by-minute measurements with the start of incremental loaded cycling.

At rest median femoral venous O_2 saturation (SfvO$_2$) was 41.7 (24.9-50.9 [22.5-62.0]) % and fell significantly to 22.0 (20.4-30.6 [13.4-46.7]) % at LT (p=0.012) (Figure 4.5). A non-significant fall was noted from LT to peak exercise (p=0.314). SfvO$_2$ rose significantly above resting values during recovery (p=0.015).

Median femoral venous oxygen pressure (fvpO$_2$) was 3.89 (2.76-4.27 [2.59-4.73]), 2.98 (2.82-3.85 [2.65-3.95]), 2.95 (2.54-3.50 [2.28-3.85]), 3.02 (2.45-3.40 [2.33-3.70]) and 4.75 (3.92-5.15 [3.28-

5.70]) kPa at rest, 3 minutes of unloaded cycling, LT, peak exercise and at recovery respectively. The fall was significant from unloaded cycling to LT (p=0.012) with no further significant change seen to peak exercise (p=0.767). Reactive rise was noted in recovery phase of exercise in both $fvpO_2$ (p=0.015) and $SfvO_2$ (p=0.015).

Median femoral venous oxygen content ($CfvO_2$) declined significantly from unloaded cycling to LT 4.61 (4.04-6.98 [3.28-10.20]) ml/dl and 3.54 (3.03-5.57 [2.68-8.09]) ml/dl respectively, p=0.008). Beyond LT, the fall was non-significant up to peak exercise.

The median femoral venous pH was 7.36 (7.34-7.38 [7.31-7.39]), 7.32 (7.27-7.34 [7.22-7.36]) and 7.24 (7.21-7.26 [7.14-7.31]) at rest, LT and peak exercise respectively. The fall in pH was significant for each stage.
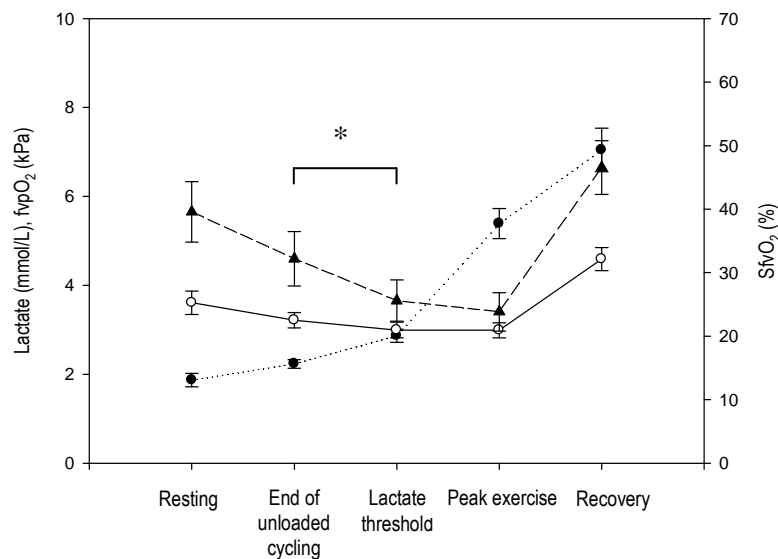
Figure 4.5: Changes in the median femoral venous O_2 pressure ($fvpO_2$, ○), O_2 saturation ($SfvO_2$, ▲) and lactate (●) levels during exercise. The $fvpO_2$ is seen to fall significantly from the end of unloaded cycling to lactate threshold (p=0.012) with no further significant change seen to peak exercise (p=0.767). Reactive rise is noted in recovery phase of exercise in both $fvpO_2$ (p=0.015) and $SfvO_2$ (p=0.015). Resting values represent baseline measurements before the start of exercise. Values at the end of 3-minute unloaded cycling are given followed by minute-by-minute measurements with the start of incremental loaded cycling.*

Median femoral venous lactate levels at rest, LT and peak exercise were 1.8 (1.6-2.0 [1.3-2.9]), 2.8 (2.6-3.0 [2.3-2.9]) and 5.3 (4.7-6.3 [3.5-6.7]) mmol/L respectively. Arterial – venous oxygen extraction was 58% at rest and increased significantly up to lactate threshold (see figure 4.3). Above LT an apparent further increase in extraction was non-significant.

4.5   Discussion

Femoral venous oxygen saturation and content fell appropriately in response to exercise. This shows that reduced oxygen consumption at LT and peak exercise level in malignant obstructive jaundice was not secondary to reduced arterial – venous oxygen extraction but impaired O_2 delivery.

Patients with obstructive jaundice have impaired exercise capacity reflected by a low anaerobic threshold and maximal oxygen consumption which are known strong predictors of adverse outcome following major abdominal surgery (Older et al., 1999, Snowden et al., 2010). Our study patients demonstrated low mean Peak $\dot{V}O_2$ and lactate threshold $\dot{V}O_2$ predicting increased risk of perioperative death.

In our study population, mean peak exercise values of $fvpO_2$ and $SfvO_2$ were not dissimilar to the values reported by Stringer and colleagues (Stringer et al., 1994) in 5 normal subjects undergoing incremental exercise testing. Mean (SD) values for $fvpO_2$ at peak exercise were 2.99 (0.50) and 2.64 (0.44) kPa in our study group and the Stringer group respectively (p=0.206) and the values for $SfvO_2$ were 23.8 (9.1) % and 18.3 (6.1) % (p=0.207). Despite differences in age, sex and training status in the two groups (Stringer group mean (SD) age 25 (6) years, height 179.0 (4.2) cm, weight 72.0 (4.9) kg, mean peak exercise $\dot{V}O_2$ 54.3 (9.4) O_2 ml/kg/min), comparable peak exercise findings of $fvpO_2$ and $SfvO_2$ suggest normal peripheral extraction in our study population.

Weber (Weber and Janicki, 1985) demonstrated that peripheral O_2 extraction exceeded 70% at peak exercise even in patients with varying degree of heart failure. Thus the capacity for extracting oxygen in peripheral tissues at peak exercise remained unimpaired despite heart failure with a wide variation in peak exercise cardiac output. Furthermore, reduced oxygen delivery results in a rightward shift of the oxy-haemoglobin dissociation curve due to build up of lactic acid (Bohr Effect). This drives

peripheral O_2 extraction reducing O_2 content at rest and peak exercise in patients with heart failure (Katz et al., 2000).

Our results endorse these findings and a normal O_2 extraction does not exclude heart failure in our patient population. Lactate threshold $\dot{V}O_2$ was associated with low $SfvO_2$ and $fvPO_2$ suggesting no failure in the peripheral oxygen cascade from capillary to mitochondria. Moreover, above lactate threshold, we demonstrated a fall in $SfvO_2$ with little change in $fvPO_2$. This suggests an appropriate right shift in the oxy-haemoglobin dissociation curve in response to rising local lactate concentration and falling pH. This is consistent with cardiovascular limitation from low cardiac output. Patients had normal renal function, normal haemoglobin and albumin concentration which do not suggest overt hypovolaemia. However we cannot exclude subclinical hypovolaemia which became more evident with exercise.

We demonstrated a raised $\dot{V}E/\dot{V}CO_2$ in the absence of a history of lung disease, exercise induced arterial desaturation or abnormal spirometry. This is consistent with left ventricular failure (Banning et al., 1995). A low $\dot{V}O_2$/HR response was also seen but this does not differentiate hypovolaemia from intrinsic cardiac dysfunction. We did not have the opportunity to retest any patient following normalisation of Bilirubin after successful biliary drainage since patients either rapidly progressed to surgery or had been informed that they had terminal disease. We therefore do not know what happens to exercise tolerance following normalisation of liver function.

This study was limited by several factors. First, the number of participants was limited to a small number by the invasive nature of the study as no prior measures and distribution of $SfvO_2$ and $fvPO_2$ were available to inform sample size calculations. Second, the majority of the patients were referred for palliative care and repeat CPET was not indicated, therefore any improvement in cardiac output after resolution of obstructive jaundice could not be evaluated. Furthermore, it is not possible to

assess the influence of deconditioning on oxygen consumption, LT and peripheral oxygen extraction in a study limited by size.

Despite this, we have demonstrated that patients with obstructive jaundice have a low peak $\dot{V}O_2$ and lactate threshold $\dot{V}O_2$ for age and gender and a predicted increase in relative risk of peri-operative death. We demonstrated that there was no failure in peripheral oxygen extraction. We were not able to confidently distinguish between subclinical hypovolaemia and intrinsic cardiac impairment. However, a raised $\dot{V}E/\dot{V}CO_2$ was suggestive of impaired left ventricular dysfunction.

In view of the predicted increased risk of death in this patient group, further research to evaluate the impact on cardiac function is required to differentiate intrinsic cardiac impairment from hypovolaemia. An assessment of the optimal period of recovery post biliary drainage assumes critical importance in not only informing decision making for surgery but reducing perioperative cardiopulmonary morbidity and mortality for a condition that continues to have dismal long-term outcomes.

CHAPTER 5

GENERAL DISCUSSION AND FUTURE DIRECTION

5.1   Overview

It is evident that the vast majority of elective operative procedures undertaken in the United Kingdom are undertaken in patients who proceed to have an uneventful postoperative course. On the other hand a smaller proportion of patients 'hidden' within the entire population does not fare well and accounts for the greater number of postoperative deaths seen (Pearse et al., 2006). The key in improving outcomes after surgery must focus on accurately identifying this 'high-risk' subgroup, as the 'failure to rescue' from complications means an increased risk of death (Ghaferi et al., 2009). Cardiopulmonary exercise testing plays a critical role in this exercise; as it offers to be the only objective, accurate, quantifiable measure of cardiopulmonary function assessing the entire chain of oxygen delivery from breathing to cellular consumption.

The knowledge that cardiopulmonary function is a major factor in predicting postoperative outcomes is not new (Lunn and Devlin, 1987). Efforts to improve on methods in recognising patients with limited reserve has evolved since the inception of the simple, subjective ASA score in the 1960s to more complex and invasive cardiorespiratory functional assessments. CPET has also evolved from its early role of a diagnostic test for dyspnoea to inform criteria for heart transplantation and therapy for heart failure (Mancini et al., 1991).

Despite demonstrating superiority over current methods of quantifying cardiopulmonary function reserve (Struthers et al., 2008), CPET remains underutilised for major intra-abdominal surgery, a fact reflected by a dearth of good quality studies in this area (Stringer et al., 2012). A recent comprehensive review of articles, guidelines and meta-analysis reveals a very limited evaluation of CPET in preoperative risk assessment (Stringer et al., 2012). A review of literature on its role in hepatopancreaticobiliary surgery paints an even starker picture. To our knowledge, this study represents the first work evaluating short and long-term outcomes in patients undergoing hepatic resection (Junejo et al., 2012). Although there are some studies evaluating the role of CPET in

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pancreatic resection, it remains limited to fewer endpoints with no long-term assessments (Ausania et al., 2012, Chandrabalan et al., 2013).

5.2   *Measuring surgical risk*

The assessment of perioperative risk to a patient is posed by the nature of the surgical procedure (degree of risk based on severity of the procedure from low to intermediate and major procedure) and the patient's condition to cope with the increased metabolic demands of surgery. Ability to respond to this increased demand has been the key characteristic seen in 'survivors' undergoing major surgery (Shoemaker et al., 1988).

The increased demand in oxygen consumption following major surgery has to be met by increase in cardiac output, as peripheral oxygen extraction has limited role in delivering oxygen (Weber and Janicki, 1985, Older and Smith, 1988). Thus the key element in avoiding adverse outcome is recognising the patients who will fail to meet these demands in the postoperative course.

This principal was well illustrated by the seminal work of Older and colleagues (Older and Smith, 1988). The authors demonstrated a 40% increase in oxygen consumption following major surgery. Using CPET, the authors defined a cut-off in the value of anaerobic threshold in representing the physiological response in meeting these demands (Older et al., 1993). This CPET-derived variable was validated in a subsequent evaluation in stratifying postoperative risk and assigning appropriate level of postoperative care to manage and hence reduce complications and subsequent cardiovascular related death. This risk identification plays an important role in recognising patients who develop complications, as inappropriate management, ineffective care or late recognition for suitable level of care is associated with poor outcomes.

A robust, national, multicentre database review from North America (Ghaferi et al., 2009) reported widespread variations in hospital deaths despite similarities in postoperative complications. A risk-

adjusted assessment of outcomes from 186 centres comprising 84,730 high-risk patients found a high prevalence of death with this group compared to the rest of the surgical population (68% vs. 32%). The failure to rescue high-risk patients from death was attributed to the lack of timely recognition of complications and the effective management of the complications. However, effective management alone is not able to reverse these adverse effects as high-risk patients requiring unplanned critical care support following a complication have worse outcomes than patients receiving planned postoperative critical care (Pearse et al., 2006).

In this context, accurate assessment of postoperative risk becomes the central objective and gains a far greater importance than the attempted effective rescue after complications, as patients who 'survive' to leave hospital following complications suffer from reduction in long-term survival (Laurent et al., 2003, Khuri et al., 2005)

CPET has been recognised as the only accurate tool in assessing the ability to meet these demands simulating a postoperative demands using exercise (Balady et al., 2010). The parameters can be effort independent (AT) and provide a quantifiable risk in informing the anaesthetist, surgeon and patient in informing consent, preoperative optimisation and appropriate level of postoperative care. This has translated in 40% increase in the use of CPET for perioperative risk assessment in the UK in a short course of 3 years (Simpson, 2009, Huddart, 2013).

5.3   CPET: 'will the patient sink or swim?'

The role of CPET in major intra-abdominal surgery has been unclear (Stringer et al., 2012). In contrast to cardiac transplantation (Mancini et al., 1991) and lung resection surgery (Benzo et al., 2007), where CPET evaluation can play a central role in offering surgery, CPET cannot be used to deny surgery. A poor performance on CPET cannot be labelled as 'failure' but recognition of high risk of adverse outcomes and can be used to inform patient choice and clinician management.

5.4   *Measuring outcomes in major hepatopancreaticobiliary surgery*

Interest in evaluation of risk assessment tools for major hepatopancreaticobiliary surgery has been historically poor. This could be explained by the complex surgical techniques involved, evolving role of neoadjuvant chemotherapy, novel techniques in optimising future liver remnant (portal vein embolisation) and a widening indication for hepatic resection.

Improvements in perioperative care and chemotherapy have seen improvement in long-term survival following surgery. Better operative techniques and centralisation to high-volume surgeons and hospitals has reduced postoperative mortality significantly in the last two decades (Birkmeyer et al., 1999, Birkmeyer et al., 2003b, Ghaferi et al., 2011). The difficulty however, stems from the continuing high rates of postoperative complications.

A major compounding element to the measure of postoperative complications is the lack of uniformity in defining complications preventing useful comparisons with the wider patient population and threatening generalisability (Martin et al., 2002). This has recently been addressed by the formation of a consensus based study group offering a standardised, clinically relevant defining criteria for major postoperative complications (Wente et al., 2007b, Wente et al., 2007a, Koch et al., 2011, Rahbari et al., 2011a, Rahbari et al., 2011b, Bassi et al., 2005).

5.5   *CPET in hepatic resection*

This study reports the first evaluation of CPET for this patient population. The prognostic role of CPET in the high-risk population is highlighted by the fact that it outperformed subjective (RCRI) and demographic measures (age and comorbidity) currently in use to define categorise risk. This utility may have been under reported as the use of testing was limited to the defined high-risk group. Despite limiting evaluation in this high-risk group of patients, the discriminatory potential of CPET was notable. As it provided a safe, dynamic evaluation of cardiopulmonary function, the test can

supersede measures of risk evaluation that rely on costly, time consuming independent organ evaluation.

5.5.1 Predicting postoperative complications

CPET-derived $\dot{V}_E/\dot{V}CO_2$ at an optimal threshold of 34.5 was the most significant independent predictor of postoperative morbidity. Consistent with the growing consensus of its utility in heart failure (Gitt et al., 2002), it outperformed age, RCRI and CPET derived AT and peak $\dot{V}O_2$. It remains unclear as to why AT was not seen to predict complications as suggested by other investigators (Older et al., 1999, Snowden et al., 2010). One explanation could be the bias from the prior knowledge of the CPET results in informing postoperative care.

A cut-off at 35 for $\dot{V}_E/\dot{V}CO_2$ was also proposed by Older (Older et al., 1999) but this parameter has not received the same attention as AT in risk evaluation. Therefore, studies reporting on outcomes following major intra-abdominal surgery have largely ignored to evaluate $\dot{V}_E/\dot{V}CO_2$.

Patients experiencing cardiopulmonary or all complications had significantly longer critical care and hospital stay. Although, $\dot{V}_E/\dot{V}CO_2$ did not impact postoperative mortality and long-term survival, it offered the strongest prediction of postoperative complication. This threshold can be utilised to inform clinicians in organising appropriate level of postoperative care to prevent and/or manage these complications.

5.5.2 Predicting postoperative mortality

An anaerobic threshold of <9.9 ml O_2/kg/min identified high-risk patients at risk of in-hospital death and adverse long-term survival following hepatic resection. Although no deaths were observed in patients above this threshold, the event rate of postoperative mortality was small, rendering this study underpowered to assess this relationship accurately.

This threshold is higher than previously reported cut-offs (Older et al., 1999, Snowden et al., 2010). This difference may represent an increased demand in the face of a unique response to surgical stress. Additionally, these patients represented a more homogenous cohort in terms of the surgical procedure and its complications which contrasts to general surgical populations for other cut-offs.

5.5.3 Predicting survival

The prognostic effect of AT continued beyond in-hospital mortality. Patients with subthreshold AT had poorer long-term survival. Although, all cause mortality recorded is useful in evaluating outcome, it could not be adjusted for postoperative chemotherapy or recurrent disease. Despite this, its value in prognosticating long-term survival can help patients weigh long-term risks and benefits of surgery and conservative therapies.

Patients should not be denied surgery on the basis of AT alone but it should help perioperative risk planning to minimise complications and inform future therapies.

5.5.4 Proposed risk stratification

Age continues to be a strong predictor of outcome and is related to survival with a progressive decline in cardiac function as assessed by CPET (Myers et al., 2008). Evidence from large risk evaluation studies attest to its continued utility in isolating high-risk populations (Ghaferi et al., 2009, Ghaferi et al., 2011).

Our evaluation was limited in exploring the effect of categorization on age alone as no CPET and disease data was available from the low-risk group to extricate the confounding influence of cardiac function and co-morbidities in prognosticating long-term survival. Despite this limitation, some useful results indicate a higher risk of complications with patients aged above 70 years. Again this likely to

be inaccurate in the context of the entire surgical population as these results were derived from the subset of patients aged above 65 years.

An algorithm proposed by Older (Older et al., 1993, Older et al., 1999) continues to appeal to clinicians as it has stood the test of time in recognising the prognostic value of CPET-derived variables in predicting postoperative outcomes (Snowden et al., 2010).

In our opinion patients undergoing hepatic resection should be evaluated using CPET to stratify risk and level of postoperative care (figure 5.1). All patients above the age of 65 years should have CPET as functional limitation is masked by lifestyle and subjective assessment of function would miss patients with higher risk of adverse postoperative outcome (Snowden et al., 2010, Struthers et al., 2008). Low-risk group can be defined on basis of age (<65 years), no pre-existing cardiopulmonary morbidity and intermediate level of surgery (<3 segment hepatic resection). High-risk patients who are older (>65 years) or younger patients with pre-existing co-morbidities, history of receiving prior chemotherapy or undergoing a major (≥3 segment hepatic resection) or complex resectional surgery (synchronous procedure) should undertake preoperative CPET.
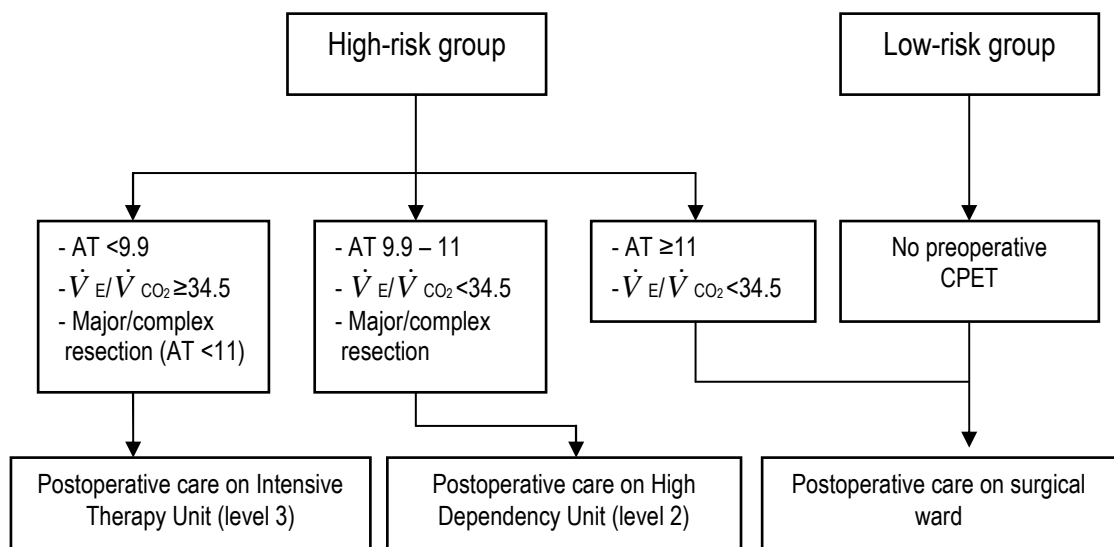
Figure 5.1: Proposed risk stratification algorithm for hepatic resection.

5.6   CPET in pancreatic resection

Pancreaticoduodenectomy remains a complex surgical intervention and associated with high postoperative morbidity and poor long-term outcome in patients with cancer (Sener et al., 1999). The true benefit of a useful preoperative tool lies in recognition of patients who may experience adverse postoperative course requiring prolonged hospital treatment at risk of delayed adjuvant treatment (Chandrabalan et al., 2013) or not gaining the proposed long-term survival benefit from surgery.

5.6.1   Predicting postoperative complications

The high-risk patient group was characterised by increased critical care and hospital stay. Cardiopulmonary complications constituted 50% of the overall morbidity. None of the standard methods of risk assessment i.e. age, ASA, RCRI, BMI and GPS, taken preoperatively prove to correlate with survival. CPET was carried out a few weeks prior to surgery and no variable proved prognostic significance for postoperative complications.

A probable explanation of this failure may be the small size of the study or more likely, the timing of preoperative CPET. As level of Bilirubin is associated with global cardiac dysfunction (Padillo et al., 2001b), patients were referred for risk evaluation around preoperative biliary drainage. Patients demonstrated significantly greater levels of Bilirubin at the time of preoperative CPET compared to levels on the day of surgery. This may have falsely reported lower values for all CPET parameters, as the patients were more likely to recover cardiac dysfunction following successful biliary drainage.

5.6.2   Predicting postoperative mortality

$\dot{V}_E/\dot{V}_{CO_2}$ proved to be the only preoperative variable predictive of postoperative in-hospital mortality when compared to age, ASA, RCRI and GPS. The optimal threshold was noted to be 41.

Although this value was also noted in predicting long-term outcome, low-event rates in postoperative in-hospital deaths mean that the study is underpowered.

5.6.3 Predicting survival

High-risk patients with suprathreshold value were at twice the risk of death in the follow-up period after pancreaticoduodenectomy. Again, standard preoperative tolls relying on subjective functional status (RCRI) or basic biomarkers (GPS) did not demonstrate any predictive value.

Age was not seen to be predictive in the study cohort, but this evaluation was limited as high-risk category consisted predominantly of older patients.

Additionally, this perceived predictive potential disappears when in-hospital postoperative deaths are excluded from the analyses. A reason for this may be the limited period of 'long-term' evaluation.

A further and possibly more relevant reason may be the nature of CPET assessment, which is a representation of functional status at a given point in the preoperative period. This can be markedly affected by changes in Bilirubin levels, preoperative interventions and complications (preoperative biliary drainage and infection) and deconditioning. Additionally changes seen in AT with progressive aging (Older et al., 1993, Older et al., 1999) may be predictive but changes in functional status with cardiopulmonary and other co-morbidities may be more variable due to changes in disease severity and associated complications.

Can patients with a high $\dot{V}E/\dot{V}CO_2$ and a low AT be denied curative pancreatic resection? This is possibly the most important question, as pancreatic cancer is associated with poor long-term survival despite surgery which is likely to add significant morbidity with a potential cost to adjuvant therapies. Unfortunately, in our limited evaluation of overall survival, we have not been able to study the influence of CPET and postoperative complications with delay to further therapy or the ability to

tolerate chemotherapy. However, despite these limitations, patients deemed to have a high-risk of adverse postoperative outcome (complications and death) limited chance of curative resection would be better informed of the risks and benefit of surgery and long-term survival.

5.6.4   Proposed risk stratification

Recent studies evaluating the role of CPET to postoperative complications have reported limited value (Ausania et al., 2012, Chandrabalan et al., 2013). This may have been influenced by the timing of the test in the preoperative period when many patients underwent biliary drainage, hence over predicting risk by yielding lower values. A potential solution to this may be a repetition of CPET to assess the improvement following biliary drainage or adjusting the cut-offs. However, as no there is no existing literature to guide theses adjusted, CPET will need further evaluation in this area.

In the context of limited value of CPET, age and co-morbidities should continue inform risk stratification strategies. All patients should at least receive a level 2 care (HDU) following pancreaticoduodenectomy as it remains associated with high cardiopulmonary and surgical morbidity.

The low-risk group is defined as patients under the age of 65 years and no existing significant cardiopulmonary or other co-morbidities. These patients would be suitable for level 2 care. In addition to age, co-morbidities would play a larger role in defining level of postoperative care as the value of CPET-derived data is limited. Although RCRI, which incorporates organ function, was of limited value, the inclusion of cardiac, pulmonary, renal and metabolic impairment (diabetes) would improve delivering appropriate level of postoperative care. Figure 5.2 shows the proposed risk stratification criteria.
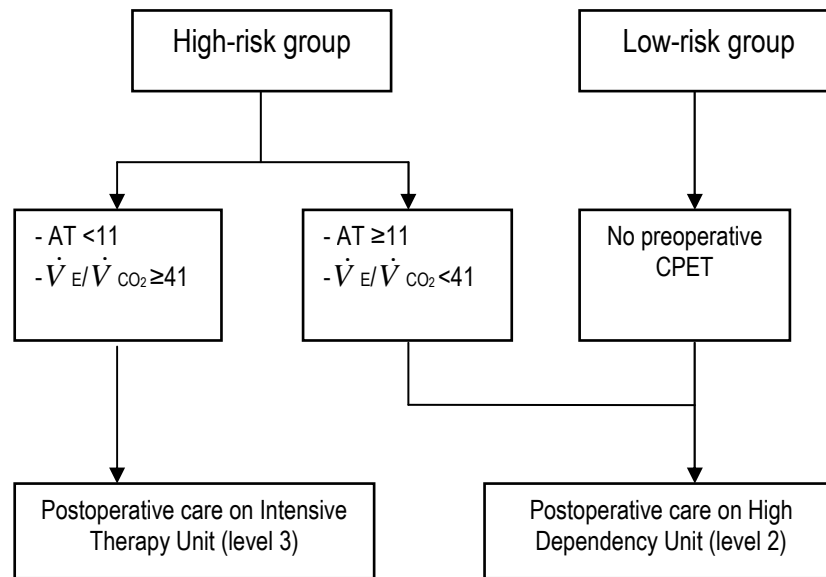
Figure 5.2: Proposed risk stratification algorithm for pancreaticoduodenectomy.

5.7   CPET in the evaluation of obstructive jaundice

Malignant obstructive jaundice continues to divide opinion in its contribution to perioperative morbidity and mortality (van der Gaag et al., 2009, van der Gaag et al., 2010). Although it is clear that an adverse association exists between obstructive jaundice and cardiovascular function (Padillo et al., 2001b, Padillo et al., 2002, Padillo et al., 2005), the impact on clinical practice remains unclear.

We demonstrated that oxygen content in the form of femoral venous partial pressure and saturation for oxygen remained normal during all stages of exercise which was comparable to findings in healthy individuals undertaking CPET(Stringer et al., 1994). The principal cause of impairment in oxygen consumption was shown to be impaired delivery from primary cardiovascular dysfunction rather than peripheral tissue oxygen extraction, which remained normal in patients with no pre-existing cardiopulmonary disease. This is further supported by evidence that reduced oxygen delivery leads to increased peripheral tissue extraction to meet the increased demands by means of

increased oxygen-haemoglobin dissociation (Bohr Effect) (Weber and Janicki, 1985, Stringer et al., 1994, Katz et al., 2000). Therefore, our findings support the focus on increasing cardiac output and oxygen delivery by means of treating obstructive jaundice before major surgery.

Limiting factors of our study included the small size of study participants. The added influence of varying levels of Bilirubin and CPET done at different stages following biliary drainage mean that a high variation (standard deviation) is present in the findings. Furthermore, there are no large sample studies demonstrating this variability to guide further evaluation. Finally, our study was limited to evaluating the impact of tissue extraction only, hence no cut-offs for the optimal levels of Bilirubin and cardiac dysfunction could be reported.

5.8   Future direction

It has become undeniable that the success of treatment cannot be measured with postoperative mortality alone (Khuri et al., 2005). The burden of complications, often hidden in patients at higher risk, is masked by the overall morbidity in the larger proportion of patients (Ghaferi et al., 2011). The role of CPET comes in recognising these patients before the level of postoperative care care be ascertained to improve outcomes (Pearse et al., 2006).

Recent developments in categorising postoperative complications in hepatobiliary surgery (Wente et al., 2007a, Wente et al., 2007b, Rahbari et al., 2011a, Rahbari et al., 2011b, Bassi et al., 2005) mean that a more comparable analyses of outcomes can be undertaken across hospitals and trusts. Robust methodologies are required to evaluating CPET as a prognostic test beyond single centres with limited post-procedural events (mortality) as current evidence from smaller studies fails to answer important questions (Stringer et al., 2012, Hennis et al., 2011).

5.8.1   Improved study designs and areas of interest

The current accepted evidence in favour of using CPET to quantify cardiopulmonary function and postoperative risk in major surgery makes it difficult to blind physicians to its utility. This limitation has led many clinicians to undertake observational studies in contrast to blinded evaluation, a fact apparent by the paucity of blinded observational or randomised control trials of its efficacy and predictive value (Hennis et al., 2011, Stringer et al., 2012). Prospective, large volume studies are required focussing on defined outcomes in disease and surgery specific populations to establish the utility of CPET-derived variables.

The last five years have witnessed an increased interest in the application of CPET in the preoperative evaluation of patients undergoing pancreaticoduodenectomy (Ausania et al., 2012, Chandrabalan et al., 2013). However, these studies are limited to the prognosis of postoperative complications and the use of CPET in the preoperative setting to optimise to moderate surgical risk has not been addressed.

If functional status, as assessed by CPET (AT and $\dot{V}_E/\dot{V}_{CO_2}$) is a predictor of postoperative outcome, improvements by offering exercise programs prior to major surgery may ameliorate risk (Stringer et al., 2012). CPET can be utilised to guide safety and effectiveness of exercise regimes for patients with high-risk of adverse postoperative outcomes. This may be applicable to patients undergoing major oncological resections as preoperative period is often utilised for neoadjuvant therapies (chemotherapy) or procedures (preoperative biliary drainage).

A well established role of CPET that has been overlooked in surgical patients, is its value in postoperative rehabilitation (Benington et al.). CPET can play a role in guiding appropriate level of subsequent therapies by offering a quantifiable approach to functional impairment.

The role of neoadjuvant chemotherapy prior to hepatic resection and the use of preoperative biliary drainage for patients undergoing pancreatic resection continue to court controversy and further evaluation is necessary to assess the impact of these therapies on cardiopulmonary functional status and perioperative outcomes to clarify its utility.

5.8.2   *Impact of chemotherapy on timing of surgery*

The benefit of chemotherapy on survival of patients with pancreatic and metastatic colorectal cancer is well established (Nordlinger and Benoist, 2006, Neoptolemos et al., 2001, Neoptolemos et al., 2010). As a minority of patients with stage IV colorectal cancer present with resectable liver disease (15-20%), the vast majority (85%) had been deemed unresectable. With a response rate of around 50% to down staging chemotherapy and biologic agents, up to 10 – 30% of these hepatic metastases are rendered resectable (Nordlinger et al., 2008, Adam et al., 2004, Baize et al., 2006, Nordlinger et al., 2007, Pozzo et al., 2008).

Although the strong argument in favour of chemotherapy has been addressed by the landmark EORTC EPOC trial (Nordlinger et al., 2008), the question of timing (neo-adjuvant/adjuvant) and impact on peri-operative outcome remains largely unanswered some studies reporting increased post-operative morbidity (Nordlinger and Benoist, 2006, Mehta et al., 2008). As the role of neo-adjuvant chemotherapy becomes well established, there is a greater need to assess the impact on peri-operative and long-term outcome.

CPET offers the ideal method in evaluating cardiopulmonary effects following chemotherapy. Patients with stage IV colorectal cancer liver metastases (resectable or unresectable) undertaking neo-adjuvant chemotherapy can be offered to undergo CPET before and after chemotherapy to assess changes in CPET variables which have validated prognostic potential (AT and $\dot{V}E/\dot{V}CO_2$). A proposed study pathway is illustrated in figure 5.3, which can be carried out in a multicentre,

prospective setting combining functional impact of chemotherapeutic agents and providing a larger

sample size to validate our current findings.


```
                        Stage IV
                     colorectal cancer
                     (liver metastasis)

           Unresectable                    Resectable
             disease                        disease

 1st CPET
 assessment
                     Neoadjuvant
                       therapy
 2nd CPET
 assessment

           Unresectable      Resectable
             disease          disease

           Palliative care              Hepatic resection
```
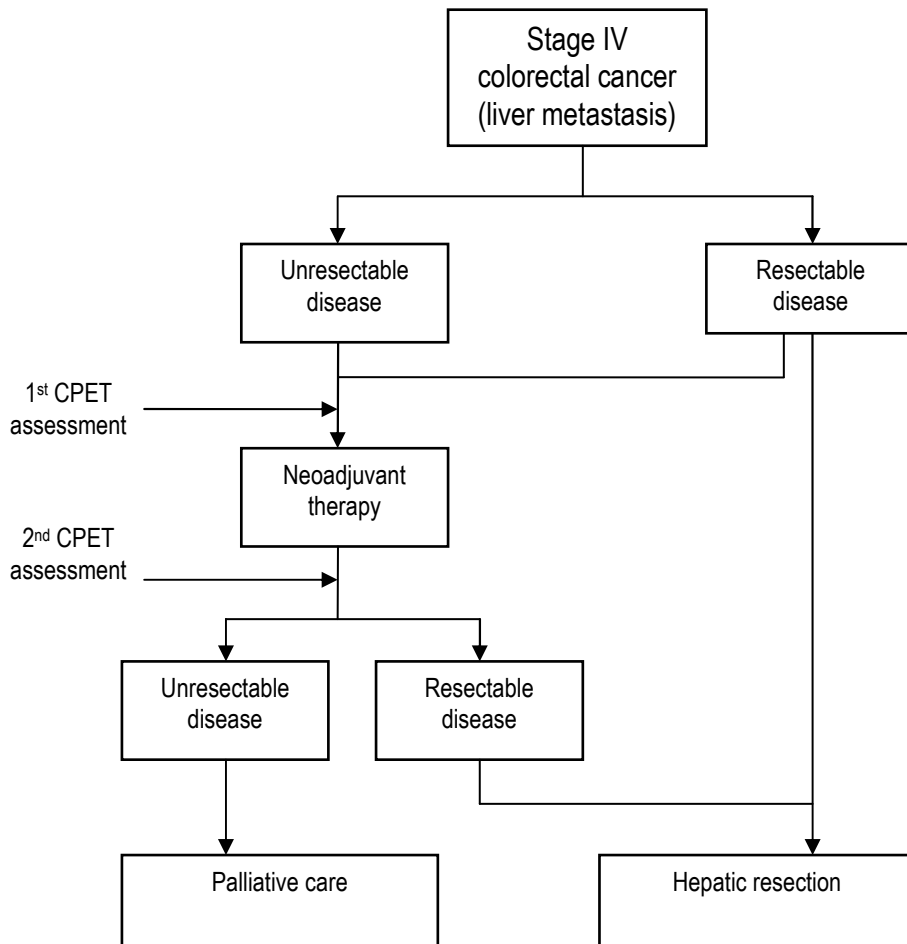
Figure 5.3: Proposed pathway for evaluating functional impact of chemotherapy.

5.8.3 *Impact of obstructive jaundice on oxygen delivery and extraction*

Accurate non-invasive monitoring of cardiac output provides an ethical and effective method of

evaluating cardiovascular impact of obstructive jaundice in patients prior to surgery (Shoemaker et

al., 1999). Comparing the accuracy of bioimpedance (intra-beat measurements of changes in trans-

thoracic voltage amplitude in response to a high frequency current) with directly recorded measures

of cardiac output using pulmonary artery catheters in a intra and postoperative setting, Shoemaker and colleagues reported a clinical utility of employing non-invasive approach to measuring cardiac function (agreement of responses from thermodilution vs. bioimpedance, r^2=0.74, p<0.001).Subsequent studies have confirmed the accuracy and reliability of trans-thoracic bioimpedance demonstrating a high degree of correlation with thermodilution method (r^2=0.82) and providing a high sensitivity and specificity (93% respectively) in detecting significant demonstrable changes in cardiac output (Squara et al., 2007).

Further development of this principal has lead to the use of trans-thoracic bioreactance technology, which analyzes blood flow-dependent changes in the phase shift of electrical currents applied across the chest. This can be utilised to patients of different body types and can be used accurately during CPET (Myers et al., Maurer et al., 2009).

Maurer and colleagues (Maurer et al., 2009) demonstrated the feasibility of combing bioreactance measurements with CPET to assess cardiac output. Using treadmill and cycle ergometer in 210 patients with varying degree of heart failure, the authors demonstrated the accuracy and utility of this adjunct.

Combining this with our standard preoperative evaluation of high-risk patients would enable safe and accurate assessment of changes in cardiac output and peripheral oxygen extraction before and after biliary drainage and reduction in total Bilirubin levels.

The future of major hepatopancreaticobiliary surgery lies in achieving a greater accuracy in defining patients who will be at high-risk of experiencing adverse postoperative outcomes. This will not only help inform patients but will also inform the clinician in providing adequate intra-operative and postoperative support in an environment that is optimal to reduce the burden of morbidity. These

efforts will not only have bearing on subsequent postoperative therapies but will also confer a

survival benefit.

The CPET- HPB outcome study   *Version 6: 6/06/2009*

Patient details

    ID. _____ Ethnicity: _____

    Date of birth: _____ Age: _____

    Gender: _____ BMI (kg/m2):_____

    Weight (kg):_____ Height (cms): _____

Preoperative co-morbidity

    ASA grade: _____ Smoking/COPD: _____

    IDDM/NIDDM: _____Hypertension: _____

    IHD: _____TIA/CVA: _____

    CRF: _____ Obstructive jaundice: _____

    Lee's RCRI: _____ GPS: _____

    Previous surgery (date/type):_____

    Prior liver resection (date): _____

    Adjuvant/neo-adjuvant chemotherapy (regimen): _____

    Cycles completed: _____

CPET

    Date of test: _____ Adequacy: _____

    Reason for termination: _____ B- blockers: _____

	Predicted	Actual	% predicted
Peak $\dot{V}_{O_2}$			
AT ml /kg/min			
$\dot{V}_E/\dot{V}_{CO_2}$ at AT			
Peak $\dot{V}_{O_2}$/HR			
$\dot{V}_{O_2}$/WR ml/Watt			
FEV1			
FVC			
FEV1/FVC			

	<AT	>AT	None
Gas exchange ischaemia			
ECG ischaemia			
Cardiac rhythm	(SVT, Other arrhythmias)		

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Operative

Operation (Open/lap/date): _____

Date of operation _____

Duration: _____ Intra-op transfusion: _____

Pre-op Hb: _____ Post-op Hb: _____

Postoperative course

ITU stay: _____ HDU stay: _____

Hospital stay: _____ Death <30 days: _____

In-hospital death: _____ Cardiovascular complication: _____

Pulmonary complication: _____ Gastrointestinal complication: _____

Renal complication: _____ Neurological complication: _____

Infectious complications: _____ Wound complication: _____

Haematological: _____ Pain: _____

Return to theatre: _____

Intervention (radiological/endoscopic): _____

Other: _____

Postpancreatectomy (ISGPS)

Major bleed (PPH):_____ Delayed Gastric emptying (DGE): _____

Postpancreatectomy fistula (PF): _____

Posthepatectomy complications

Major bleeding: _____ Liver failure: _____

Biliary leak: _____

Histology & survival

Histology: _____

Grading/ TNM staging: _____

Resection margin: _____ Vascular invasion: _____

Perineural invasion: _____

Adjuvant chemo (cycles): _____

Date of recurrence: _____ Site: _____

Palliative treatment: _____

Date of death: _____ Cause (related):_____

Status (date):_____

_____

Study protocol version 6: 22/09/2009

Full title

Assessing the effect of obstructive jaundice on cardio-pulmonary exercise testing

(CPET) in patients being assessed for pancreaticoduodenectomy for cancer

Short title

Impact of jaundice on cardiopulmonary exercise testing (CPET)

Hepatobiliary Surgery Unit

Manchester Royal Infirmary

Manchester M13 9WL, UK

Introduction

Up to 90% of patients present with jaundice as the first symptom of pancreatic malignancy. The incidence of pancreatic cancer increases with age and in certain high-risk groups, giving a global incidence figure of about 10 cases per 100,000. Overall survival is about 12 months. Surgery is the only therapeutic option associated with long-term survival but the operation of pancreaticoduodenectomy remains a major operative intervention. Although operative mortality is now less than 5% in most centres, morbidity remains high. There has been much debate about the relative merits (or otherwise) of pre-operative biliary drainage in patients with obstructive jaundice being considered for pancreaticoduodenectomy. Biliary drainage results in relief of jaundice but surgery undertaken in the presence of an indwelling stent, means undertaking resection in the presence of bacterial colonisation of the biliary tree at the time of operation. However, obstructive jaundice has adverse effects on cardiac contractility, liver and renal function, immunity, mucosal integrity/barrier function and wound healing. Therefore undertaking major cancer resectional surgery in the presence of jaundice may be unwise.

Routine preoperative biliary drainage remains a part of treatment algorithms in most centres without good evidence to support its role. In a recent Cochrane review, the authors found studies with low methodological quality and long recruitment periods adding bias. However the pooled data showed no difference in mortality or overall morbidity between preoperative biliary drainage and immediate surgery. Morbidity with preoperative endoscopic intervention was slightly higher resulting in prolonged hospital stay and resultant costs. An earlier meta-analysis with similar methodological pitfalls also found similar results with no difference in overall mortality and morbidity; with preoperative drainage resulting in longer hospital stay and higher costs. This however does not provide 'evidence' for or against pre-operative biliary drainage.

Background

Oxygen (O_2) serves as a 'proton accepter' within mitochondria during oxidative processes of metabolic substrates yielding high energy compounds such as adenosine triphosphate (ATP). During incremental exercise, increased muscle demand for energy is met by an increase in cardiovascular and ventilatory capacity to supply oxygen and remove carbon dioxide (CO_2). Adequate tissue oxygenation is dependent on oxygen delivery (Cardiac output x arterial O_2 content) and extraction [Cardiac Output x (arterial O_2 – venous O_2)]. O_2 delivery is the primary limiting factor for $\dot{V}O_2$ max (maximal oxygen consumption) in exercising humans. As demand increases, supplementation by anaerobic metabolism takes place. The $\dot{V}O_2$ (oxygen consumption) at which anaerobic metabolism commences is known as the anaerobic threshold (AT). Lactate and H+ are produced and eventually production exceeds removal leading to accumulation of both. Bicarbonate (HCO_3) buffering of H+ leads to increase in CO_2 production. The $\dot{V}O_2$ at which lactate production increases is known as the lactate threshold (LT). Increased CO_2 elimination elicited by the cardiopulmonary response to exercise allows determination of the lactate threshold. Physiologically, although the lactate threshold and anaerobic threshold describe different events, they are closely linked and occur at the same $\dot{V}O_2$. They are therefore frequently used interchangeably. Above the AT, the rate of rise in lactate concentration exceeds pyruvate and the Lactate/Pyruvate (L/P) ratio increases. Thus AT defines $\dot{V}O_2$ at which L/P ratio increases reflecting oxidative phosphorylating capacity. Development of lactic acidosis and increase in L/P ratio has been shown to correlate with multi organ failure and death in critically ill septic patients.

Evidence of reduced tissue oxygen extraction in humans in chronic renal failure, diabetes, sepsis and acute respiratory distress syndrome is well documented. Animal studies of obstructive jaundice reveal reduced mitochondria capacity to consume O_2 and synthesize ATP in cardiac and liver cells. This ability was further impaired in liver by the presence of cholangitis. Liver function and

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mitochondrial function recovered 4-6 weeks following relief of obstruction and correlated with degree

and duration of obstruction. Changes in capillary endothelium, structure and mitochondrial enzymatic

activity may influence conductance of oxygen from capillary to myocyte and cellular utilisation of

oxygen. Mitochondrial activity increases with endurance exercise training and reduces in sedentary

subjects and patients deconditioned after prolonged bed rest.

Exercise testing (ET) is a common outpatient procedure which takes approximately 1 hour to

complete. The contra-indications to exercise testing are well established and overall the mortality

rate is 1: 10 000. Patients rapidly recover from the test. Cardiopulmonary exercise testing (CPET) is

a simple extension of ET and involves the non invasive measurement of $\dot{V}O_2$ (oxygen consumption),

$\dot{V}CO_2$ (eliminated CO_2), $\dot{V}E$ (pulmonary ventilation) and pulse rate in response to incremental

exercise. There are important derived variables such as $\dot{V}O_2$/pulse, $\dot{V}CO_2/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ and

$\dot{V}E/\dot{V}O_2$ which are used clinically. The patient is non-invasively monitored and is required to pedal a

static cycle for approximately 10 minutes against an increasing load. A mouth piece is used to

measure respiratory gases. $\dot{V}O_2$/pulse normally increases with incremental exercise and is

proportional to stroke volume and O_2 extraction. A low $\dot{V}O_2$ / pulse reflects either low stroke volume

or low tissue extraction of O_2 or a combination of the two. In normal individuals, oxygen extraction is

very predictable such that a low $\dot{V}O_2$/pulse normally reflects poor stroke volume.

CPET is used to evaluate cardiopulmonary fitness of patients for pancreaticoduodenectomy. It

provides a range of measures of which the Lactate threshold (LT) and Ventilatory equivalents for

CO_2 are validated measures predicting post operative cardiopulmonary mortality. We have observed

that patients with a recent history of obstructive jaundice have abnormally low peak $\dot{V}O_2$, lactate

threshold and $\dot{V}O_2$ / pulse in the absence of known heart disease. As $\dot{V}O_2$/pulse is dependent on

cardiac function and tissue oxygen extraction, in jaundiced patients it is likely to represent poor

oxygen extraction rather than cardiac dysfunction. Techniques measuring cardiac function (stroke volume) directly include Fick principle, pulse contour analysis or echo Doppler. However these techniques require a pulmonary artery catheter, arterial line or oesophageal probe respectively which is too invasive or impractical for use during exercise testing. Peripheral oxygen extraction can be measured directly via femoral vein accurately during exercise testing with minimal risk.

Hypothesis and aim

This study tests the hypothesis that tissue oxygen extraction is compromised in jaundiced patients and that this in turn affects cardiopulmonary exercise testing. To test this hypothesis, tissue oxygen extraction will be measured by femoral vein catheter in jaundiced patients undergoing CPET and then repeated in the same patient after relief of jaundice and prior to surgery.

Methods

I.   *Setting and study population*

- The study will take place in the Manchester Royal Infirmary and will recruit patients with jaundice referred for consideration for pancreaticoduodenectomy for suspected pancreatic cancer. The regional hepatobiliary service sees about 100 new cases per annum with about 30% undergoing pancreaticoduodenectomy. The diagnosis of obstructive jaundice for study recruitment will be based on the presence of a serum bilirubin value > 50 µmol/L (laboratory reference range 0 -20 µmol/L). Although the majority of patients are turned down for surgery on the grounds of disease progression, some are not offered surgery because of cardiovascular co-morbidity.

- The CPET test (Medgraphics, Minnesota. USA) is used routinely in the service and all patients undergoing major surgery will undergo testing as part of standard medical care to assess post-operative risk.

- In this study CPET will incorporate femoral venous blood sampling as a research procedure only and it will be carried out on two occasions before surgery (undertaken before and after successful biliary drainage - < 35 µmol/L). The study will be carried out for the duration of 24 months. We anticipate recruiting 10 patients who meet the inclusion criteria for the study.

II.   *Inclusion/exclusion criteria*

Patients will be considered for inclusion in this study if they are:

- Over 18 years of age.

- Able to give informed consent.

- Present with obstructive jaundice (Bilirubin >50 µmol/L, twice the normal range) with cross-sectional imaging evidence (computed tomography or magnetic resonance scanning) of pancreatic / peri-ampullary cancer.

- Potential candidates for pancreaticoduodenectomy (no metastatic disease on cross-sectional imaging).

Exclusion criteria are:

- Inability to give informed consent.

- Patient is not a candidate for pancreaticoduodenectomy (for whatever reason).

- Unable to perform CPET or contraindication to perform

    ─ Recent myocardial infarction within 6 months

    ─ Unstable angina (patient should be pain free for 4 days before CPET)

    ─ Deep vein thrombosis of lower extremities within 3 months

    ─ Uncontrolled arrhythmias causing symptoms or haemodynamic compromise.

    ─ Malignant hypertension

    ─ Pulmonary oedema

    ─ Desaturation at rest to less than 85% while breathing room air

    ─ Syncope

III   Study design and interventions

- The proposed study is a focused clinical evaluation, assessing CPET in patients with obstructive jaundice who are being considered for pancreaticoduodenectomy. CPET is undertaken after admission during the jaundiced phase and repeated after relief of jaundice and prior to surgery.

- The study takes the form of a case-control clinical cohort study, with each patient acting as his or her own control. The first CPET results on admission (whilst jaundiced) will be compared to those obtained after relief of jaundice. A standardised CPET protocol

(Consensus Protocol for Pre-operative CPX testing for York, Torbay and UCLH. 2006) will be used. It will be carried out by a fully-trained CPET clinician, supervised by a consultant in intensive care medicine (as for routine non-study CPET). Variables used will be $\dot{V}_{O_2}$/pulse and AT.

- Additional blood samples (four to five x 5 millilitre samples with each CPET per patient) will be taken during each procedure by placing a 20 gauge cannula in the femoral vein in order to measure venous oxygen saturation and lactate/pyruvate ratio. The femoral vein catheter will be inserted after infiltration with local anaesthetic under ultrasound guidance by a single operator and will be left *in situ* for the duration of the test. This period is likely to be about 1 hour. The cannula will be placed 10cm below the inguinal ligament to reduce the risk of displacement caused by movement at the hip during exercise testing. All patients will receive routine thromboprophylaxis as per standard clinical care and NICE guidelines.

- The second CPET examination will be carried out after relief or resolving obstructive jaundice.

IV   *Data collection and analysis*

Data will be collected onto a standard, paper-based clinical case record form and transcribed to a password-protected database for storage. Analysis will be carried out on completion of the study to assess the changes in oxygen extraction before and after treatment of obstructive jaundice. CPET derived $\dot{V}_{O_2}$/pulse and lactate threshold will be correlated with serial femoral venous blood results (O_2 extraction) before and after biliary drainage. Markers of intracellular metabolism will also be assessed to evaluate intracellular respiratory changes linked to reduced oxygen extraction and consumption.

Impact of jaundice on cardiopulmonary exercise testing *Version 1: 30th April 2009*

Patient details

1. No. _____ 2. Age: _____

3. Gender: _____ 4. Ethnicity: _____

5. BMI (kg/m2): _____

Co-morbidity

6. ASA grade: _____ 7. COPD: _____

8   IDDM/NIDDM: _____ 9. Hypertension: _____

10. Coronary artery disease: _____ 11.TIA/CVA: _____

12. CRF: _____ 13.PVD: _____

Presentation

14. Mode of presentation: _____

15. Duration of jaundice: _____

16. Referral centre and service: _____

17. Primary diagnosis: _____

18. Basis of diagnosis (USS, CT, MRI) date and findings:_____

Pre CPET status

19. Date of admission to Hospital (MRI): _____

20. Presence of sepsis/ source: _____

21. Antibiotics (regimen) and duration: _____

22. Blood results before 1st CPET. Date and time taken: _____

Haemoglobin		Urea	
White cell count		Creatinine	
Platelets		Bilirubin	
PT		ALT	
CRP		ALP	
		Albumin	

First CPET results

23. Date: _____ 24. Adequacy: _____

25. Reason for termination: _____

26. Pre-test obs (HR, temp, BP):_____

27. β – blockers:_____

28. Comments: _____

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Variable	Predicted	Actual	Comments
$\dot{V}$ O$_2$ ml/kg/min			
AT			
Peak $\dot{V}$ O$_2$/HR			
$\dot{V}$ E/$\dot{V}$ CO$_2$ at AT			
$\dot{V}$ O$_2$/WR ml/Watt			
FEV1			
FCV			
FEV1/FVC			

Femoral venous results with 1st CPET

29. Side of catheterization: _____ 30. Duration in-situ (minutes): _____

31. Complications: _____

Variable	At rest/start	At 3 minute	Every minute	At peak Effort	During recovery
pH					
O$_2$ saturation					
SfvO$_2$					
SfvCO$_2$					
Lactate					
HCO$_3$					

Biliary drainage

32. Date and mode (ERCP, PTBD) of drainage: _____

34. Endoprosthesis: _____

35. Complications: _____

36. Additional interventions: _____

37. Period of resolution of jaundice (days):_____

Blood results before 2nd CPET. Date and time taken _____

Haemoglobin		Urea	
White cell count		Creatinine	
Platelets		Bilirubin	
PT		ALT	
CRP		ALP	
		Albumin	

Second CPET results

37. Date: _____ 38. Observation (HR, temp, BP): _____

39. Comments: _____

Variable	Predicted	Actual	Comments
$\dot{V}$ O$_2$ ml/kg/min			
AT			
Peak $\dot{V}$ O$_2$/HR			
$\dot{V}$ E/$\dot{V}$ CO$_2$ at AT			
$\dot{V}$ O$_2$/WR ml/Watt			
FEV1			
FCV			
FEV1/FVC			

Femoral venous results

40. Side of catheterization: _____ 41. Duration in-situ (minutes): _____

42. Complications: _____

Variable	At rest/start	At 3 minute	Every minute	At peak Effort	During recovery
pH					
O$_2$ saturation					
SfvO$_2$					
SfvCO$_2$					
Lactate					
HCO$_3$					

CONSENT FORM

Version 2: 8th November 2009.

Study ref. no. NW5REC 09/H1010/51

Title of study: **Impact of jaundice on Cardiopulmonary Exercise Testing (CPET)**

Patient identification: _____ Please initial

box

1. I confirm that I have read and understood the information sheet for the above research study (Version 3: 8th November 2009) and have had the opportunity to consider the information, ask questions and have these answered satisfactorily.

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

3. I understand my participation involves exercise testing (CPET) before and after treatment for jaundice.

4. I understand blood tests will be taken during the exercise testing via a femoral vein catheter. I understand the risks involved with the procedures.

5. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the research team in department of surgery, department of anaesthesia, regulatory authorities from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

6. I agree to use of my results for the research study and understand that it will remain confidential.

7. I agree to my GP being informed of my participation in the study if necessary.

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

Name of patient: _____ Signature: _____ Date

Name researcher: _____ Signature researcher: _____ Date

1 copy for participant, 1 for researcher. Original filed in medical notes.

PARTICIPANT INFORMATION SHEET

Version 3: 8th November 2009

Study ref. no. NW5REC 09/H1010/51

Study title: **Impact of jaundice on cardiopulmonary exercise testing (CPET)**

We would like to invite you to take part in our study which is being carried out at the Manchester Royal Infirmary, Central Manchester Foundation Trust. Before you decide we would like you to understand what this research is about, why you have been invited to participate and what it would involve for you. Please take time to read through the information sheet which answers these questions.

PART 1: Explains the purpose of the study and impact on your care if you choose to take part.

PART 2: Entails detailed information regarding the conduct of the study.

PART 1

Why have I been invited to take part?

As you have been admitted with jaundice from a probable tumour, you will undergo standard operative risk assessment with cardiopulmonary exercise testing. By participating in this study, you will allow us to study the affect of jaundice on risk assessment for surgery using CPET and help understand the processes involved in harmful effects of jaundice. This will help in improved assessment, management and selection for surgery in the future.

What is Jaundice?

Obstruction to flow of bile from liver into gut leads to accumulation of bilirubin in blood causing yellow skin discolouration, itching, pale coloured stools and dark urine. The cause is often a stone or a

suspected tumour as in your case. Persistently elevated levels can cause liver damage and is treated with a stent until definite care, which may be surgery, is planned and carried out.

What is Cardiopulmonary exercise testing (CPET)?

CPET now forms an important part of assessing for surgery. It involves exercising on a special bicycle whilst breathing through a special mouth piece. You will be asked to pedal at a constant, steady pace, normally 10 – 15 minutes. The test will not push you to exhaustion but may cause you to feel breathless or tired during the test. This will recover once the test has stopped. It will be stopped immediately if you feel unwell. Trained medical staff will be present at all times during the test.

Stress induced by exercise testing is very similar to the stress experienced by the body during an operation. Thus it provides important information on how well your body will cope with the demands of surgery.

What is the purpose of the study?

The purpose of this study is to understand the impact of jaundice on oxygen which is required by the body for normal function. Carrying out exercise testing before and after treatment of obstructive jaundice will help understand the direct effect of jaundice on body's ability to utilise oxygen. Reduced oxygen capacity is proven to adversely affect heart and lung function and lead to increased complications.

Results from this study may help in deciding whether surgical complications can be reduced significantly by treating jaundice before surgery to improve outcome or if it provides no additional benefit and may lead to added risk and unnecessary delay. Hence apart from providing useful, novel information about jaundice, it will also provide rationale for preoperative treatment of jaundice and accurate risk assessment of surgical risk.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

CPET is part of a standard clinical care for patients undergoing major surgery. It is carried out before surgery to formulate post-operative care according to individual risk factors.

If you decide to take part in the study you will undergo two separate CPET examinations as opposed to a single standard test. The first CPET will be carried out on admission with jaundice followed by treatment of jaundice. The second CPET will be undertaken just before surgery. Blood tests will be carried out as a research procedure only, i.e. patients would not ordinarily undergo blood tests during CPET as part of standard clinical care. The details of blood tests are included in part 2.

Is there of any possible benefit for me?

Apart from being an important integral part of assessment before surgery CPET is a reliable diagnostic test. It may help detect undiagnosed heart or lung condition which will direct appropriate management. Primarily it will inform us of potential risks of surgery and aid in making an informed decision.

Regarding the information on effects of jaundice, we cannot promise the study will help you but the information we get from this study will help improve the treatment of people with similar condition in the future.

This completes PART 1. If the information in PART1 has interested you and you are considering participation, please read the additional information in PART 2 before making any decision.

PART 2

What are the procedures involved?

Once you have decided to take part you will undergo cardiopulmonary exercise test on admission (in presence of jaundice). Blood tests will be carried out during exercise testing via a femoral vein catheter. This is a research procedure only and does not constitute standard clinical practice. A catheter is placed in the femoral vein (upper thigh vein) under local anaesthetic and five small blood samples are obtained. The femoral vein catheter will be removed immediately after the test and the total duration of its placement will be less than an hour. You will then undergo treatment for jaundice as standard clinical practice and discharged to return for surgery. The second CPET with blood tests will be undertaken on admission before surgery completing your participation in the study.

What are the risks of taking part in the study?

CPET is a safe procedure. It is carried out under medical supervision and stopped if you feel discomfort or are unwell. Recovery after exercise is quick. Blood tests are carried out via a catheter in the femoral vein. A small risk of developing a clot in the vein is minimised by a small sized catheter inserted for a short duration by an experienced doctor under ultrasound guidance. Prevention for deep vein thrombosis is provided to all patients as part of standard clinical care.

What happens to my blood samples?

The blood tests will be analysed to reveal your ability to utilise oxygen in presence and absence of jaundice during exercise. They will also determine the effect of poor oxygen consumption. Once the results have been obtained the samples will be disposed of in accordance with the Human Tissue Authority's Code of Practice.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be kept strictly confidential, and have your name and address removed so that you cannot be recognised. Some parts of your medical records and the data collected for the study will be looked at by authorised persons such as research team members and NHS regulatory authorities to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

What will happen if I don't want to carry on with the study?

Participation in the study is voluntary and you will be free to withdraw at any stage during the study. This will not affect your standard of medical care. The data collected up to your withdrawal will only be used subject to your wishes.

What happens to the results of the study?

The results obtained from CPET will be discussed with you immediately after the test. They will help your care before and after the operation. Results obtained from analysing the effect of jaundice on oxygen may not provide any benefit in your care but will shape future management by contributing towards a greater understanding of the subject. We will present our findings in scientific meetings and journals.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee (REC), to protect your interests. This study has been approved by REC (Protocol version 6: 22nd October 2009) and the Research & Innovation Division of Central Manchester Foundation Trust.

Will my GP be informed?

Your GP will be informed and details of the study and your hospital management will be communicated to address any concerns that might arise as a result of your participation.

What happens if there is a problem?

If you have a concern about any aspect of this study, you should speak to the researchers who will do their best to answer your questions. Any complaint about the way you have been dealt with during the study or any possible harm you suffer will be addressed. If you remain unhappy and wish to complain formally, you can do this. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Central Manchester Foundation Trust. The normal National Health Service complaints mechanisms will still be available to you.

Further information and contact details

- Researcher contact details:

  Dr. Muneer Junejo   Telephone: 0161 276 4244

- Independent contact for general advice about research:

  Specialist nurse: Clare Newton   Telephone: 0161 276 4263

- Independent contact for further details about research project:

  Consultant Hepatobiliary Surgeon: Mr. Aali Sheen   Telephone: 0161 276 8533

- Patient Advice and Liaison Services (PALS): Provide confidential advice and support to patients, families and their carers, and can provide information on the NHS and health related matters.

  Contact: Peter Lacey   Telephone: 0161 276 8686

  E-mail: pals@cmft.nhs.uk

GENERAL PRACTITIONER INFORMATION LETTER

Version: 2. 22nd October 2009

Ref. no. NW5REC 09/H1010/51

General practitioner details:

Patient information:

Study title: **Assessing the effect of obstructive jaundice on cardio pulmonary exercise testing (CPET) in patients being assessed for pancreaticoduodenectomy for cancer.**

This is to inform you that your patient has volunteered to participate in our above mentioned study which is being carried out by the department of hepatobiliary surgery, under Professor A. Siriwardena. This is entirely voluntary and no restrictions or conditions are placed on withdrawal from the study. In such a case the overall medical care will not be affected.

Cardiopulmonary exercise testing (CPET) is a reliable and safe exercise based preoperative assessment of cardiopulmonary function and yields clinically validated variables on oxygen delivery and consumption which help assess perioperative risk and formulate appropriate care. It forms part of standard clinical care for all patients undergoing major surgery.

Your patient will undergo CPET assessment and additionally undergo blood sampling during the test via femoral venous catheter which is a research procedure only and not part of standard CPET. This will be placed for the duration of the test only which will not last longer than an hour. CPET will be repeated after successful biliary drainage. Patients will henceforth proceed to scheduled surgery. This will help us evaluate effect of jaundice in oxygen delivery and oxygen extraction hence explaining the poor oxygen consumption seen in these patients.

Please don't hesitate to contact us if you have any queries or require further information.

Impact of jaundice on Cardiopulmonary Exercise Testing (CPET)

Study ref. NW5REC 09/H1010/51

Study ID: _____

<div align="center">Inclusion criteria</div>

- Over 18 years of age.   ☐

- Able to give informed consent.   ☐

- Present with obstructive jaundice (bilirubin >35 µmol/L)   ☐

- Cross-sectional imaging evidence (computed tomography or magnetic resonance   ☐

  scanning) of pancreatic or peri-ampullary cancer.

- Potential candidates for pancreaticoduodenectomy (no metastatic disease on cross-   ☐

  sectional imaging).

Date recruited:

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