An investigation of preoperative cardiopulmonary exercise testing in patients undergoing major pancreatic surgery.

by

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SUBMITTED IN FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF MEDICINE

to

THE UNIVERSITY OF GLASGOW

BASED ON RESEARCH CONDUCTED IN THE
UNIVERSITY DEPARTMENT OF SURGERY,
GLASGOW ROYAL INFIRMARY
AUGUST 2015

1 *Pebbles on the beach.*

Dedicated to A, I, A

UNIVERSITY OF GLASGOW (IN BLOCK CAPITALS)

Abstract

Faculty Name

School of Medicine

Doctor of Medicine

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To be finalised...

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Acknowledgements

I would like to thank the following people, for their help, advice and encouragement:

Professor Donald C McMillan,

University Department of Surgery, Glasgow Royal Infirmary

Professor Paul Horgan,

University Department of Surgery, Glasgow Royal Infirmary

Declaration of Authorship

I declare that the work presented in this thesis was carried out solely by me, as a clinical research fellow in the University Dept of Surgery, Royal Infirmary, Glasgow, except where indicated below:

Measurement of biochemical and haematological data was performed by the hospital laboratory service.

Statistical analysis was performed with the assistance of Prof Donald C McMillan, University Dept of Surgery, Royal Infirmary, Glasgow.

In addition, no work referred to in this thesis has been submitted in support of an application for another degree or qualification in this or any other university.

Abbreviations

LAH **L**ist **A**bbreviations **H**ere

Chapter 1

Introduction

1.1 Pancreatic Neoplasia

1.1.1 Epidemiology of pancreatic cancer

[Crozier et al. 2007] Tumours involving the head of the pancreas and the peri-ampullary region account for a small proportion of gastrointestinal tumours. They may be broadly classified as benign and malignant. Most pancreatic neoplasia are malignant and arise from the exocrine component of the gland, the ductal epithelium.

Pancreatic ductal adenocarcinoma is the most common cancer of the pancreas. However, the head of the pancreas is anatomically related to several other epithelium lined structures that can also give rise to cancers. These include the distal common bile duct that can give rise to cholangiocarcinoma, the duodenum that can give rise to duodenal adenocarcinoma and the ampulla that can give rise to ampullary adenocarcinoma. The endocrine portion of the pancreas can give rise to a variety of tumours that are collectively called neuroendocrine tumours (NET). The milieu of tumours is complicated by other neoplasia such as intra-ductal papillary neoplasms (IPMN) as well as rare stromal tumours. Occasionally, chronic pancreatitis may present with features similar to pancreatic cancer and can be morphologically, radiologically and histologically difficult to differentiate from cancer.

Pancreatic cancer is the tenth most common cancer in the UK but the fifth most common cause of cancer death with only 21% surviving beyond the first year and 3%

surviving beyond 5 years.[CancerResearchUK 2014] The majority of patients (80-85%) with pancreatic cancer present with inoperable disease.[CancerResearchUK 2014; Sener et al. 1999]

In patients with resectable disease, surgery [Sener et al. 1999; Sohn et al. 2000; Geer and Brennan 1993] followed by adjuvant chemotherapy [John P Neoptolemos, Stocken, Friess, et al. 2004; J P Neoptolemos et al. 2009] remains the primary modality of cure. However, major pancreatic surgery places significant physiological stresses on multiple organ systems. The ability of the cardiac and respiratory systems, in particular, to cope with the increased physiological demand placed by general anaesthesia and major pancreatic surgery plays an important role in determining outcome after surgery.

1.1.2 Clinical presentation

The anatomical location of the pancreas, deep within the retroperitoneum surrounded by numerous vital blood vessels including the coeliac trunk and its branches, the superior mesenteric artery, portal vein and superior mesenteric vein as well as proximity to other viscera such as the stomach, duodenum, transverse colon result in early involvement of these structures even by relatively small tumours. Moreover, symptoms are often absent in the early stages and when present are too non-specific to help with diagnosis. Obstructive jaundice is the most common presenting symptom and painless, obstructive jaundice in an elderly patient should always raise the suspicion of a neoplastic process in the head of the pancreas or the periampullary region. Other non-specific symptoms include weight loss, early satiety, vomiting, fatigue and pain in the epigastrium or the back.

1.1.3 Diagnosis and staging

Aside from a thorough history, clinical examination, blood tests including liver function tests, diagnosis requires cross-sectional imaging in the form of a contrast-enhanced computerised tomogram (CECT) of the abdomen using a pancreas-specific protocol (a modified form of the portal-venous phase). CECT of the pancreas when combined with CT Thorax also provides accurate information on staging of the disease with regards to metastasis and this can be supplemented by further imaging such as Positron Emission Tomography (PET-CT) or contrast-enhanced MRI Liver in specific cases. CECT-pancreas is also useful for assessing local resectability with regards to vascular involvement. Endoscopic ultrasound (EUS) is also useful in assessing vascular involvement and for obtaining tissue samples for histological examination. In jaundiced patients, endoscopic retrograde cholangio pancreatography (ERCP) plays an important role in the alleviation of jaundice by placing stents across the obstructed bile ducts, accurate visualisation of the biliary anatomy as well as obtaining brushings from within the bile ducts for cytological examination. The role of preoperative biliary drainage is discussed in more detail in section

1.1.4 Treatment of pancreatic cancer

Pancreaticoduodenectomy followed by adjuvant chemotherapy offers the only chance of cure in patients with resectable pancreatic cancer who are fit enough to undergo surgery. In patients with unresectable disease or who are not fit to undergo surgery, palliative chemotherapy plays a limited role in prolonging survival. Assessing the resectability is discussed in the next section while the assessment of patient fitness and the impact of comorbidity are discussed in detail in section 1.4 on p14.

1.2 Surgical treatment of pancreatic cancer

Pancreaticoduodenectomy remains a technically challenging and complex surgical procedure over a hundred years after its description. The procedure was performed as a two-stage operation by a German surgeon, Walther Kausch in 1909 at Augusta-Viktoria-Krankenhaus in Berlin-Schöneberg.[Kausch 1912]. The operation was further popularised initially as a two-stage procedure by Whipple[Whipple, Parsons, and Mullins 1935] before evolving into the current single stage operation by the 1950s.[Whipple 1941; Whipple 1950]

1.2.1 Patient selection

1.2.1.1 Resectability criteria

Resectable pancreatic cancer is defined as a tumour that - does not involve the coeliac axis or the superior mesenteric artery - and is not associated with distant metastatic disease

Tumours involving the portal vein or superior mesenteric vein are considered borderline resectable and can still be resected completely (R0) with en-bloc venous resection. Research is ongoing to assess the role of neoadjuvant therapy and newer treatment modalities such as electroporation in these patients to improve resectability.

1.2.1.2 Patient factors

1.2.2 Operative technique

Pancreaticoduodenectomy is considered one of the most technically challenging operations on the gastrointestinal tract. While the procedure is carried out in a broadly similar fashion in all major centres, there remain some variations in perioperative care as well as some operative steps. The following is a description of the procedure as performed at the West of Scotland Pancreatic Unit.

After a comprehensive preoperative work-up including both assessments of the tumour as well as patient fitness, informed consent was obtained. Patients received thrombo-prophylaxis on the night before surgery which was continued until discharge from hospital. General anaesthesia with complete muscle relaxation was used in all patients. Epidural analgesia was used routinely in patients during the early part of the study period while all patients in the later half of the study period received spinal diamorphine. Antibiotic prophylaxis is administered at induction. While the use of Octreotide, a somatostatin analogue, to reduce the risk of postoperative pancreatic fistula formation is still debated, it was routinely used in all patients at this centre. Octreotide was administered intra-operatively (200 mcg s.c.) and was continued for 5 days postoperatively (200 mcg s.c., t.d.s.).

A roof-top incision was used for access. After assessing the peritoneal cavity for absence of metastatic disease, an early assessment was made for local resectability. This involved complete Kocherisation of the duodenum to assess the retroperitoneum. Both the superior mesenteric artery and coeliac axis were assessed early for tumour involvement ('artery-first' approach). The rest of the procedure was performed as described extensively elsewhere. The gastrocolic omentum was divided to enter the lesser sac. The superior mesenteric vein was identified and a retro-pancreatic tunnel was created between the pancreatic neck and the portal vein. If less than half the circumference of the SMV or PV was involved, an en-bloc resection was performed with vein repair at the same time. The hepatoduodenal ligament was dissected after a fundus-first cholecystectomy to isolate the common bile duct which was transected after ascertaining the hepatic artery anatomy. The gastro-duodenal artery was divided. Resection was then completed by dividing the stomach (classical Whipple procedure) or the first part of the duodenum (pylorus-preserving pancreaticoduodenectomy, PPPD) and transecting the pancreatic neck.

Reconstruction was performed as follows: Either a pancreatico-jejunostomy was performed using 4-0 Biosyn sutures in a two-layer duct-to-mucosa technique or a pancreatico-gastrostomy was performed using 3/0 Biosyn sutures placed in a similar manner. Hepaticojejunostomy was performed using interrupted 4/0 Biosyn sutures while the gastrojeunonostomy or duodenojejunostomy (in PPPD) was performed using continuous 3/0 PDS sutures in a 2-layers. One or two surgical drains were placed and the abdomen was closed after ensuring haemostasis.

1.2.3 Postoperative care

All patients were routinely admitted to the Surgical High Dependency Unit unless intra-operative events necessitated admission to the Intensive Care Unit. A standardised regimen of intravenous fluids, naso-jejunal feeding, mobilisation and physiotherapy was implemented in all patients. Standard physiological parameters including haemodynamic parameters, renal function and arterial blood gases were used to monitor adequate end organ perfusion. All patients received proton pump inhibitors and octreotide. Patients were discharged to the general surgical ward as early as possible.

1.2.4 Complications

The incidence of complications after pancreaticoduodenectomy remains high in spite of a steady decline in postoperative mortality from over 40% in the 1950's to less than 5% in most large volume centres around the world.[DeOliveira et al. 2006; Emick et al. 2006; C J Yeo et al. 1997; Winter, Cameron, Campbell, et al. 2006; Teh et al. 2009; Gouma et al. 2000]

1.2.4.1 Postoperative pancreatic fistula

Postoperative pancreatic fistula is one of the most dreaded complications after a pancreaticoduodenectomy and can be associated with significant short-term morbidity as well as long-term disability. The reported incidence of postoperative pancreatic fistula varies from 2% to 30% after pancreaticoduodenectomy.[C J Yeo et al. 1997; DeOliveira et al. 2006; Bassi et al. 2005; Winter, Cameron, Charles J Yeo, et al. 2007; W. B. Pratt, Callery, and Vollmer 2008] The variation in reported incidence has been largely due to lack of clear definition of what constituted a postoperative pancreatic fistula. It can be a result of breakdown or poor healing at the pancreaticojejunostomy/pancreaticogastrostomy or may be the result of direct parenchymal leak unrelated to the anastomosis. It is now generally accepted that 1 in 4 patients will develop a pancreatic fistula as defined by the International Study Group for Pancreatic Fistula (ISGPF) which has published a consensus statement on the definition and grading of postoperative pancreatic fistula.[Bassi et al. 2005] A postoperative pancreatic fistula is defined as drain output of any measurable quantity after the third postoperative day with amylase content greater than three times the upper limit of the normal serum amylase value at the laboratory used for testing. Three grades of postoperative pancreatic fistula have been defined based on clinical severity as described in Table 1.1 on p12. Grade B and C fistulae are considered to be clinically significant in that they alter patient management and are often associated with other secondary complications such as intra-abdominal sepsis, post-pancreatectomy haemorrhage, delayed gastric emptying as well as need for intervention (either radiological or operative) and/or prolonged critical care support.

1.2.4.2 Post-pancreatectomy haemorrhage

Post-pancreatectomy haemorrhage is reported to occur in 1 to 8% of patients undergoing pancreaticoduodenectomy. However, it accounts for 11% to 38% of mortality after pancreaticoduodenectomy. Post-pancreatectomy haemorrhage may either be intra-luminal into the gastrointestinal tract or intra-abdominal into the peritoneal/retro-peritoneal space. Post-pancreatectomy haemorrhage may be from any of a number of potential sources although bleeding from the stump of the gastroduodenal artery is the most common cause. Other potential sources include suture lines at the anastomoses, gastric/duodenal ulcers or diffuse gastritis, pseudoaneurysms of the gastro-duodenal, splenic or rarely the hepatic artery or rarely, haemobilia.

Haemorrhage is often secondary to non-healing of the pancreatico-jejunal anastomosis leading to leakage of amylase-rich pancreatic juices into the retroperitoneum or secondary to intra-abdominal sepsis or bile leak.[Tien et al. 2005; Koukoutsis et al. 2006; Choi et al. 2004; Balladur et al. 1996] This can then lead to erosion of ligated blood vessels, most commonly the stump of the gastro-duodnenal artery. Post-pancreatectomy haemorrhage is often managed with angiographic embolisation of the bleeding vessel and surgical intervention is only rarely required. The grading of severity of post-pancreatectomy haemorrhage as described by the International Study Group of Pancreatic Surgery[Wente et al. 2007] is shown in Table 1.2 on p12.

1.2.4.3 Clavien-Dindo classification of complications

A number of other adverse events may occur following pancreaticoduodenectomy including cardiopulmonary complications such as myocardial infarction, cardiac arrythmias, pneumonia, pleural effusions, wound complications such as wound sepsis and dehiscence, intra-abdominal sepsis including intra-abdominal sepsis, leakage from the hepaticojejunostomy or the gastrojejunostomy, renal dysfunction, etc. The Clavien-Dindo method grades the severity of complications based on the impact the complication has on the management of the patient and has been validated on large numbers of surgical patients.[P. A. Clavien et al. 2009; Dindo, Demartines, and P.-A. Clavien 2004] This is summarised in Table 1.3 on p13 and has been used to grade complications in this thesis.

1.3 Adjuvant and Neoadjuvant treatment

TABLE 1.1: Postoperative pancreatic fistula: ISGPF definition.

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

TABLE 1.2: Postpancreatectomy haemorrhage: ISGPS definition.

Grade	A	B	C
Time of onset, location, severity and clinical impact of bleeding	Early, intra- or extraluminal, mild	Early, intra- or extraluminal, severe or Late, intra- or extraluminal, mild	Late, intra- or extraluminal, severe
Clinical condition	Well	Often well/ intermediate, very rarely life-threatening	Severely impaired, life-threatening
Diagnostic consequence	Observation, blood count, ultrasonography and, if necessary, computed tomography	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy	Angiography, computed tomography, endoscopy
Therapeutic consequence	No	Transfusion of fluid/blood, intermediate care unit (or ICU), therapeutic endoscopy,† embolization, relaparotomy for early PPH	Localization of bleeding, angiography and embolization, (endoscopy†) or relaparotomy, ICU

Table 1.3: The Clavien-Dindo Classification of Surgical Complications

Grade	Description
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
	Grade III-a: - intervention not under general anesthesia
	Grade III-b: - intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
	Grade IV-a: - single organ dysfunction (including dialysis)
	Grade IV-b: - multi organ dysfunction
Grade V	Death of a patient
Suffix 'd':	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

1.4 Comorbidity and Risk Stratification

1.4.1 Comorbidity

Comorbidity is defined as the presence of or the effect of other diseases that a patient has in addition to the primary disease of interest. The presence of comorbid conditions is associated with adverse outcomes in patients undergoing treatment for pancreatic cancer[Mann et al. 2010] and often limits therapeutic options available due to the associated complications or side effects of surgery or chemoradiotherapy.[Sandroussi et al. 2010]

Patients with multiple comorbidities are more likely to have higher readmission rates, morbidity and mortality following discharge after pancreaticoduodenectomy.[Schneider et al. 2012] DeOliveira and co-workers reported that cardiovascular disease was a risk factor not only for overall morbidity but also complication severity after pancreaticoduodenectomy.[DeOliveira et al. 2006] Cancer cachexia is associated with increased incidence of complications and mortality after pancreaticoduodenectomy[Pausch et al. 2012] while obesity is known to be associated with greater incidence and severity of postoperative complications.[Benns et al. 2009]

Major pancreatic surgery requires the patient to have adequate physiological reserve to cope with the increased demand during and immediately after surgery. However, existing methods of measuring the impact of comorbidity on physiological fitness are limited and do not adequately predict outcomes after major pancreatic surgery. [Shah et al. 2012]

1.4.2 Risk Stratification

Physiological fitness or reserve may be defined as the ability of the patient's organ systems to respond appropriately and adequately to the stress of major surgery. Major surgery places a significant physiological stress on multiple organ systems, especially the cardiorespiratory system. The ability of the cardiorespiratory system as well as other physiological systems including renal, gastrointestinal, hepatic, coagulatory and immunological systems to cope with major surgery and the postoperative recovery plays a major role in determining short-term outcomes.

Accurate measurement of physiological fitness

1.4.3 Static Versus Dynamic Testing

Objective measurement of oxygen delivery at the tissue level at times of physiological stress allows for identification of patients who may struggle during the perioperative phase. Identification of such high-risk patients allows not only for improved patient selection, but also for risk-stratified, anaesthetic and postoperative critical care. Preoperative risk stratification will also allow for prehabilitation of these patients in an attempt to improve outcomes.

Several tests have been used for preoperative assessment of cardiac function. These include - electrocardiography - echocardiography - exercise tolerance testing - myocardial perfusion scans

Tests of respiratory function that are commonly performed in selected patients undergoing major surgery include - pulmonary function tests including forced expiratory volume and forced vital capacity - spirometry

However, neither of the above cardiac or respiratory function tests adequately measure the ability of the cardiopulmonary and circulatory systems to deliver oxygen to the tissues at times of increased demand.

1.5 Cardiopulmonary Exercise Testing

1.5.1 History of CPET in Surgery

1.5.2 Cardiopulmonary Exercise Test Methodology

CPET is composed of several components that involve measuring not only the response of the cardiac and respiratory system to exercise but the test also helps establish the adequacy of this response to sustain oxygen delivery to skeletal muscle as demand increases with increasing exercise.

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire Health, Longmont, CO 80501, USA). The equipment was calibrated regularly to the standards set by the manufacturer and currently published guidelines[]. All tests were performed by specialist respiratory physiologists. Suitable equipment for cardiopulmonary resuscitation were available in the department in case of unexpected problems. The department was situated within the main hospital premises and therefore was easily accessible to the hospital cardiac arrest team. All patients were fully informed of the steps involved in the procedure, the reasons for performing the test as well as the risks involved.

Spirometry was performed in all patients prior to CPET. Capillary blood gases were measured in all patients after CPET. An electronically braked cycle ergometer was used to increase resistance to pedalling in preset increments. A tight-fitting face mask was placed on the patient covering the nose and the mouth. This allowed breath-by-breath gas analysis thus allowing measurement of several respiratory parameters as listed in table []. 12-lead electocardiogram was recorded at the same time.

The test started with an initial 3-minute rest period to allow measurement of baseline parameters. This was followed by an incremental work-load test that involved the patient pedalling approximately at 60 revoultions per minute while the resistance to pedalling was gradually increased in preset increments. The test was terminated when patients reached volitional fatigue (maximal exercise tolerance), significant ischaemic changes on ECG or for other safety reasons.

The parameters measured at spirometry are shown in Table 1.4 and those measured during cardiopulmonary exercise testing are shown in Table 1.5 on p26.

1.5.3 Measuring the Anaerobic Threshold

The anaerobic threshold (variously described as the lactate threshold or ventilatory threshold) is the point during exercise when oxygen demand by exercising skeletal muscle outstrips supply. Therefore, muscle tissues use anaerobic respiration to supplement aerobic respiration to continue generation of ATP. The resulting metabolic lactic acidosis is almost immediately compensated by the bicarbonate buffer as below:

$$H^+ + HCO3^- \Longleftrightarrow H_2CO_3 \Longleftrightarrow H_2O + CO_2 \tag{1.1}$$

The resulting excess CO_2 is exhaled and is one of the many parameters measured during cardiopulmonary exercise testing. This transition from aerobic to anaerobic respiration may be determined using the V-slope method[Sue et al. 1988] or the ventilatory equivalents method.[Beaver, Wasserman, and Whipp 1986] Most centres, like ours, use both methods supplemented by information from a variety of other parameters to enable accurate determination of the anaerobic threshold as recommended by the American Thoracic Society/American College of Chest Physicians Statement on cardiopulmonary exercise testing.[Society and Physicians 2003]

The software presents a standard 9-panel view of trending plots of various parameters measured during incremental exercise. All of these trends are taken into consideration rather than any one particular parameter value in determining the overall outcome of the test. A sample 9-panel view derived from parameters belonging to one of the patients studied is shown in Figure 1.1. The data used to generate these plots is included in Appendix A.

1.5.3.1 V-slope method

During aerobic exercise, VO2 and VCO2 share a linear relationship as shown in segment A of the graph in figure 1. However, as anaerobic respiration starts to supplement aerobic respiration, VCO2 increases disproportionate to VO2 as a direct result of the respiratory buffer described in equation 1.1 on p18. This results in a distinct difference in the slope of the initial part of the graph (seg A) and the later part (seg B). The point at which the two slopes intersect is the anaerobic threshold and the V02 at this point in exercise is commonly referred to as the anaerobic threshold, VO2at or simply AT.

1.5.3.2 Ventilatory equivalents method

[...]

1.6 Description of CPET Parameters

1.6.1 Exercise Load

The most common form of cardiopulmonary exercise testing for clinical purposes involves a cycle ergometer with steadily increasing resistance delivered through electric braking allowing accurate measurement of work load in Watts. The relationship between $\dot{V}_{O_2}$ and work rate is usually linear and the slope of this relationship is independent of sex, age or height. An abnormality in this relationship is usually due to cardiopulmonary or circulatory causes.

1.6.2 Minute Ventilation, $\dot{V}_E$

Minute ventilation or respiratory minute volume is the volume of air that is inhaled/expired in a minute.

$$\dot{V}_E = \dot{V}_T \times Bf \tag{1.2}$$

where $\dot{V}_T$ = Tidal Volume and Bf = Breathing Frequency.

Increasing $\dot{V}_E$ is one of the main mechanisms involved in increasing oxygen delivery during exercise. It is also an important factor in clearing CO_2 from the blood.

1.6.3 Oxygen Uptake, $\dot{V}_{O_2}$

$\dot{V}_{O_2}$ or oxygen uptake is measured breath-by-breath using digital analysis of the inspired and expired gases. This is then averaged, usually over time, to smooth-out any signficant breath-by-breath variation. $\dot{V}_{O_2}$ increases with increasing work load and is influenced by several factors that have a role in the transport and utilisation of oxygen. These may be broadly classified as cardiac, pulmonary, circulatory and tissue factors. Some of the factors are encompassed in the following formula for $\dot{V}_{O_2}$.

$$\dot{V}_{O_2} = CaO_2 \times Cardiac\ Output \tag{1.3}$$

where CaO_2 is O_2 content per ml of blood and is defined by,

$$CaO_2 = Haemoglobin \times 1.34 \times SaO_2 \tag{1.4}$$

and cardiac output, the primary cardiac factor that influences $\dot{V}_{O_2}$, is:

$$Cardiac\ Output = Stroke\ Volume \times Heart\ Rate \tag{1.5}$$

Stroke volume is in turn influenced by ventricular function and end-diastolic volumes. The heart rate response to exercise is discussed in section 1.6.8 on p23.

Pulmonary gas exchange plays an important role in the oxygenation of blood and removal of CO_2 and is influenced by numerous factors, the detailed discussion of which is beyond the scope of this chapter. However, ventilation, pulmonary blood flow, gas-exchange across the alveolar membrane and ventilation-perfusion mismatches (V/Q mismatch) all play an important role in determining the response of the lungs to exercise.

The quality of the peripheral circulation, both anatomical and its physiologic response to exercise which involves redistribution of blood flow to exercising muscle, has an important role in increasing availability of oxygen. The oxygen carrying capacity of blood determined by haemoglobin concentration, its saturation and the O_2 dissociation curve as well as the ability of tissues to extract and utilise oxygen are equally important factors that influence $\dot{V}_{O_2}$.

1.6.4 Oxygen Pulse, O_2Pulse

Oxygen pulse is defined as the oxygen uptake per heart beat.

$$O_2Pulse = \frac{\dot{V}_{O_2}}{Heart\ rate} \tag{1.6}$$

While some authors have suggested that oxygen pulse may be a surrogate for stroke volume others disagree. The clinical application of oxygen pulse in surgical patients remains unclear.

1.6.5 Respiratory Exchange Ratio, RER

The ratio of $\dot{V}_{CO_2}/\dot{V}_{O_2}$ is called the Respiratory Exchange Ratio. An RER greater that 1.0 may be caused either by lactic acidosis or due to hyperventilation. The RER is also a marker of the fuel being used for metabolism with RER less than 1.0 indicating mixed fuel source in the form of carbohydrate and fat while an RER of 1.0 or greater indicates a primarily carbohydrate source.

1.6.6 Ventilatory Equivalent for O_2 and CO_2, $\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$

The change in $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ during exercise provide valuable information regarding the ventilatory response to exercise. Both $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ tend to decrease initially during exercise. However, as the anaerobic threshold is passed, $\dot{V}_E/\dot{V}_{O_2}$ starts increasing before $\dot{V}_E/\dot{V}_{CO_2}$. This change in direction is yet another method to confirm the anaerobic threshold. $\dot{V}_E/\dot{V}_{CO_2}$ eventually starts increasing as well as respiratory compensation of metabolic acidosis results in increased $\dot{V}_E$.

1.6.7 End-tidal O_2 and CO_2, $P_{ET_{O_2}}$, PET_{CO_2}

PET_{O_2} and PET_{CO_2} are the partial pressures of O_2 and CO_2 at the end of an exhaled breath and are closely related to PaO2 and PaCO2 respectively. PET_{CO_2} is dependent on pulmonary gas-exchange which is in turn influenced by the right ventricular output, pulmonary blood flow and alveolar gas exchange. The changes in $P_{ET_{O_2}}$ and PET_{CO_2} during exercise help identify ventilation-perfusion mismatch as well as hyperventilation.

1.6.8 Heart Rate, HR

The heart rate response during exercise in healthy individuals is a linear function of $\dot{V}_{O_2}$ increasing linearly with increasing work load and increasing $\dot{V}_{O_2}$. The difference between the predicted peak heart rate and the observed peak heart rate is called the Heart Rate Reserve or HRR. Failure to achieve the predicted peak heart rate or a wide HRR may be due to cardiac disease or due to medication used to treat cardiovascular disorders such as beta-blockers or calcium-channel blockers. This information in conjunction with 12-lead ECG evidence of ischaemia provides undeniable evidence of primary cardiac dysfunction.

1.6.9 Breathing frequency, B_f

1.7 Role of CPET in preoperative assessment

1.7.1 General Surgery

1.7.2 Oesophago-gastric Surgery

1.7.3 Colorectal Surgery

1.7.4 Vascular Surgery

1.7.5 Hepato-pancreato-biliary surgery and Transplantation

1.7.6 Thoracic Surgery

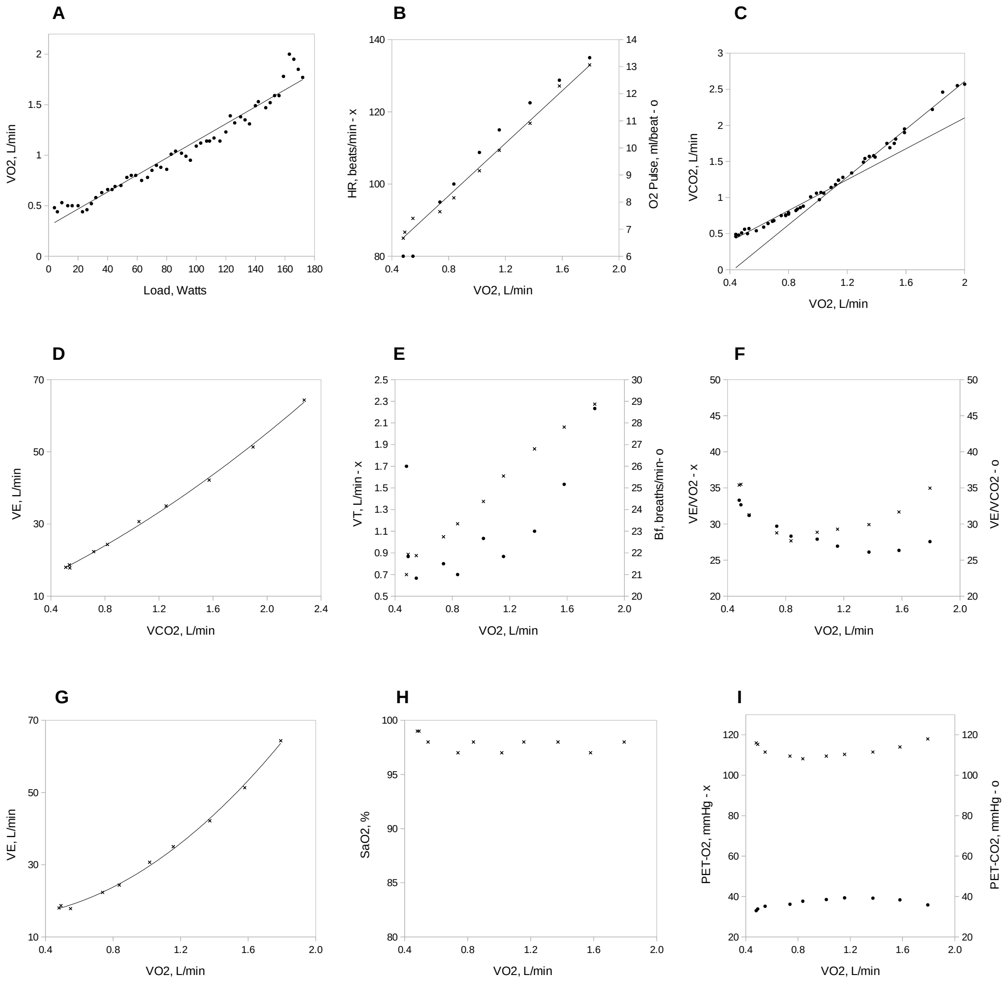


FIGURE 1.1: 9-panel view of trending parameters during incremental cardiopulmonary exercise.

Table 1.4: Parameters measured at spirometry.

Parameter	Units	Description
FVC	litres	Forced Vital Capacity
FEV1	litres	Forced Expiratory Volume in 1 second
FEV1/FVC	%	Tiffeneau-Pinelli[1] index

Table 1.5: Common parameters measured at cardiopulmonary exercise testing.

Parameter	Units	Description
%peakVO2	%	VO2 as a % of predicted VO2Peak
Load	Watts	Exercise Workload
VE	litres/min	Ventilatory Equivalent
Vt	litres	Tidal volume
VO2	litres/min	Absolute Oxygen uptake/consumption
VO2/kg	ml/(kg*min)	Corrected Oxygen uptake/consumption
VE/VO2		Ventilatory Equivalent for O_2
VCO2	litres/min	Carbon-dioxide output
VE/VCO2		Ventilatory Equivalent for CO_2
RER		Respiratory Exchange Ratio
PETO2	mmHg	End Tidal O2
PETCO2	mmHg	End Tidal CO2
O2Pulse	ml/beat	Oxygen pulse
HR	beats/min	Heart Rate
Bf	/min	Breathing Frequency
P(A-a)O2	mmHg	Alveolar-arterial PO2 difference
Vd/Vt		Physiologic dead space-to-tidal volume ratio
SBP	mmHg	Systolic blood pressure
DBP	mmHg	Diastolic blood pressure
O2sat	%	Oxygen saturation

1.8 Systemic inflammation and outcome

The host inflammatory response to cancer, comorbidity and surgical trauma has been known to influence both short-term and long-term outcomes after major cancer surgery. Moreover, postoperative complications have been reported to be associated with poorer oncologic outcomes and cancer-specific survival in patients undergoing potentially curative surgery for cancer. The complex interactions between pro-inflammatory cytokines and anti-inflammatory cytokines at different phases during the perioperative period further impact upon the incidence of complications as well as survival.

1.8.1 Measuring systemic inflammation

Numerous tests are available to not only measure systemic inflammation in general but also to quantify the various components of the inflammatory response. The most commonly employed measures in the clinical setting are the serum levels of C-reactive protein (CRP)and the differential leucocyte count.

One of the earliest reports on the use of CRP to predict cancer-specific survival was by McMillan and co-workers in 1995 when they reported that an elevated CRP 4 months after curative resection for colorectal cancer was associated with earlier recurrence.[McMillan et al. 1995] The modified Glasgow Prognostic Score (mGPS)[Elahi et al. 2004] is based on a combination of C-reactive protein and serum albumin and is outlined in Table 1.6. Since its introduction, mGPS has been validated in over a hundred studies looking at several thousand patients with a wide-range of cancers and an increasing score is associated with poorer long-term survival in patients with operable as well as inoperable cancers.

Table 1.6: The modified Glasgow Prognostic Score

mGPS	CRP (mg/dL)	Albumin (mg/dL)
0	≤ 10	≥ 35
1	> 10	≥ 35
2	> 10	< 35

1.8.2 Systemic inflammation and long-term survival

Systemic inflammation is associated with poorer survival in patients undergoing potentially curative surgery for pancreatic cancer [Jamieson et al. 2005; Clark et al. 2007; Bhatti et al. 2010] as well as in patients with inoperable pancreatic cancer.[Glen et al. 2006] Patients with ductal adenocarcinoma of the head of the pancreas undergoing potentially curative resection survived for a median of 21.5 months if their CRP was $\leq$ 10 mg/dl a month after their surgery but only 8.4 months if their CRP remained persistently elevated at over 10 mg/dl approximately a month after their operation.[Jamieson et al. 2005] Similar findings have been reported in cancers involving other organs using both the mGPS and other scores such as the neutrophil-lymphocyte ratio (NLR). A selection of these studies are presented in Table

1.8.3 Systemic inflammation and postoperative complications

Abnormalities of systemic inflammatory processes present as a continuum that starts in the preoperative phase possibly as a consequence of underlying comorbid illnesses, presence of cancer, or an abnormality of the immune system or a due to a combination of all of these factors. Surgical trauma in such 'primed' patients results in a cascade of events that trigger several inflammatory pathways that have now shown to have a direct impact not only on the incidence of postoperative complications but also on cancer recurrence and long-term survival.

1.8.3.1 Preoperative systemic inflammation

Elevated levels of interleukin-6, alpha-1 antitrypsin and CRP and decreased levels of albumin and prealbumin before surgery have been reported to be associated with a more exaggerated postoperative systemic inflammatory response and infectious complications after major abdominal surgery.[Haupt et al. 1997]

Preoperative systemic inflammation has been reported to be associated with infectious complications in patients undergoing potentially curative surgery for colorectal cancer.[Moyes et al. 2009] In a study of 455 patients, Moyes and coworkers reported that an elevated preoperative modified Glasgow Prognostic Score (1.6) was associated with increased incidence of infectious complications in patients undergoing elective as well emergency colorectal cancer surgery. They postulated that several mechanisms may have a role including disregulation of cell-mediated immunity, impaired T-lymphocyte response, disorders in the complement pathway and possibly due to loss of lean tissue and protein as a consequence of systemic inflammation. Preoperative mGPS has also been shown to predict postoperative morbidity in patients undergoing oesophageal resection for cancer.[Vashist et al. 2010]

1.8.3.2 Postoperative systemic inflammation

An exaggerated and persistent systemic inflammatory response in the early postoperative period is associated with an increased incidence of complications. One of the earliest studies comparing several 'acute-phase proteins' and their role in predicting postoperative complications reported that in patients who developed surgical inflammatory complications, CRP remained elevated after the third postoperative day while other acute-phase proteins such as ceruloplasmin and alpha-1 antitrypsin where not useful in monitoring the postoperative course.[Fischer et al. 1976]

Further studies have established the value of monitoring trends in serum CRP levels in predicting complications after both elective and emergency surgery.[Mustard et al. 1987]

In a study of 383 patients undergoing elective rectal cancer surgery with primary anastomosis, Welsch and co-workers reported that persistently raised CRP level over 140 mg/L after the third/fourth postoperative day was associated with anastomotic leak.[Welsch et al. 2007] They also reported in a separate study of 688 patients undergoing pancreatic resection with pancreaticojejunostomy for neoplastic disease or chronic pancreatitis, that persistently elevated CRP levels greater than 140 mg/L on the fourth postoperative day was associated with increased incidence of complications.

Similar findings have been reported after elective colorectal surgery[Ortega-Deballon et al. 2010; Woeste et al. 2010], oesophago-gastric surgery[Dutta et al. 2011], spinal surgery[Meyer et al. 1995; Mok et al. 2008], neurosurgery[Al-Jabi and El-Shawarby 2010], simultaneous pancreas-kidney transplantation[Wullstein et al. 2004], stem-cell transplantation[McNeer et al. 2010] and paediatric surgery[Laporta Baez et al. 2011].

While CRP level between the third and fifth postoperative day has been reported to be most predictive of complications, the complications themselves do not become clinically apparent until a later in the postperative course, ofter after the fifth post-operative period. This has led some authors to postulate that the elevated CRP levels may in fact be due to an abnormally modulated postoperative inflammatory response resulting in an initial exaggerated systemic inflammatory response syndrome (SIRS) followed by a compensatory anti-inflammatory response syndrome (CARS).

1.8.3.3 Compensatory Anti-inflammatory Response Syndrome (CARS)

The compensatory anti-inflammatory response syndrome is characterised by several features including reduction in lymphocyte numbers by apoptosis, decreased responsiveness of monocytes to cytokines, reduced number of human leukocyte antigen presenting receptors on monocytes, expression of cytokines that suppress Tumour Necrosis Factor (TNF) and clonal anergy.

In their seminal work on the role of SIRS and CARS in the pathogenesis of sepsis and organ dysfunction, Bone and co-workers described a state of 'immunologic dissonance' where a 'pre-primed' immune system may result in an inappropriate, out-of-balance massive pro-inflammatory response which is followed by a proportionately large compensatory anti-inflammatory response that leaves the patient immunosuppressed and prone to further organ dysfunction, infections and death. [Bone, Grodzin, and Balk 1997; Bone 1996] It is very likely that similar mechanisms are involved in surgical patients except that the initial stressor in this case is surgical trauma rather than a bacterial infection as in sepsis.

This form of 'immunoparalysis' was first described in patients after major trauma with tissue damage [Abraham and Chang 1985; Bandyopadhyay et al. 2007] or after haemorrhage on its own without associated tissue trauma. [Stephan et al. 1987] In a detailed review of the mechanisms underlying the compensatory anti-inflammatory response syndrome, Ward and coworkers describe SIRS and CARS to be mirror images suggesting that a disproportionately high SIRS is followed by a period of immunosuppression that leaves the patient prone to further complications.[Ward, Casserly, and Ayala 2008]

Patients who developed infectious complications after major cancer surgery had higher levels of interleukin-10 (IL-10), an anti-inflammatory cytokine and marker of the compensatory anti-inflammatory process.[Mokart et al. 2002] Major surgery and the associated surgical trauma is associated with elevated levels of IL-10 which in turn is associated with increase in lymphocyte apoptosis [Delogu et al. 2001], reduced monocyte expression of HLA-DR antigens [Klava et al. 1997] and a blunted response to endotoxins [Ogata et al. 2000; Kawasaki et al. 2001], all considered to be key features of a compensatory anti-inflammatory response syndrome.

Yamaguchi and co-workers compared the levels of pro- and anti-inflammatory cytokines in patients undergoing cholecystectomy versus patients undergoing trans-thoracic oesophagectomy. They reported that the initial inflammatory phase was followed by an immunosuppressive phase that started around the seventh postoperative day in patients undergoing oesophagectomy. However, patient who underwent underwent an open cholecystectomy did not experience this immunosuppressive phase, leading them to postulate that the degree of immunosuppression was directly proportional to the intial pro-inflammatory process. This in turn was related to the greater degree of surgical stress and tissue trauma that occurs with a trans-thoracic oesophagectomy. They also reported that in a randomised cohort that received an infusion of lymphokine-activated natural killer cells immediately after oesophagectomy, there was a trend towards fewer infectious complications.[Yamaguchi et al. 2006]

1.8.4 Postoperative complications and long-term survival

There has been increasing evidence that postoperative complications not only have an impact on the short-term outcomes but also on long-term survival after major cancer surgery. A recent meta-analysis of 21 studies including 21,902 patients found that anastomotic leakage was associated with earlier local recurrence after rectal cancer surgery, a trend towards early local recurrence in other colonic cancer surgery and a significant reduction in overall survival.[Mirnezami et al. 2011] The reviewers suggested that several mechanisms may be involved in early recurrence including local spillage of cancer cells from within the bowel lumen. However, the role of the local inflammatory processes that occur as a consequence of anastomotic leakage may play a more important role. This inflammatory process with the attendant milieu of pro-inflammatory cytokines and angiogenic factors may provide a fertile ground for tumour seeding and proliferation.

McArdle and co-workers reported in their study of 2235 patients undergoing colorectal cancer surgery that anastomotic leakage was associated with early local recurrence and reduced survival. They suggested that the 'double-hit' of surgery followed by anastomotic leak may result in an inflammatory response that is greater and more protracted and that this may explain the poorer cancer outcomes in these patients.[McArdle, McMillan, and Hole 2005] In a study of 207 patients undergoing surgery for Duke's B colorectal cancer, Katoh and co-workers reported that anastomotic leakage and persistently elevated CRP 2 weeks after surgery were independent risk factors for systemic recurrence, further emphasising the important role of inflammation in cancer recurrence as a consequence of complications.[Katoh et al. 2011] Wound infections and intra-abdominal infections have also been associated with poorer survival in colorectal cancer patients.[Nespoli et al. 2006] Similar findings have been reported after curative surgery for advanced gastric cancer with patients who develop an anastomotic leak surviving for 30.5 months while patients who did not have a leak survived for a median of 96.2 months ($p<0.001$). [Yoo et al. 2011]

Patients who develop severe postoperative complications after pancreaticoduodenectomy for cancer had significantly shortened survival in a study involving 428 patients (16.5 vs. 12.4 months, $p=0.002$) and this was independent of other recognised risk factors such as tumour grade and lymph node status. [Kamphues et al. 2011] Similar finding were reported by Raut and co-workers in their study of 360 patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma [Raut et al. 2007] and by Kang and co-workers in their report on 103 patients undergoing R0 resections for cancer of the pancreatic head. [Kang et al. 2009]

These reports in conjunction with the studies on preoperative inflammation, sepsis, SIRS and CARS emphasise the important role of peri;operative systemic inflammation as a causative factor in postoperative complications and the impact of the 'second-hit' of postoperative complications on long-term survival after curative cancer surgery.

1.8.5 Relationship between systemic inflammation and co-morbidity

1.9 The Jaundiced Patient

Obstructive jaundice is the most common presenting symptom in patients with pancreatic cancer involving the head of the pancreas and the periampullary region due to the anatomical location of the distal bile duct. Obstructive jaundice is known to have a wide range of effects on multiple organ systems including the cardiovascular system, immune system, coagulation cascade, as well as hepatic function.

Until recently, major surgery in the jaundiced patient has been considered to be more prone to adverse postoperative events. While this concept has been recently challenged, surgeons remain wary of the severely jaundiced patient.

Pancreaticoduodenectomy -Whipple was initially described as a two-stage procedure where the first stage involved a biliary bypass aimed at relieving obstructive jaundice before the second stage of resection was carried out.

1.9.1 Impact of jaundice on cardiovascular physiology

1.9.2 Impact of jaundice on renal physiology

1.9.3 Impact of jaundice on the immune system

1.9.4 Jaundice and postoperative outcomes

1.9.5 Role of preoperative biliary drainage

Chapter 2

An investigation into the role of preoperative cardiopulmonary exercise testing in predicting adverse postoperative events after major pancreatic surgery.

2.1 Introduction

Pancreatic cancer is the tenth most common cancer in the UK but the fifth most common cause of cancer death with only 16-17% surviving beyond the first year and 3% surviving beyond 5 years. [CancerResearchUK 2014] The majority of patients (80-85%) with pancreatic cancer present with inoperable disease.[CancerResearchUK 2014; Sener et al. 1999] In patients with resectable disease, surgery [Sener et al. 1999; Sohn et al. 2000; Geer and Brennan 1993] followed by adjuvant chemotherapy[John P Neoptolemos, Stocken, Friess, et al. 2004; J P Neoptolemos et al. 2009] remains the primary modality of cure.

The decision to operate on these patients depends not only on preoperative tumour stage but also on patient factors.[Bilimoria et al. 2007; Sandroussi et al. 2010] Patient factors, in particular those that affect fitness, are also important in determining short term outcome in those that do undergo potentially curative surgery. [Mann et al. 2010; S. C. Mayo et al. 2012] However, major pancreatic surgery is associated with significant morbidity and mortality and patients who have postoperative complications are less likely to get adjuvant therapy.[Teh et al. 2009]

There have been a number of attempts to objectively define patient fitness and its relationship with postoperative outcome. Copeland and co-workers (1991) reported that the Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM) criteria, in particular the POSSUM physiology score (PPS) could be used to quantify the risk of postoperative morbidity and mortality.[Copeland, D. Jones, and Walters 1991] However, the role of POSSUM in predicting postoperative outcome after surgery for pancreatic cancer is not entirely clear.[Castro et al. 2009; Khan et al. 2003; Kocher et al. 2005; W. Pratt et al. 2008; Tamijmarane et al. 2008] The physiological component of POSSUM as well as other similar risk scoring systems such as E-PASS (Estimation of Physiologic Ability and Surgical Stress)[Haga, Ikei, and Ogawa 1999] are calculated based on known comorbidities, clinically evident abnormalities in patient physiology or blood tests.

More recently, there has been some evidence that the presence of an ongoing systemic inflammatory response before surgery is associated with the development of postoperative complications in patients undergoing surgery for colorectal cancer[Moyes et al. 2009], oesophageal cancer[Vashist et al. 2010] as well as pancreatic cancer.[Knight et al. 2010]

Older and co-workers (1993) reported that cardiopulmonary exercise testing (CPET) was an objective evaluation of the response of the cardiovascular and respiratory systems to an increase in oxygen demand during exercise and was useful in predicting perioperative morbidity and mortality in patients undergoing major abdominal surgery.[P Older, Smith, et al. 1993]

The aim of the present study was to evaluate the role of various measures of patient physiological fitness including cardiopulmonary exercise testing in predicting postoperative adverse events as well as fitness for adjuvant therapy in patients undergoing major pancreatic surgery.

2.2 Methods

Patients who underwent pancreaticoduodenectomy or total pancreatectomy for pancreatic head lesions between August 2008, when cardiopulmonary exercise testing was first used for fitness assessment at our hospital, and January 2012 were considered for this retrospective study. Patients who had not undergone cardiopulmonary exercise testing as part of their preoperative assessment and patients who underwent cardiopulmonary exercise testing but did not undergo surgery were excluded.

Data on patient demographics, comorbidity including cardiovascular and respiratory disease, preoperative blood tests, chest x-ray and cardiopulmonary exercise tests were collected from prospectively maintained databases (march 2009 - January 2012) and case note review (August 2008 - March 2009). Data was also collected for patients who did not undergo cardiopulmonary exercise testing to allow comparison with the study group. The POSSUM Physiology Score was calculated based on 11 physiological parameters (cardiac disease including hypertension, ischaemic heart disease and heart failure, respiratory disease causing breathlessness on exertion and COPD, ECG changes, pulse rate, blood pressure, haemoglobin, white cell count, serum sodium, serum potassium, serum urea and Glasgow Coma Scale) as described previously.

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire Health, Longmont, CO 80501, USA). An electrically-braked cycle ergometer was used to perform a symptom-limited, incremental work-load test preceded by a 3-minute rest period. The test was stopped at maximum exercise tolerance, significant ischaemic changes on ECG or for other safety reasons. The VO_2AT was calculated using the V-slope[Beaver, Wasserman, and Whipp 1986; Sue et al. 1988] and ventilatory equivalents[Sue et al. 1988] methods. Low VO_2AT was defined as oxygen consumption less than 10ml/kg/min based on work by Snowden and co-workers[Snowden et al. 2010] who reported that VO_2AT less than 10.1 ml/kg/min was associated with an increase in postoperative complications after major abdominal surgery.

The decision to operate was based on overall preoperative evaluation of the patient's comorbid conditions and performance status and not exclusively on the result of cardiopulmonary exercise testing. Whilst the results of cardiopulmonary exercise tests were available to the clinicians before surgery, no specific changes were made to perioperative management based exclusively on these results. These results were used in conjunction with other established forms of preoperative evaluation for risk assessment and perioperative care. All patients were routinely admitted to the surgical high dependency unit unless intra-operative events or postoperative complications required admission to the intensive care unit. Patients were discharged after resolution of organ dysfunction and/or sepsis and when nutrition, analgesia and mobilisation were adequately established to the clinician's and patient's satisfaction.

Postoperative adverse events were recorded using internationally recognised definitions. The International Study Group for Pancreatic Surgery (ISGPS) definitions were used to classify pancreatic fistulae[Bassi et al. 2005] and post-operative haemorrhage[Wente et al. 2007]. The Clavien-Dindo (CD) classification[P. A. Clavien et al. 2009; Dindo, Demartines, and P.-A. Clavien 2004] was used to grade other complications and CD grades III-V were considered major. Multiple admissions to critical care as well as re-operations were recorded. Operative mortality was defined as postoperative death in-hospital regardless of duration of stay or occurring within 30 days of the surgery. All complications were discussed at a weekly multidisciplinary meeting attended by three pancreatic surgeons and a radiologist with a specialist interest in pancreatic diseases and recorded in a prospective database.

Primary outcome measures were length of stay in hospital, major postoperative adverse events including operative mortality and fitness to undergo adjuvant therapy when indicated. Secondary outcome measures included cumulative length of stay in critical care and number of critical care admissions.

2.2.1 Statistics

Grouping of the variables was carried out using standard or previously published thresholds. In the absence of such thresholds, the variables were treated as continuous variables and analysed using non-parametric statistical methods. Cox proportional hazards regression analysis was used to study the relationship between preoperative risk factors and length of hospital stay. Chi-square test was used to examine the relationship between complications and VO_2AT as a categorical variable. Univariate binary logistic regression analysis with calculation of hazard ratios (HR) and 95% confidence intervals was used to explore the association between perioperative clinico-pathological factors and receipt of adjuvant therapy. Multivariate binary logistic regression analysis was performed on all variables showing a significant association on univariate analysis. Backward stepwise regression was used starting with a saturated model and variables with P-value>0.1 were excluded at each step until no more variables could be excluded. SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

2.3 Results

One hundred and twenty-nine patients had undergone pancreaticoduodenectomy (n=127), sub-total pancreatectomy (n=1) or total pancreatectomy (n=1) during the study period. Sub-total and total pancreatectomy were performed in patients scheduled for a pancreaticoduodenectomy but were found to have pancreatic remnants either too friable or too atrophic during the operation to perform an anastomosis. Of these, 100 patients (pancreaticoduodenectomy - 98, sub-total/total pancreatectomy - 2) had undergone cardiopulmonary exercise testing as part of their preoperative assessment and were included in the study. Pathological examination of the resected specimen showed pancreatic ductal adenocarcinoma (n=37), ampullary adenocarcinoma (n=18), cholangiocarcinoma (n=17), duodenal adenocarcinoma (n=6), intraductal papillary mucinous neoplasia (n=4), neuroendocrine tumours (n=7), other neoplasia (n=4) or chronic pancreatitis (n=2).

Twenty-nine patients did not undergo cardiopulmonary exercise testing due to reasons including subjective assessment of fitness, resource constraints and logistics. Table 2.1 shows the clinico-pathological characteristics of patients included in the study compared to the excluded patients. The median age in the study cohort was higher than in the excluded cohort (66 vs. 54 years, p=0.001). However, there was no difference in gender, body mass index, preoperative biliary drainage, jaundice at the time of surgery, modified Glasgow Prognostic Score, POSSUM physiology score, preoperative blood tests including haemoglobin and liver function tests and length of critical care/hospital stay. The overall postoperative mortality during the study period was 5.4% (7/129) with all deaths occurring in the study cohort (p=0.144).

The median VO_2AT was 10.3 ml/kg/min (inter-quartile range, IQR 8.8 - 11.6). The VO_2AT was less than 10ml/kg/min in 49 patients. The distribution of VO_2AT across the study cohort is shown in Figure 2.1.

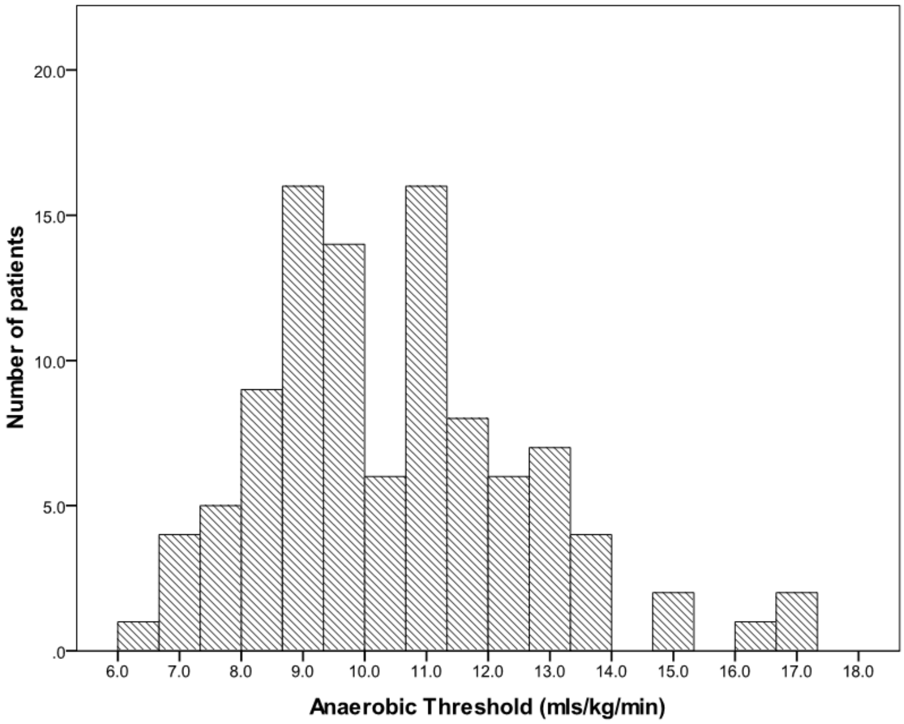


FIGURE 2.1: Distribution of VO_2AT across the study population.

The relationship between VO_2AT and major postoperative adverse events including mortality is shown in Table 2.2. Patients with VO_2AT less than 10ml/kg/min had significantly greater incidence of postoperative pancreatic fistula (35.4% vs.16%, p=0.028) as well as major intra-abdominal abscesses (Clavien-Dindo Grade III - V, 22.4% vs.7.8%, p=0.042). While there was an association between low VO_2AT and grade of pancreatic fistula, this was not statistically significant (p=0.091). There was

Table 2.1: Clinico-pathological characteristics of patients undergoing major pancreatic surgery during the study period.

	All Patients	Excluded	Included	p
n = 129	n = 29	n = 100		
Age (years)				
$\leq$ 65	71 (55%)	24	47	0.001
> 65	58 (45%)	5	53	
Sex				
Male	77 (60%)	17	60	0.894
Female	52 (40%)	12	40	
BMI (kg/sq.m)				
$\leq$ 25	53 (44%)	8	45	0.817
> 25	66 (56%)	11	55	
Preoperative Biliary Drainage				
No	68 (59%)	12	56	0.154
Yes	48 (41%)	4	44	
mGPS				
0	76 (59%)	13	63	0.279
1	11 (9%)	5	6	
2	41 (32.0%)	10	31	
Haemoglobin (g/dl)				
$\geq$ 12	80 (64%)	18	62	0.353
< 12	45 (36%)	7	38	
POSSUM Physiology Score				
11-14	61 (51%)	12	50	0.701
> 14	59 (49%)	10	50	
Serum Bilirubin (micromol/L)				
$\leq$ 35	70 (55%)	12	58	0.156
> 35	58 (45%)	16	42	
Operation Type				
Pancreatico-duodenectomy	127 (98%)	29	98	0.045
(Sub-)Total Pancreatectomy	2 (2%)	0	2	
Operative mortality	7 (5%)	0	7	0.144
Postoperative stay (days)	17 (13-27)	20 (13-30)	17 (13-26)	0.518
Critical care stay (days)	7 (6-12)	7 (6-14)	7 (6-12)	0.448

Values are either median (inter-quartile range) with p statistic using Mann-Whitney test or number of patients (percentage) with p statistic using Chi-square test.

no association between low VO_2AT and cardiopulmonary complications or postoperative mortality. Major cardiopulmonary complications occurred more often in patients with major intra-abdominal adverse events including major intra-abdominal abscesses or Grade B and C pancreatic fistulae or haemorrhage than in patients who did not have these complications (5/31,16.1% vs. 2/69,2.9%, p=0.017). Postoperative mortality was not associated with VO_2AT (HR 0.77, 95% CI 0.16-3.61, p 0.737) or the POSSUM Physiology Score (HR 0.39, 95% CI 0.07-2.12, p 0.277). Postoperative mortality was associated with postoperative pancreatic fistula (n=5), post-pancreatectomy haemorrhage (n=3), major intra-abdominal sepsis (n=6) and major cardiorespiratory complications (n=4) with 6 patients requiring radiological or operative intervention.

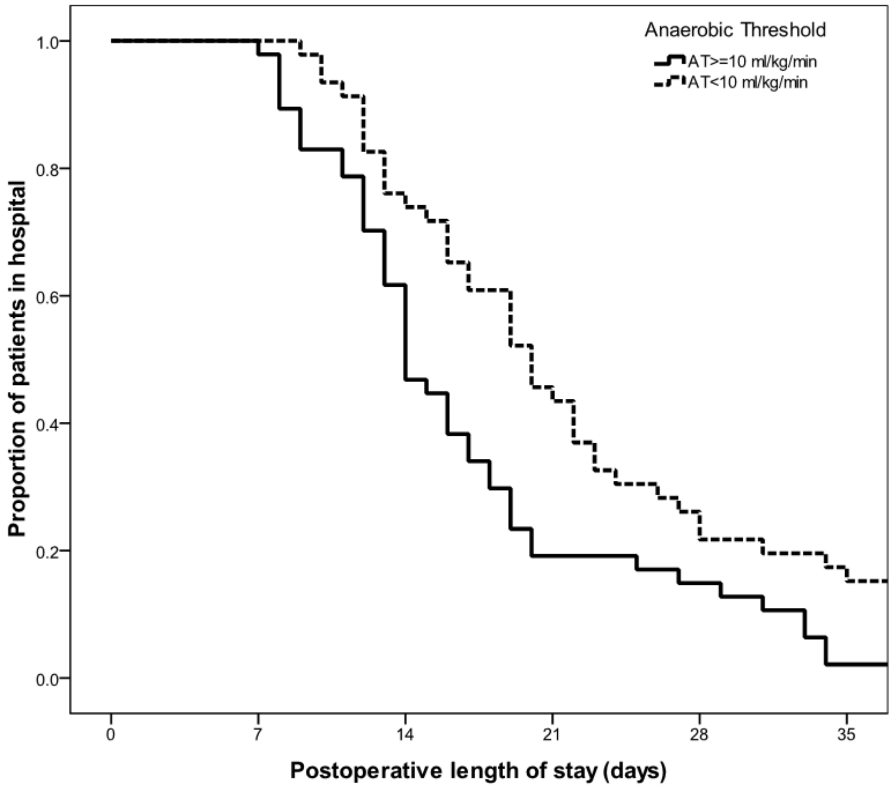
The median length of postoperative stay was 17 days (IQR 13 - 26). The median cumulative length of stay in critical care was 7 days (IQR 6 - 12). Twenty-six patients were admitted to critical care more than once. The relationship between preoperative clinico-pathological characteristics and length of postoperative stay in patients who were discharged from hospital (n=93) is shown in Table 2.3. On univariate analysis, age over 65 years (p=0.072) and low VO_2AT (p=0.010) were associated with prolonged postoperative stay. On multivariate Cox proportional hazards regression analysis, VO_2AT less than 10ml/kg/min (hazard ratio 1.74, 95% confidence intervals 1.14-2.65, p=0.010) was the only significant factor associated with prolonged postoperative stay. A Kaplan-Meier plot for the probability of remaining in hospital over time for patients with low and normal VO_2ATs is shown in Figure 2.2. Patients with a low VO_2AT stayed a median 6 days longer in hospital (14 versus 20 days,

Table 2.2: The relationship between anaerobic threshold and complications in patients undergoing major pancreatic surgery.

Complications		$VO_2AT \geq 10$	$VO_2AT < 10$	
	n	n	n	p*
Cardiac complications				
Grade 0 - II	99	51	48	0.308
Grade III - V	1	0	1	
Respiratory complications				
Grade 0 - II	93	48	45	0.657
Grade III - V	7	3	4	
Intra-abdominal abscess				
Grade 0 - II	85	47	38	0.042
Grade III - V	15	4	11	
Pancreatic Fistula (Total/Sub-total pancreatectomies excluded)				
No	73	42	31	0.028
Yes	25	8	17	
Pancreatic Fistula (ISGPS Classification)				
No	73	42	31	0.091
Grade A	9	3	6	
Grade B	8	1	7	
Grade C	8	4	4	
Post-Pancreatectomy Haemorrhage (ISGPS Classification)				
No	84	41	43	0.207
Grade A	4	2	2	
Grade B	4	2	2	
Grade C	8	6	2	
Admissions to critical care				
1	74	38	36	0.906
>1	26	13	13	
Reoperation				
No	89	47	42	0.306
Yes	11	4	7	
Operative mortality				
No	93	47	46	0.737
Yes	7	4	3	

* Chi-square test

Mann-Whitney Test p=0.001). There was no significant association between any of the preoperative factors including VO_2AT and length of critical care stay or number of critical care admissions.



Number of patients remaining in hospital						
Postoperative Day	0	7	14	21	28	35
AT≥10 ml/kg/min	46	46	22	9	7	1
AT<10 ml/kg/min	45	45	34	20	11	7

FIGURE 2.2: Kaplan-Meier Plot of postoperative length of stay in patients with $VO_2AT >= 10$ml/kg/min versus < 10ml/kg/min.

The relationship between clinico-pathological patient factors and receipt of adjuvant therapy is shown in Table 2.4. Fifty-five patients were included in the analysis. Patients were excluded if chemotherapy was not indicated (n=28), in the event of operative mortality (n=7), if chemotherapy was offered but declined by the patient

Table 2.3: The relationship between clinico-pathological characteristics and postoperative stay in patients (excluding operative mortality) undergoing major pancreatic surgery (n=93): Cox regression analysis

Variable		n	HR	95% CI	P	HR	95% CI	p
Age (years)								
	≤ 65	44						
	> 65	49	1.47	0.97-2.24	0.072	1.48	0.97-2.25	0.068
Sex								
	Male	56						
	Female	37	1.32	0.86-2.03	0.199			
BMI (kg/sq.m)								
	≤ 25	42						
	> 25	51	0.87	0.58-1.32	0.512			
Smoking								
	No	56						
	Yes	37	1.26	0.82-1.94	0.294			
POSSUM Physiology Score								
	≤ 14	45						
	> 14	48	1.28	0.85-1.95	0.24			
Preoperative Biliary Drainage								
	No	53						
	Yes	40	1.08	0.71-1.65	0.724			
Serum Bilirubin (micromol/L)								
	≤ 35	54						
	> 35	39	1.26	0.83-1.92	0.277			
mGPS								
	0	59						
	1	5	1.22	0.78-1.92	0.387			
	2	29	1.87	0.71-4.88	0.204			
Haemoglobin (g/dl)								
	≥ 12	57						
	< 12	36	1.19	0.78-1.81	0.422			
Anaerobic Threshold (ml/kg/min)								
	≥ 10	47						
	< 10	46	1.74	1.14-2.64	0.01	1.74	1.14-2.65	0.01
Anaerobic Threshold (ml/kg/min)								
	≥ 11	33						
	< 11	60	1.44	0.94-2.22	0.097			0.395

(n=4), or where they had not been seen by an oncologist yet (n=6). On binary logistic regression analysis, VO_2AT less than 10ml/kg/min was the only preoperative factor that was associated with with non-receipt of adjuvant therapy (HR 6.30, 95% CI 1.25-31.75, p=0.026).

Table 2.4: The relationship between clinico-pathological characteristics and receipt of adjuvant therapy in patients undergoing major pancreatic surgery (n = 55) - Binary logistic regression

Variable		n = 55	HR	95% CI	P
Age (years)					
	≤ 65	25			
	> 65	30	2.63	0.71-9.74	0.149
Sex					
	Male	31			
	Female	24	2.08	0.61-7.13	0.242
BMI (kg/sq.m)					
	≤ 25	25			
	> 25	30	0.78	0.23-2.64	0.693
Smoking					
	No	35			
	Yes	20	0.96	0.27-3.41	0.953
POSSUM Physiology Score					
	≤ 14	25			
	> 14	30	1.63	0.46-5.73	0.447
Preoperative Biliary Drainage					
	No	27			
	Yes	28	0.95	0.28-3.21	0.937
Serum Bilirubin (micromol/L)					
	≤ 35	27			
	> 35	28	2.08	0.60-7.30	0.251
mGPS					
	0	32			
	1	2	0	0	
	2	21	1.2	0.35-4.15	0.773
Haemoglobin (g/dl)					
	≥ 12	31			
	< 12	24	0.96	0.28-3.26	0.946
Anaerobic Threshold (ml/kg/min)					
	≥ 10	23			
	< 10	32	6.3	1.25-31.75	0.026
Anaerobic Threshold (ml/kg/min)					
	≥ 11	16			
	< 11	39	3.11	0.61-15.88	0.172

2.4 Discussion

The results of the present study show that a low VO_2AT is associated with prolonged postoperative stay in hospital, postoperative pancreatic fistula and intra-abdominal abscesses in patients undergoing major resections for pancreatic head lesions. The results of this study also show that patients with low VO_2AT are less likely to receive adjuvant therapy.

Therefore, it would appear that objective measurement of patient physiological fitness using cardiopulmonary exercise testing is superior to conventional measures of patient fitness including the POSSUM Physiology Score or the modified Glasgow Prognostic Score and may have a role in predicting short-term outcome which in turn affects the overall management of these patients including receipt of adjuvant therapy.

Patients with a low VO_2AT stayed longer in hospital after their operation. While length of stay in hospital is influenced by multiple factors including postoperative complications, it would appear that patients with a low VO_2AT take longer to recover from the physiological stress placed by major pancreatic surgery and its sequelae.

The incidence of pancreatic fistula was greater in patients with a low VO_2AT. This association needs further evaluation taking into consideration other well-recognised risk factors for pancreatic fistula such as pancreatic texture, pancreatic duct size and intra-operative blood loss.[Braga et al. 2011; W. Pratt et al. 2008; Winter, Cameron, Campbell, et al. 2006] It is possible that local or operative factors may be compounded by poor oxygen delivery and organ perfusion as measured by cardiopulmonary exercise testing. There was a non-significant trend towards clinically relevant pancreatic fistulae (ISGPS Grades B and C) as well as a significant association with major intra-abdominal abscesses (Clavien-Dindo Grades 3-5 i.e., requiring intervention, associated with organ dysfunction requiring intensive care or resulting in mortality). This would suggest that complications in patients with low VO_2AT are more likely to be severe than in patients with normal VO_2AT. However, there was no difference in mortality between patients with normal or low VO_2AT, indicating that multiple factors including preoperative patient fitness, local and operative factors, systemic inflammatory response, number of complications as well as perioperative critical care all play a role.

The results of this study also show that patients with a low VO_2AT were less likely to receive adjuvant therapy. Adjuvant therapy in patients undergoing pancreatic resections for cancer has been shown in multiple randomised trials to improve survival significantly.[John P Neoptolemos, Stocken, Friess, et al. 2004; J P Neoptolemos et al. 2009] While postoperative mortality after pancreatic surgery has steadily improved over the years with major improvements in the quality of surgical and critical care over the past decade[Winter, Cameron, Campbell, et al. 2006] even in elderly patients[Makary et al. 2006], postoperative morbidity remains high.[Mann et al. 2010] The results of this study show that poor preoperative fitnees is not only associated with a protracted protracted postoperative course with complications but also with non-receipt of adjuvant therapy.

In the present study, VO_2AT was less than 10ml/kg/min in 49% of patients and less than 11 ml/kg/min in 64% of patients. The proportion of patients with VO_2AT less than 11 ml/kg/min in this study was much greater than reported in studies involving patients undergoing oesophageal surgery (16%),[Forshaw et al. 2008] liver transplantation (39%)[Epstein et al. 2004] or other major abdominal surgery (29%)[P Older, Smith, et al. 1993] and may indicate the poor preoperative fitness levels of patients undergoing major pancreatic surgery at our unit. While several studies have shown that low VO_2AT and/or low VO_2peak are associated with postoperative complications or prolonged hospital stay following major abdominal surgery as well as non-abdominal surgery,[P Older, Smith, et al. 1993; Epstein et al. 2004; McCullough 2006; Nagamatsu et al. 2001; P Older, A Hall, and Hader 1999; Paul Older and Adrian Hall 2004] others have disputed this.[Forshaw et al. 2008; Clayton et al. 2011; Hightower et al. 2010] Older and co-workers reported in 1993 that low VO_2AT less than 11ml/kg/min was associated with a significantly higher risk of postoperative mortality from cardiovascular causes in a series of 187 elderly patients undergoing major abdominal surgery.[P Older, Smith, et al. 1993]

However, Snowden and co-workers[Snowden et al. 2010] reported that patients with an VO_2AT less than 10.1 ml/kg/min had significantly greater cardiopulmonary complications as well as non-cardiopulmonary and infectious complications while Forshaw and co-workers[Forshaw et al. 2008] reported that using a cut-off of 11 ml/kg/min for the VO_2AT did not predict postoperative adverse events less after oesophagectomy. The lack of association between low VO_2AT and cardiopulmonary complications in this study may have been due to two reasons. Major cardiopulmonary complications occurred more often in association with major intra-abdominal adverse events which are determined largely by pancreatic morphology and local anatomy.[Braga et al. 2011] Moreover, the stringent fitness criteria for undergoing pancreaticoduodenectomy may have excluded patients with known co-morbid cardiorespiratory diseases such as severe chronic obstructive pulmonary disease or cardiac failure.

The results of this study are consistent with the results of the study by Ausania and co-workers[Ausania et al. 2012] who reported increased incidence of pancreatic fistula and prolonged postoperative stay in patients with VO_2AT less than 10.1 ml/kg/min. However, this study did not report the association between VO_2AT and receipt of adjuvant therapy.

The physiological demands placed on a patient undergoing major pancreatic surgery are significant, both during and after the operation. It is not entirely surprising therefore, that conventional parameters of patient fitness like the POSSUM Physiology Score or the modified Glasgow Prognostic Score are limited in their ability to distinguish patients based on their performance under physiological stress. Cardiopulmonary exercise testing overcomes this disadvantage by replicating some of the physiological burden major pancreatic surgery places on the functional capacity of the patient's cardiovascular and respiratory systems.

This functional capacity of patients to withstand the physiological burden of major surgery can be improved by the process of 'prehabilitation'.[Topp et al. 2002] It has been suggested that prehabilitation not only improves aerobic capacity[L. W.

Jones et al. 2007] but may also improve postoperative recovery.[N. E. Mayo et al. 2011; Pehlivan et al. 2011] The results of this study show that impaired aerobic capacity is associated with postoperative adverse events. Therefore, it would appear that prehabilitation using interventions such as exercise and nutrition, by improving physiological fitness, may have a role in improving postoperative outcomes after major pancreatic surgery and may improve the proportion of patients receiving adjuvant therapy.

Further work needs to be carried out to study the value of cardiopulmonary exercise testing in predicting postoperative complications in conjunction with previously established factors such as pancreatic morphology and operative factors before it can be used on its own to select or exclude patients for pancreaticoduodenectomy. Cardiopulmonary exercise testing would play an important role not only in identifying patients who will benefit from prehabilitation, but also in the objective measurement of the effects of such interventions on aerobic capacity as well as in identifying high risk patients who may not be able to complete oncological treatment. Prehabilitation and optimised perioperative care may allow a greater proportion of high risk patients to progress to oncological treatment after surgery.

Chapter 3

An investigation into the relationship between obstructive jaundice and preoperative pathophysiology in patients undergoing major pancreatic surgery.

3.1 Introduction

Patients with tumours involving the pancreatic head or the periampullary region often present with inoperable disease. In the minority of patients with operable disease, resectional surgery in the form of a pancreaticoduodenectomy remains the main modality of treatment and only chance of a potential cure. However, major pancreatic surgery is associated with significant morbidity and mortality and is only undertaken in specialist centres. Patient selection, preoperative optimisation, good surgical technique and improvements in postoperative care have all contributed to a reduction in mortality[Winter, Cameron, Campbell, et al. 2006] but morbidity remains high. While several technical strategies have been described in recent years to minimise morbidity, these strategies are not necessarily based on a better understanding of the physiological basis of postoperative complications in these patients.

The anatomical relationship between the distal bile duct, distal pancreatic duct, head of the pancreas and the duodenum is responsible for obstructive jaundice being the most common presenting symptom in patients with tumours affecting this region. Distal bile duct strictures also occur in a small proportion of patients with severe chronic pancreatitis involving the pancreatic head. The perioperative management of the patient with obstructive jaundice is complex and management algorithms are still evolving.

Obstructive jaundice has been reported to be associated with abnormal cardiovascular physiology in several animal and human studies. Surgery in the jaundiced patient has been reported to be associated with adverse postoperative haemodynamic events and renal dysfunction.[Pain, Cahill, and Bailey 1985; Green and Better 1995] The association between jaundice and cardiovascular physiology was reported over a hundred years ago by King and co-workers who found that injection of porcine bile pigment into dogs resulted in bradycardia, hypotension and eventually death.[King and Stewart 1909] Green and co-workers (1986) described the effects of 'cholemia' in dogs that were subjected to choledochocaval anastomosis. The resultant myocardial depression was described by them as the 'jaundiced heart'[Green, Beyar, et al. 1986] and has been reported to be associated with poor myocardial response to inotropic stimulation in dogs[Binah et al. 1985; Bomzon et al. 1986] as well as humans.[Lumlertgul et al. 1991]

Preoperative biliary drainage used to be advocated before subjecting a patient to pancreaticoduodenectomy with the intention of reducing postoperative morbidity. However, several recent studies have reported that routine PBD is associated with increased complication rates as a consequence of the drainage procedure itself as well as increased incidence of postoperative complications. The DROP trial reported that PBD was associated with drainage related complication as well as postoperative infectious complications. However, this trial excluded patients with a bilirubin levels greater than 250 mg/dl from the study.

We have recently reported that poor performance at cardiopulmonary exercise testing (CPET) was associated with adverse outcomes after pancreaticoduodenectomy resulting in an increased incidence of POPF and prolonged hospital stay. However, the effects of 'severe jaundice' where bilirubin levels exceed 250 on preoperative patient physiology have not been studied adequately.

The aim of the present study was to evaluate the relationship between obstructive jaundice and preoperative pathophysiology including cardiopulmonary exercise physiology in patients undergoing pancreaticoduodenectomy.

3.2 Patients and Methods

Patients who underwent classical or pylorus-preserving pancreaticoduodenectomy for periampullary lesions (both benign and malignant) between August 2008 and April 2013 and had undergone cardiopulmonary exercise testing as part of their preoperative workup at the West of Scotland Pancreatic Unit, Glasgow Royal Infirmary, Glasgow were included in the study. Established criteria for resectability in patients with malignant disease were used as outlined in previous published work. Segmental or wedge resection of the portal vein or superior mesenteric vein was carried out if the lesion was otherwise resectable.

3.2.1 Preoperative Data

Patient demographics, preoperative clinico-pathological characteristics including cardiorespiratory comorbidity, results of preoperative blood tests, chest x-ray, ECG and cardiopulmonary exercise tests were collected from prospectively held databases. The POSSUM Physiology Score was calculated based on 11 physiological parameters (cardiac disease, respiratory disease, ECG changes, pulse rate, blood pressure, haemoglobin, white cell count, serum sodium, serum potassium, serum urea and Glasgow Coma Scale) and was used as an objective score of comorbidity. Cardiovascular comorbidity was defined as a score of 2 or more for either the cardiac disease or ECG component of the POSSUM score. Respiratory comorbidity was defined as a score or 2 or more for the respiratory disease component of the POSSUM score.

3.2.2 Obstructive Jaundice

Serum bilirubin levels were measured in all patients on the day before surgery. Obstructive jaundice (OJ) was defined as bilirubin levels greater than 35 micromol/litre and severe obstructive jaundice (sOJ) was defined as bilirubin levels greater than 250 micromol/litre. This threshold was selected because the DROP trial did not investigate patients with bilirubin levels greater than 250 micromol/litre and this study aimed to evaluate preoperative pathophysiology in this particular group.

Data on PBD (PBD) was also recorded. Serum bilirubin levels before and after biliary stenting were recorded [I will expand this section when I get the updated stent data]

3.2.3 Cardiopulmonary Exercise Test

Cardiopulmonary exercise tests were performed in the Department of Respiratory Medicine at the Glasgow Royal Infirmary using the ZAN-600 CPET suite (nSpire Health, Longmont, CO 80501, USA) (9). All patients underwent standard pulmonary function tests and spirometry prior to cardiopulmonary exercise testing. A cycle ergometer was used to perform a symptom-limited, incremental work-load test preceded by a 3-minute rest period. The test was stopped when patients achieved their maximum exercise tolerance, when significant ischaemic changes occurred on ECG or for other safety reasons. Peak oxygen consumption achieved at this stage was defined as VO_2Peak. The VO_2AT was calculated using the V-slope[Beaver, Wasserman, and Whipp 1986; Sue et al. 1988] and ventilatory equivalents[Society and Physicians 2003] methods. VO_2AT less than 10 ml/kg/min was considered to be low based on previous work by us[Chandrabalan et al. 2013] as well as Ausania and co-workers[Ausania et al. 2012] which has shown increased incidence of complications in these patients. Oxygen consumption at peak exercise (VO_2Peak) was dichotomised using a cut-off of 16 ml/kg/min. Detailed description of cardiopulmonary exercise testing as well as the physiological parameters described in this study are published elsewhere.[Balady et al. 2010]

3.2.4 Statistics

Grouping of the variables was carried out using standard or previously published thresholds. In the absence of such thresholds, the variables were treated as continuous variables. Non-parametric tests were used to analyse the association between categorical and continuous variables while Chi-square tests were used to analyse the association between categorical variables. Univariate and multivariate binary logistic regression analysis was used to study the relationship between preoperative patient characteristics and VO_2AT / VO_2Peak. SPSS software (Version 17.0; SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.

3.3 Results

One-hundred and thirty eight patients had undergone pancreaticoduodenectomy (n=138), with preoperative cardiopulmonary exercise testing during the study period. Over half the patients were male (n=93, 67%). Approximately half the number of patients were over the age of 65 (n=68, 49%) and overweight or obese (n=69, 50%). Cardiovascular comorbidity was present in 58 patients (42%) and respiratory comorbidity was present in 12 patients (9%). Fifty patients (36%) had a history of cigarette smoking. The POSSUM Physiology Score was greater than 14 in 61 patients (44%). Obstructive jaundice (serum bilirubin 35 – 250) was present in 32 (23%) patients while severe obstructive jaundice (serum bilirubin ¿ 250) was present in 19 (14%) patients. The baseline demographic and clinical characteristics of non-jaundiced and jaundiced patients are shown in Table 3.1. A larger proportion of jaundiced patients were females compared to the non-jaundiced cohort (p¡0.05) and smokers (p¡0.05). Patients with jaundice were more likely to have an elevated POSSUM Physiology Score (p¡0.005). Patients with cancer were more likely to be jaundiced (p¡0.001). However, there was no statistically significant difference in age, BMI, cardiovascular comorbidity, or respiratory comorbidity between the non-jaundiced and jaundiced patients.

The relationship between obstructive jaundice and preoperative blood tests is shown in Table 3.2. While obstructive jaundice was statistically associated with multiple haematological and biochemical abnormalities, most of these did not appear to be of clinically significance. As expected, obstructive jaundice was associated with

Table 3.1: Association between obstructive jaundice and preoperative patient characteristics in patients undergoing pancreaticoduodenectomy (n=138)

	Preoperative Serum Bilirubin				
	≤ 17	18-35	35-250	> 250	P
Age (≤65/>65)	32/33	13/9	16/16	9/10	0.935
Sex (Male/Female)	48/17	14/8	22/10	9/10	0.028
BMI (Normal/Overweight)	30/35	12/10	20/12	7/12	0.82
Smoking (No / Yes)	48/17	12/10	18/14	10/9	0.038
PPS (≤14/>14)	39/22	16/5	9/23	8/11	0.004
Cardiac disease (No/Yes)	35/28	13/9	17/15	13/6	0.539
Respiratory disease (No/Yes)	57/6	20/2	29/3	18/1	0.664
Bilirary Stent (No/Yes)	29/20	3/12	6/17	18/0	0.201
Cancer (No/Yes)	26/39	3/19	3/29	0/19	<0.001

markedly elevated liver enzymes with severity of derangement associated with severity of jaundice. Obstructive jaundice and sOJ were associated with increasing CRP levels (p¡0.001) and decreasing serum albumin levels (p¡0.001). Obstructive jaundice was not associated with deranged renal function with both urea and creatinine remaining similar across all cohorts (p=0.09 and p=0.22 respectively).

There was no association between obstructive jaundice and preoperative pulmonary function tests (Table 3.3).

3.3.0.1 Univariate analysis of obstructive jaundice versus CPET

The relationship between obstructive jaundice and multiple physiological parameters measured at cardiopulmonary exercise testing is shown in Table 3.4. There was an inverse relationship between oxygen consumption at the anaerobic threshold

TABLE 3.2: Association between obstructive jaundice and preoperative biochemical parameters in patients undergoing pancreatico-duodenectomy (n=138)

	Preoperative Serum Bilirubin				
	≤ 17	18-35	35-250	> 250	P
Hb	13(6.1-16.8)	13.2(10.8-15.8)	11.85(9.2-15.5)	11.7(10.3-13.6)	¡0.001
Hct	0.391(0.201-0.484)	0.397(0.34-0.456)	0.355(0.285-0.449)	0.355(0.294-0.392)	¡0.001
MCV	90.1(72-109.2)	93.85(88.4-102.5)	92.95(80-104.7)	87.85(61-94.7)	0.001
WCC	7.6(4-12.7)	7.55(5-19.3)	8.15(4.6-11.7)	7(3.9-11.1)	0.591
PT	11(10-14)	11(9-14)	11(9-17)	11(10-16)	0.618
Urea	5(3-11.2)	5.2(3-14.4)	5.5(2.3-9.5)	4.5(1.6-8.6)	0.093
Creatinine	71(49-121)	74.5(54-129)	71(42-140)	65(40-129)	0.221
Sodium	138(131-143)	138(131-142)	138(129-142)	135(128-140)	0.001
Potassium	4.1(3.4-5.1)	4.3(3.8-5.5)	4.1(3-4.8)	3.8(2.9-4.3)	¡0.001
Chloride	104(97-110)	104(98-112)	104(92-113)	99(92-107)	0.002
AST	21(8-123)	29(17-120)	68.5(20-374)	92.5(33-420)	¡0.001
ALT	25(6-227)	31(18-239)	86.5(18-671)	95(34-427)	¡0.001
GGT	81(9-3165)	111(10-916)	263(37-1921)	495(51-1881)	¡0.001
ALP	110(47-1438)	150(69-413)	233(97-1517)	372(166-1432)	¡0.001
CRP	3.6(0.3-89)	4.3(0.3-135)	6.85(0.7-94)	13(1.7-51)	¡0.001
Albumin	37(18-46)	36(26-42)	31(19-38)	25(18-33)	¡0.001

Table 3.3: Association between obstructive jaundice and preoperative pulmonary function tests in patients undergoing pancreaticoduodenectomy

	Preoperative Serum Bilirubin				
	≤ 17	18-35	35-250	> 250	P
FVC	4.09 (2.48-6.75)	3.76 (1.5-5.79)	3.76 (2.26-5.96)	3.35 (2.36-5.37)	0.092
FEV1	2.95 (1.14-5.27)	2.90 (1.3-4.77)	2.68 (1.83-3.86)	2.72 (1.31-4.76)	0.556
PREDICTED FEV1 (%)	105.00 (36-153)	98.50 (59-148)	103.00 (79-140)	101.00 (81-137)	0.761
FEV1/FVC	72.00 (29-88)	73.00 (58-86)	75.50 (60-85)	78.00 (55-88)	0.115
PREDICTED FEV1/FVC	94.00 (37-117)	96.00 (73-114)	99.00 (77-111)	102.00 (72-112)	0.107

(VO_2AT) and increasing severity of jaundice (p¡0.05). However, no such linear relationship was noted between any of the other parameters measured both at anaerobic threshold and at peak exercise in spite of apparent statistically significant associations.

3.3.0.2 Association between preoperative clinico-pathological factors and VO_2AT

On multivariate analysis female sex (HR 3.75 CI 1.57-8.95 p¡0.005), high BMI (HR 3.65 CI 1.61-8.26 p¡0.005), presence of cancer (HR 4.02 CI 1.33-12.16 p¡0.05) and raised CRP (HR 2.98 CI 1.29-6.86 p¡0.05) were independently associated with low VO_2AT (¡10mls/kg/min). However, jaundice was not associated with low VO_2AT. These results are shown in Table 3.5

3.3.0.3 Scatter-plot analysis

Scatter-plot analysis comparing serum bilirubin and VO_2AT as continuous variables is depicted in Figure 1. This shows that the relationship between serum bilirubin and AT is weak with an r2 value of only 0.04 (I will have to confirm this but it is not more than 0.1).

Table 3.4: Association between obstructive jaundice and CPET in patients undergoing pancreaticoduodenectomy (n=138)

	Preoperative Serum Bilirubin				
	≤ 17	18-35	35-250	> 250	P
At Anaerobic Threshold					
Load (Watts)	44.34 (0-120)	33.50 (7.33-69)	41.00 (0-68)	38.33 (11-96)	.313
Min Ventilation (VE) (l/min)	25.00 (14-41)	23.04 (13-34.5)	23.00 (14-35)	22.00 (13-39)	.107
Tidal Volume (litres)	1.26 (0.83-2.37)	1.09 (0.59-1.73)	1.06 (0.54-1.76)	1.08 (0.58-2.02)	.017
VO2 (ml/kg/min)	11.20 (6-16.9)	10.65 (7.2-13.3)	10.30 (7.7-16.5)	9.83 (6.7-17.4)	.033
Heart Rate	108.25 (75-149.5)	107.25 (70-139.5)	101.00 (66.5-136)	112.33 (76.67-153)	.393
Respiratory Rate	19.00 (12-36.67)	22.00 (15-31)	21.00 (10.33-32)	19.00 (14.5-26)	.022
At Peak Exercise					
Load	94.00 (48-192)	87.50 (41-134)	73.00 (30-160)	85.00 (38-153)	.150
Minute Ventilation(VE) (l/min)	53.50 (30-125)	46.50 (25-79)	46.00 (22-88)	48.00 (32-100)	.066
Tidal Volume (litres)	1.95 (1.22-3.3)	1.64 (0.82-3.27)	1.62 (1.05-2.82)	1.86 (1.03-2.71)	.088
VO2 (ml/kg/min)	16.60 (10.2-33.2)	14.80 (10.5-24.7)	15.55 (9.6-28.1)	15.20 (9.8-24.8)	.093

Table 3.5: The relationship between clinico-pathological characteristics and low anaerobic threshold (< 10 ml/kg/min) in patients undergoing pancreatic surgery: Univariate and multivariate binary logistic regression analysis

Variable		n (%)	HR	95% CI	P-value	HR	95% CI	P-value
Clinical Characteristics								
Age	≤ 65	70						
	> 65	68	1.19	0.60-2.35	0.628			
Sex	Male	95						
	Female	43	2.74	1.30-5.74	0.008	3.75	1.57-8.95	0.003
BMI	≤ 25	69						
	> 25	69	3.09	1.51-6.32	0.002	3.65	1.61-8.26	0.002
Smoking	No	88						
	Yes	50	1.38	0.68-2.79	0.378			
Cardiovascular disease	No	78						
	Yes	58	0.82	0.41-1.64	0.569			
Respiratory disease	No	124						
	Yes	12	2.37	0.71-7.91	0.159			
Cancer	No	32						
	Yes	106	3.59	1.36-9.43	0.010	4.02	1.33-12.16	0.014
POSSUM Physiology Score	≤ 14	72						
	> 14	61	2.06	1.02-4.17	0.044			0.164
PBD	No	56						
	Yes	49	0.69	0.32-1.50	0.347			
Bilirubin (μmol/L)	≤ 17	65						
	18-35	22	1.49	0.54-4.16	0.444			0.911
	36-250	32	2.30	0.95-5.56	0.064			0.537
	> 250	19	5.66	1.87-17.16	0.002			0.443
Haemoglobin (g/dL)	≥ 12	95						
	< 12	43	2.74	1.30-5.74	0.008			0.214
CRP (mg/dL)	≤ 10	90						
	> 10	46	2.18	1.06-4.51	0.035	2.98	1.29-6.86	0.010
Albumin	≥ 35	65						
	< 35	73	1.53	0.76-3.05	0.231			
Prothrombin Time	≤ 12	117						
	> 12	21	2.38	0.93-6.12	0.071			

3.4 Discussion

The optimal preoperative management of obstructive jaundice, especially with extremely high serum bilirubin levels, in the patient with periampullary cancer requiring pancreaticoduodenectomy is still unclear. The results of the present study also show for the first time that while obstructive jaundice is associated with a range of biochemical and haematological abnormalities, it does not affect cardiopulmonary physiology as measured by cardiopulmonary exercise testing.

The use of CPET in preoperative risk prediction was first made popular over two decades ago by Older and co-workers.[P Older, Smith, et al. 1993] Since then cardiopulmonary exercise testing has been reported to be useful in identifying high risk patients prior to major general[Snowden et al. 2010], pancreatic[Chandrabalan et al. 2013; Ausania et al. 2012], oesophagogastric[Nagamatsu et al. 2001] as well as vascular[J. Carlisle and M Swart 2007] surgery. Cardiopulmonary exercise testing has been reported to be superior to conventional measures of comorbidity chiefly due to the dynamic nature of the test that evaluates the adequacy of oxygen delivery to tissues under physiological stress. However, the factors responsible for poor aerobic capacity in preoperative patients have not been adequately studied.

The association between jaundice and cardiovascular physiology was reported over a hundred years ago by King and co-workers who found that injection of porcine bile pigment into dogs resulted in bradycardia, hypotension and eventually death.[King and Stewart 1909]

Jaundice has been reported to be associated with myocardial depression[Green, Beyar, et al. 1986], poor myocardial response to inotropic stimulation[Lumlertgul et al. 1991], impaired sympathetic baroreflex sensitivity[Song et al. 2009], deranged atrial natriuretic peptide levels[Pereira et al. 1994; Gallardo et al. 1998] as well as multiple other bile-acid receptor mediated effects on the cardiovascular system.[Khurana, Raufman, and Pallone 2011] Moreover, some of these effects appear to be partly reversible by biliary drainage as demonstrated by Padillo and coworkers.[Padillo et al. 2001]

Historically, obstructive jaundice has also been reported to be associated with adverse haemodynamic events in patients undergoing major surgery. Intraopertive blood loss, postoperative hypotension, increased susceptibility to shock and renal dysfunction were all more common in patients with obstructive jaundice. This increased incidence of complications as a consequence of obstructive jaundice resulted in routine PBD being recommended in these patients in order to alleviate their jaundice before undertaking major surgery. In fact, Whipple described his earliest pancreaticoduodenectomy as a two-stage operation, with the first stage aimed at performing a biliary bypass to reduce jaundice levels before undertaking the resection at a later second operation.

However, more recently, there has been increasing evidence that such routine PBD may itself be associated with increased complications both associated with the drainage procedure itself as well as the effects of PBD on surgical outcomes.

Pitt and coworkers in a prospective randomised trial comparing outcomes in jaundiced patients undergoing surgery with or without PBD reported that PBD was associated with increased cost without any decrease in postoperative complications.[Pitt et al. 1985] But, this study looked at a heterogenous group of patients of which only 7 underwent pancreaticoduodenectomy.

A recent meta-analysis[Sewnath et al. 2002] analysed data from 5 randomised controlled trials comparing surgery with PBD versus surgery without PBD and concluded that PBD not only did not improve postoperative complication rates or mortality but resulted in a higher overall complication rate due to the morbidity associated with the procedure itself. All five RCTs included in this meta-analysis included a heterogenous group of operations with only a few undergoing pancreaticoduodenectomy while more than 50% of patients underwent palliative bypass or exploratory laparotomy making comparison of outcomes difficult. A recent Cochrane Collaboration review of six trials including 520 patients concluded that PBD may be associated with serious adverse events and must not be performed routinely outwith trial settings.[Wang et al. 2008]

The DROP trial sought to clarify the role of PBD in patients undergoing pancreaticoduodenectomy.[Gaag et al. 2010] It randomised patients with bilirubin levels between 40 and 250 either to undergo surgery without PBD or to undergo PBD followed by surgery after 4 - 6 weeks. The authors reported that PBD resulted in an increase in incidence of complications of which the majority were related to the drainage procedure itself. However, this trial excluded patients with bilirubin levels over 250.

While the aforementioned studies have undermined the role of PBD in jaundiced patients undergoing pancreaticoduodenectomy, the results of the present study show for the first time that the premise for performing PBD, namely the adverse effect of jaundice on cardiopulmonary physiology may itself be flawed in patients undergoing pancreaticoduodenectomy. In our study, obstructive jaundice including severe obstructive jaundice did not affect cardiopulmonary exercise capacity as measured by VO_2AT or the peak oxygen consumption. These findings taken together with previously published findings of adverse effects of PBD further support the fact that major surgery may be safe in jaundiced patients without subjecting them to pre-operative biliary drainage. The basis of the relationship between low VO_2AT and raised BMI is not clear.

However, such an association has been previously reported.[Horwich et al. 2009] This may reflect the difficulty in obtaining accurate VO_2AT values in obese patients as a result of the calculations involved rather than due to true cardiopulmonary dysfunction. Other authors have suggested that different thresholds for CPET parameters may have to be considered in obese patients to improve risk-prediction.[Donnelly et al. 1990; Hulens et al. 2001] Cardiopulmonary exercise testing measures oxygen delivery to skeletal muscle. Adipose tissue, however, does not contribute to the metabolic activity that is measured during CPET. However, AT as normally reported, is calculated by dividing the oxygen consumption per minute at the 'anaerobic threshold' into the weight of the patient. However, this does not account for the disproportionately higher amount of adipose tissue in overweight/obese patients resulting in a spuriously low AT (in mls/kg/min). The present study found no association between cardiorespiratory comorbidity and VO_2AT. Low VO_2AT in female patients and overweight/obese patients should be interpreted with caution as this may not be due to true poor aerobic capacity.

3.5 Conclusions

Obstructive jaundice, including severe obstructive jaundice (serum bilirubin¿250 mg/dl) does not affect preoperative cardiopulmonary exercise physiology. Reduction of cardiovascular adverse events can no longer be the rationale for preoperative biliary drainage even in patients with severe obstructive jaundice. Future studies must evaluate the safety of elective surgery in patients with severe jaundice and show comparable outcomes to non-jaundiced patients before PBD can be completely abandoned except in special circumstances.

Chapter 4

An investigation into the relationship between cardiopulmonary exercise testing and body composition in patients undergoing major pancreatic surgery.

4.1 Introduction

Major abdominal surgery especially for pancreatic disease is associated with significant morbidity and mortality. Patient selection is as important as identifying surgical treatable pathology in ensuring optimal outcomes. [Balthazar 2002]

4.1.1 Role of preoperative CPET

The role of cardiopulmonary exercise testing in the preoperative evaluation and risk assessment/stratification of patients undergoing major thoracic and abdominal surgery has become well established. A number of studies have shown that poor aerobic fitness demonstrated by a low anaerobic threshold or low peak VO_2 or both as measured at cardiopulmonary exercise testing is associated with increased morbidity and mortality after major surgery including bariartic[McCullough 2006], pancreatic[Chandrabalan et al. 2013; Ausania et al. 2012], liver [Epstein et al. 2004], cardiothoracic[Brunelli 2010; Campione et al. 2010; Torchio et al. 2010] and abdominal aortic aneurysm surgery.[J. Carlisle and M Swart 2007; Thompson et al. 2011] CPET is now routinely used as part of the preoperative processes used to select patients for surgery as well as to help in decision making regarding preoperative care including the need for additional tests, preoperative and intraoperative optimisation, admission to critical care and postoperative care. Patients are sometimes denied surgery if their performance at cardiopulmonary exercise testing is felt to be poor based on currently available evidence.

4.1.2 The pathophysiological basis of CPET

Aerobic fitness, as defined by the ability to perform physical exercise, is dependant on and often limited by the ability of the cardiorespiratory and circulatory systems (henceforth simply the cardiorespiratory system) to supply O2 to skeletal muscles at times of increased demand as well as remove the main end product of aerobic metabolism, namely CO2. Several factors play an important role in this increased response of the cardiorespiratory system. The most important factor is an increase in cardiac output which in healthy adults can increase by upto six-fold during exercise. Aside from increased stroke volume and heart rate, the redistribution of blood volume from the splanchnic circulation increases venous return to the heart. A consequent increase in pulmonary blood flow and skeletal blood flow occurs which in turn is assisted by vasodilation in these circulatory beds.

Oxygenation of the increased pulmonary blood flow and removal of the excess CO2 generated by aerobic exercise is effected by increased minute ventilation as a result of increase in its constituent factors namely respiratory rate and tidal volume. Oxygenation of skeletal muscle is further dependant on numerous other factors including the oxygen carrying capacity of blood (primary determinant being haemoglobin), adequate peripheral circulation and the ability of the mitochondria within the skeletal muscle to utilise the oxygen that is being delivered to them.

It is clear that limitations in the patient's physiology resulting in inadequate or inappropriate response in any of the above mentioned factors will result in overall limitation of their aerobic fitness. Cardiopulmonary exercise testing allows the accurate measurement of most of these factors either directly or indirectly during dynamic exercise thus allowing identifying not only limitations in aerobic fitness but also the cause for such limitation.

4.1.3 Factors influencing aerobic fitness

A low anaerobic threshold and/or low peak VO_2 have universally been attributed to low aerobic fitness due to an inadequate response of the cardiovascular and respiratory systems to increased oxygen demand during exercise. This is often thought to be due to cardiorespiratory disease either overt or subclinical. Occasionally other factors such as anaemia, peripheral vascular disease and rarely mitochondrial diseases have been recognised as factors contributing to low anaerobic threshold/peak VO_2 or abnormalities in other parameters measured at cardiopulmonary exercise testing but this is uncommon in patients undergoing major abdominal surgery.

The most common parameters used to quantify perioperative risk in surgical patients are oxygen consumption at the anaerobic threshold (VO_2AT) and at peak exercise capacity (VO_2Peak). Conventionally these have been reported as per weight ratios in mls/kg/min. However, numerous studies on cardiorespiratory exercise physiology have reported that normalising VO_2 using total body weight leads to spurious correlation errors unfairly penalising obese subjects.[Seltzer 1940; Tanner 1949; Toth et al. 1993; Batterham et al. 1999; Goran et al. 2000; Krachler et al. 2014]

4.1.4 Aims

In chapter 2, we reported that low anaerobic threshold in patients undergoing pancreaticoduodenectomy was associated with an increased incidence of postoperative pancreatic fistula and prolonged hospital stay. We also reported that patients with a VO_2AT less than 10mls/kg/min were less likely to receive postoperative adjuvant chemotherapy as a result of postoperative complications, prolonged hospital stay and likely due to lack of physiological reserve post-surgery to be fit enough to undergo chemotherapy.

However, we noted that high BMI was associated with a low VO_2AT independent of all other clinicopathological characteristics. Moreover, most of our patients did not have overt cardiac or respiratory comorbidity to explain the very low levels of VO_2AT. The aim of the present study was to explore the association between body composition, total body weight and the physiological parameters measured at cardiopulmonary exercise testing.

4.2 Methods

4.2.1 Patients

Patients who underwent major abdominal surgery for malignant or benign disease involving the head of the pancreas and periampullary region at a single institution between August 2008 and October 2010 were included in this study. All data were recorded in a prospectively maintained database. Data was collected on demographics, preoperative clinicopathological characteristics including blood tests, body mass index, weight, height and the underlying surgical pathology. Detailed breath-by-breath data on a variety of physiological and gas-exchange parameters measured at cardiopulmonary exercise testing were also collected from a prospectively maintained database. A detailed description of methodology of cardiopulmonary exercise testing and a description of the measured parameters is provided in CHAPTERX.

4.2.2 Body composition calculation

Preoperative computed tomography that had been performed as part of the routine assessment of these patients was used to calculate body composition. Previously published and well established methods were used were used to calculate body composition information from single CT slices.[Bredella et al. 2010; Shen et al. 2004]

The coronal and saggital reconstructions were used to accurately identify the L3 and L4 vertebrae.The cross-sectional images at these levels where then exported as bitmap images with C40 W350 settings [speak to a radiologist about what these numbers mean]. The scale in millimeters was included with every image. A representative image is shown in Fig. 1.The GNU Image Manipulation Program (GIMP), an advanced, free, open-source, raster graphics editor was used for analysis of all images (www.gimp.org). The use of GIMP to analyse cross-sectional imaging for body composition has been described previously although by using a different technique to what has been employed by us. [Anblagan et al. 2013]

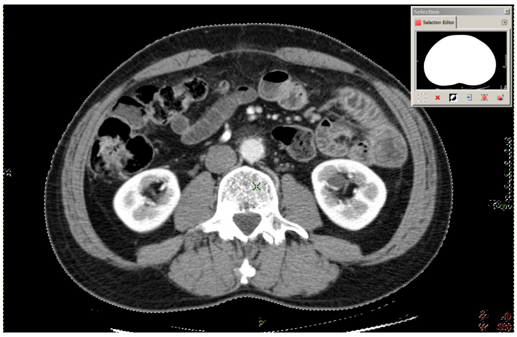
The first step involved converted the bitmap images into JPEG images using lossy compression set at 85% to minimise sharp transitions between grey areas of very similar colour values. This aided easier automatic selection of contiguous areas of similar grey shades.

The next step involved standardising the scale of all images by dividing the length of the scale on every image by the number of pixels along the scale thus providing a length in millimetres for each pixel in each image. As pixels on a CT image are square, the area of each pixel was calculated as a square of its length.

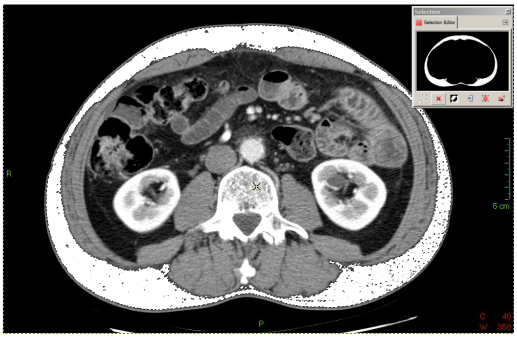
The Fuzzy Select (Magic Wand) tool was used to select contiguous areas of similar colour while simultaneously using visual confirmation that the correct anatomical structures had been selected without overspill into unwanted areas. The number of pixels within the selection was obtained using the 'Histogram' dialog window and entered into an excel spreadsheet against the selected area of interest. The area in mm2 was calculated by multiplying the number of pixels by the area of each pixel.

Body compartment selection methodology:

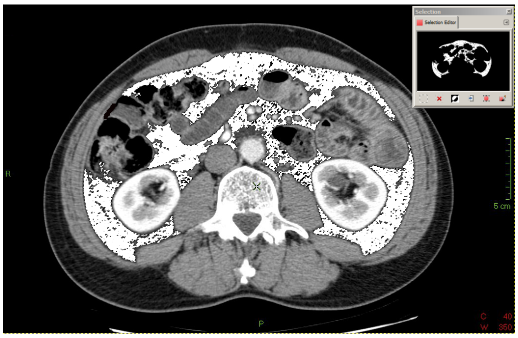
The sequence of steps is depicted in Fig. 4.1 on p 85. The total cross-sectional area of the abdomen at the level of L3/L4 was calculated by first selecting all the empty space outside the image followed by inverting this selection. This is depicted in Fig. 4.1a. Subcutaneous fat in the image was selected using the Fuzzy Select tool (if necessary by choosing multiple times and removing any unnecessary areas) as depicted in Fig. 4.1b. The same process was repeated for visceral adipose tissue and skeletal muscle as depicted in Fig. 4.1c and Fig. 4.1d respectively. Every selection was visually confirmed for anatomical accuracy by using the layer selection tool to inspect the area under selection as shown in the insets in each of the images.



(A) Total Cross-sectional Area



(B) Subcutaneous Adipose Tissue*



(C) Visceral Adipose Tissue*

(D) Skeletal Muscle*

FIGURE 4.1: Selection of components of body composition from CT images using GIMP.
(* The selected area has been removed for representation purposes. The inset confirms the area selected.)

4.2.3 Cardiopulmonary exercise testing

All patients performed cardiopulmonary exercise testing on a cycle ergometer as described in chapterx. Raw data of all breath-by-breath parameters averaged every 10 seconds was collected for analysis. The first three minutes of the recorded data were during the rest period when the patients were on the exercise bike but did not do exercise. The average of each parameter measured between the first and second minute was treated as the rest value. Anaerobic threshold was identified using previously established methods. [Beaver, Wasserman, and Whipp 1986; Sue et al. 1988] Peak exercise was identified by the maximum oxygen consumption recorded towards the end of the exercise period and all other parameters recorded at this point were considered as peak exercise values.

4.2.4 Statistics

All analyses were performed using the SPSS statistical package for Microsoft Windows (version 22). Comparisons between body composition and cardiopulmonary exercise testing parameters were done using the partial correlations controlling for the effect of gender (and/or age). All p-values reported are two-sided. The relationship between body composition and various preoperative clinico-pathological characteristics (in the form of categorical variables) was analysed using the Mann-Whitney U test for variables with two categories and the Kruskal-Wallis Test for variables with more than two categories. Previously established cut-offs were used for categorising continuous variables where applicable. The level of significance was set at $p < 0.05$.

4.3 Results

4.3.1 Body composition and Clinico-pathological characteristics

Eighty-two patients (35 male) were included in the study. The clinico-pathological characteristics of the study patients and their relationship to body composition is shown in Table 4.1 on page 89. There were several significant associations between clinico-pathological variables and body composition as depicted in this table.

4.3.2 Body Composition in Normal BMI vs Overweight/Obese Patients

The body composition differences between patients with a normal BMI and patients who are overweight or obese is shown in Figure 4.2 on page 90. There were significant differences in the proportion of subcutaneous adipose tissue versus visceral adipose tissue between males and females. Men had generally larger cross-sectional area, less SAT but greater VAT and SM areas. However, the proportion of skeletal muscle in both males and females decreased significantly with increasing BMI.

The proportion of skeletal muscle area at L3/L4 decreases from 38% in male patients with normal BMI to 22% in males who are obese. There was a greater decrease in the proportion of skeletal muscle area in females with normal BMI (32%) and obese females (14%). The higher weight in the high BMI patients was due to a

TABLE 4.1: The relationship between body composition and clinico-pathological characteristics of patients undergoing major pancreatic surgery.

			CSA			TAT			SM		
		n	Mean	SD	p	Mean	SD	p	Mean	SD	p
Age	< 65	35	688.6	192.8	0.386	297.0	178.5	0.309	128.7	29.4	0.590
	≥ 65	47	704.3	150.6		322.7	156.6		124.1	31.3	
Gender	M	52	738.4	171.2	<0.001	316.6	170.8	0.665	141.3	26.1	<0.001
	F	30	626.9	141.6		303.0	159.3		99.7	15.6	
BMI	≤ 25	39	579.9	103.6	<0.001	205.9	97.0	<0.001	114.6	26.6	0.002
	25-30	31	754.0	109.4		350.6	99.6		136.0	30.4	
	> 30	12	934.6	145.4		554.6	185.9		137.6	30.9	
SMID	> 3	49	684.4	163.1	0.366	288.7	175.5	0.040	123.2	31.6	0.380
	≤ 3	21	718.5	187.2		365.7	165.0		128.2	31.9	
Pathology	Benign	10	737.9	228.4	0.766	352.8	278.1	0.955	122.4	24.0	0.788
	Malignant	72	692.0	160.3		305.9	145.9		126.6	31.3	
VO_2AT	≥ 10	39	659.8	173.1	0.035	257.2	144.3	0.003	131.5	33.2	0.111
	< 10	43	731.9	159.4		361.0	170.1		121.2	27.1	
VO_2Peak	≥ 16	35	663.8	172.5	0.112	249.3	143.0	0.002	136.9	31.1	<0.001
	< 16	47	722.8	163.6		358.1	167.7		118.0	27.5	
CRP	≤ 10	50	691.4	183.1	0.512	303.7	145.2	0.985	128.7	33.5	0.392
	> 10	32	707.3	146.4		324.0	195.6		122.0	24.7	
Albumin	≥ 35	32	743.8	173.5	0.062	339.4	179.3	0.213	134.5	34.1	0.054
	< 35	50	668.1	160.8		293.8	155.8		120.7	26.7	
Hb	≥ 12	50	698.0	172.4	0.725	292.5	145.4	0.372	133.4	32.1	0.005
	< 12	32	697.1	166.2		341.5	192.2		114.6	23.6	
PPS	≤ 14	41	708.7	169.8	0.444	323.2	155.0	0.347	129.8	34.5	0.351
	> 14	41	686.5	169.5		300.0	177.1		122.4	25.5	
Cardiac	No	43	675.2	185.7	0.109	305.5	195.5	0.208	120.7	33.0	0.047
disease	Yes	39	722.3	146.8		318.4	127.6		132.0	26.4	
Resp.	No	72	704.8	170.8	0.269	319.0	169.3	0.342	125.8	30.5	0.810
disease	Yes	10	646.1	153.2		258.3	133.3		128.0	30.9	

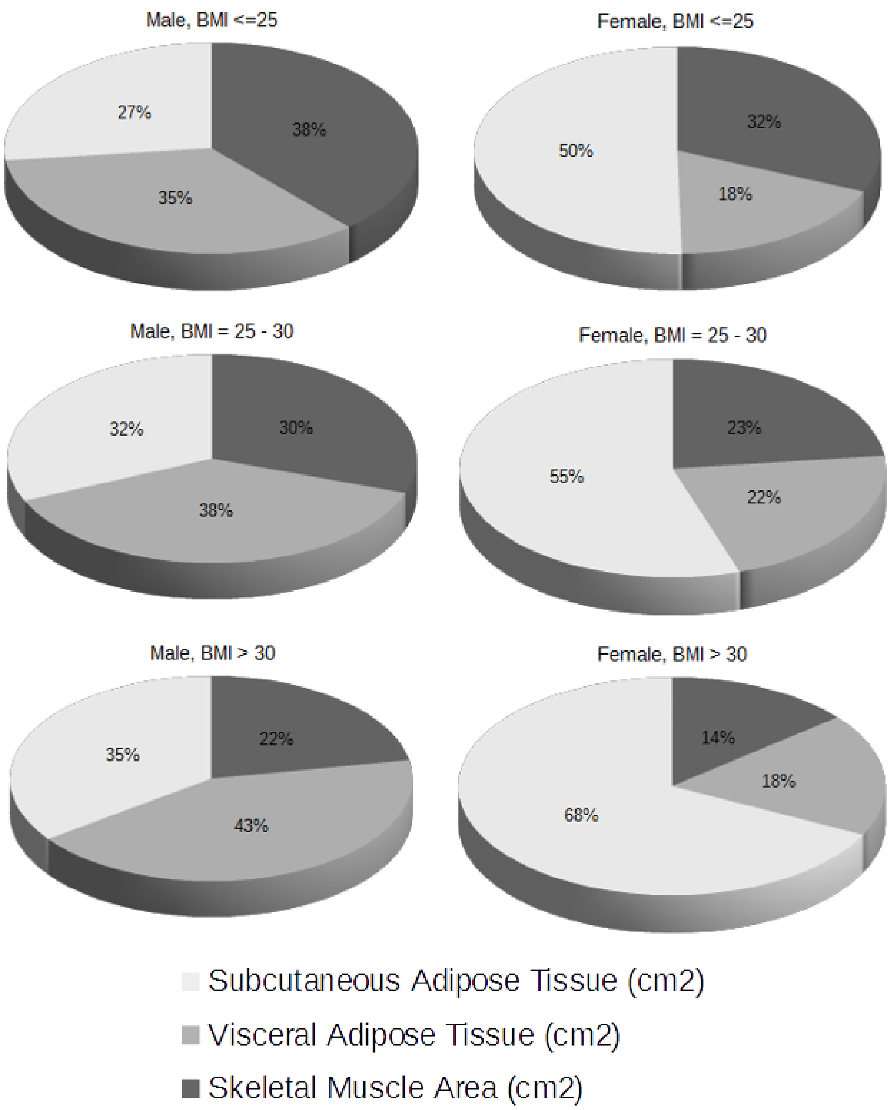


FIGURE 4.2: Differences in body composition according to gender and body mass index.

disproportionate increase in adipose tissue rather than skeletal muscle. Moreover, the distribution of the adipose tissue differed between males and females with visceral adipose tissue contributing more to weight in obese males (43% VAT vs. 35% SAT) while obese females had a greater proportion of subcutaneous adipose tissue than visceral adipose tissue (68% SAT vs. 18% VAT)

4.3.3 Correlation with Pulmonary Function Tests

Partial correlation analysis was performed to study the relationship between pulmonary function tests and body composition. It has been well-established in previous studies that pulmonary function tests are correlated with age and gender and the analysis was therefore adjusted for these two variables. Forced Vital Capacity (FVC, litres), Forced Expiratory Volume in 1 second (FEV1, litres) and the ratio FEV1/FVC (Tiffeneau-Pinelli index,%) were compared against the various components of body composition. Both FVC and FEV1 were positively correlated with skeletal muscle area but not with adipose tissue area or total cross-sectional area. FEV1/FVC was not correlated with any of the body composition components. This would indicate that pulmonary function was dependent on skeletal muscle area while FEV1/FVC, a calculated index to quantify restrictive or obstructive lung disease, was not associated with skeletal muscle area. These results are shown in Table 4.2 on page 92.

4.3.4 Correlation with Exercise Load

Exercise loads achieved at anaerobic threshold and at peak exercise capacity (at volitional stop rather than maximal exercise) were plotted against skeletal muscle area and subcutaneous adipose tissue area measured at L3/L4 to create scatterplots(Fig. 4.3, p93. Exercise load correlated positively with skeletal muscle area both at anaerobic threshold ($r^2 = 0.284, p < 0.001$, Fig. 4.3a) and at peak exercise ($r^2 = 0.350, p < 0.001$, Fig. 4.3b). However, no correlation was identified between

Table 4.2: The relationship between body composition and cardiopulmonary exercise testing controlled for gender.

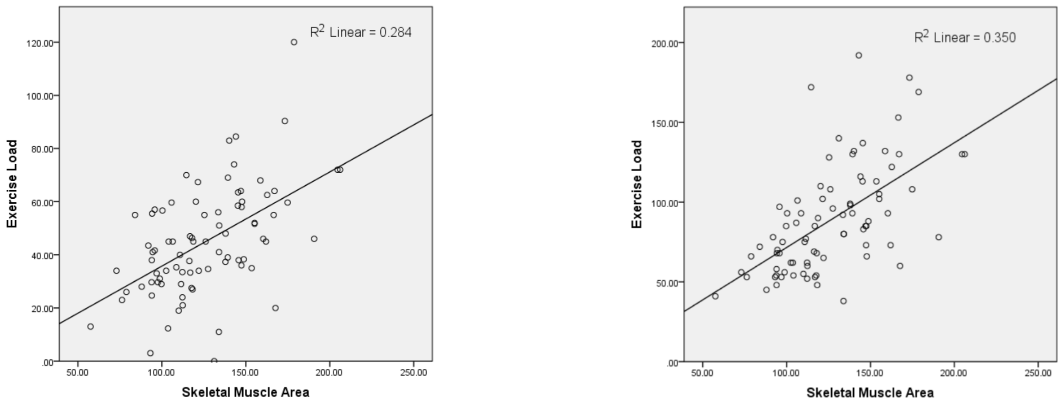
Variable	CSA		TAT		SM	
	ρ	p	ρ	p	ρ	p
Pulmonary Function Tests[a]						
FVC	-0.026	0.823	-0.112	0.325	0.303	0.007
FEV1	0.083	0.468	-0.012	0.919	0.350	0.002
FEV1/FVC	0.096	0.398	0.101	0.374	0.003	978
At Rest[b]						
Minute Ventilation	0.104	0.358	0.116	0.307	0.136	0.230
Tidal Volume	0.234	0.037	0.116	0.305	0.301	0.007
Absolute VO2	0.251	0.025	0.164	0.145	0.353	0.001
Corrected VO2	-0.473	<0.001	-0.482	<0.001	-0.194	0.085
O2 Pulse	0.303	0.006	0.141	0.212	0.192	0.087
At Anaerobic Threshold[b]						
Exercise Load	0.173	0.123	0.105	0.349	0.377	0.001
Minute Ventilation	0.203	0.069	0.198	0.076	0.263	0.018
Tidal Volume	0.259	0.020	0.170	0.128	0.436	<0.001
Absolute VO2	0.340	0.002	0.231	0.038	0.463	<0.001
Corrected VO2	-0.373	0.001	-0.400	<0.001	-0.078	0.487
O2 Pulse	0.432	<0.001	0.242	0.029	0.338	0.002
At Peak Exercise[b]						
Exercise Load	0.113	0.314	0.020	0.859	0.373	0.001
Minute Ventilation	0.139	0.217	0.112	0.321	0.242	0.029
Tidal Volume	0.239	0.032	0.138	0.219	0.409	<0.001
Absolute VO2	0.192	0.086	0.093	0.407	0.375	0.001
Corrected VO2	-0.334	0.002	-0.374	0.001	-0.027	0.813
O2 Pulse	0.377	0.001	0.261	0.019	0.363	0.001

CAT - Cross-sectional area, TAT - Total Adipose Tissue area

SM - Skeletal Muscle area, all in cm^2.

ρ - Pearson's r adjusted for a - gender and sex and b - gender.

exercise loads achieved and subcutaneous adipose tissue area either at anaerobic threshold ($r^2 = 0.004, p = 0.587$) or peak exercise ($r^2 = 0.020, p = 0.206$).



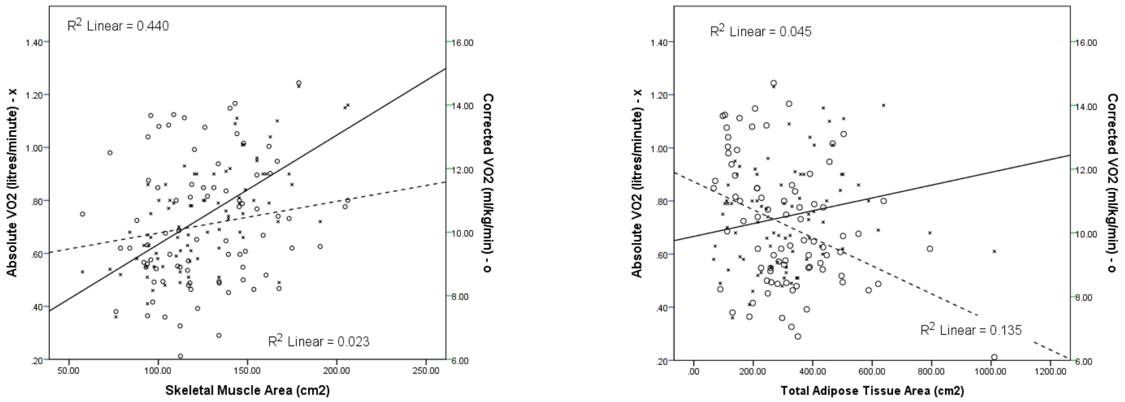
(A) Anaerobic Threshold (B) Peak Exercise

FIGURE 4.3: Correlation between exercise load and skeletal muscle area.

4.3.5 Correlation with Oxygen consumption

The correlations between cardiopulmonary exercise parameters and body composition were adjusted for gender. Our own findings (3) and the findings of other authors suggest that age is not related to VO_2AT or VO_2Peak and therefore no adjustments were made for age. The results of this analysis are shown in Table 4.2 (p92).

Tidal volume (litres) was significantly correlated with skeletal muscle area at all phases of exercise including at rest, anaerobic threshold and peak exercise. There was a statistically significant but weak positive correlation between Minute Ventilation (Tidal Volume x Respiratory Rate) and skeletal muscle at anaerobic threshold and peak exercise but not at rest. There was no correlation between either of these measures of pulmonary function and total adipose tissue area at any phase of exercise.



(A) VO_2AT vs. Skeletal Muscle (B) VO_2AT vs. Total Adipose Tissue

FIGURE 4.4: Correlation between body composition and VO_2AT before and after correction for total body weight.

Absolute oxygen consumption (litres/min) had a strong positive correlation with skeletal muscle area at rest ($\rho = 0.125, p = 0.001$), at anaerobic threshold ($\rho = 0.463, p < 0.001$) and at peak exercise ($\rho = 0.375, p < 0.001$). However, this correlation was lost after correction of oxygen consumption for total body weight and in fact there was a non-significant change in the direction of correlation to the negative.

Absolute oxygen consumption (litres/min) had no correlation with total adipose tissue at rest or at peak exercise and only a weak correlation at anaerobic threshold. However, when it was corrected for total body weight, there was a strong correlation between corrected oxygen consumption (mls/kg/min)and total adipose tissue at rest ($\rho = -0.482, p < 0.001$), anaerobic threshold ($\rho = -0.400, p < 0.001$) and peak exercise ($\rho = -0.374, p = 0.001$).

The loss of the physiological relationship between VO_2 and skeletal muscle after correcting for total body weight is shown in Fig.4.4a and the creation of a spurious relationship with total adipose tissue after correction for total body weight is shown in Fig. 4.4b.

4.4 Discussion

The results of this study show that the most important cardiopulmonary exercise test parameters as used for preoperative risk evaluation in surgery are influenced significantly by the patient's body composition.

4.4.1 Oxygen consumption and body composition

The positive correlation between absolute oxygen consumption and skeletal muscle area is easily explained by the physiology of aerobic exercise. During periods of increased physical activity, the greater oxygen demand is primarily due to increased metabolic activity within the skeletal muscle.

Current convention is to report oxygen consumption measured at cardiopulmonary exercise testing according the following formula:

$$Corrected\ VO_2(mls.kg^{-1}.min^{-1}) = \frac{Absolute\ VO_2\ (litres.min^{-1}) * 1000}{Total\ body\ weight\ (kg)}$$

In a previous analysis (refer to chapter and table), we reported that there was a significant negative correlation between oxygen consumption at anaerobic threshold and the patient's body mass index in spite of no observable cardiopulmonary comorbid disease.

The results of the present study suggest that the negative correlation between corrected VO_2 (mls/kg/min) and BMI is consequent to the reporting convention rather than due to any pathophysiological effect of obesity.

The loss of the strong positive correlation between absolute VO_2 (litres/min) and skeletal muscle area after correcting for body weight further supports the argument that the corrected value under-reports aerobic capacity in obese patients. Moreover, the lack of correlation between pulmonary function tests, tidal volume and minute ventilation and adipose tissue area as well as the slight but statistically significant positive correlation between O2Pulse and adipose tissue area appear to suggest that adiposity did not contribute to poor cardiopulmonary exercise performance in this cohort of patients.

4.4.2 Comparison with previous studies

Our findings are similar to those reported by several authors previously. The relationship between body size, body composition and aerobic capacity both at rest and during exercise has been studied extensively for over a hundred years.

Seltzer reported in his 1940 study of 34 subjects, that the individuals who were more "lateral" than "linear" had lower oxygen intakes per kilo body weight.[Seltzer 1940] Tanner in his article titled *"Fallacy of per-weight and per-surface area standards, and their relation to spurious correlation"*[Tanner 1949] in the Journal of Applied Physiology in 1947 recognised the dangers of expressing physiological variables as a function of total body mass. In a detailed anaysis comparing oxygen consumption and body build, he concludes that *"as the index wt./stature increases, O2/wt. must be expected to decrease purely as a result of the method used for representing the data."*

Batterham et al studied 1314 apparently healthy men employed at the National Aeronautics and Space Administration Johnson Space Center in Houston, Texas.[Batterham et al. 1999] The authors report that as body mass increased, the proportion composed of fat-free mass decreased. They also found that fat-free mass had a linear relationship with oxygen consumption while total body mass did not. They suggest that ideally estimates of fat-free mass should be used in the representation of oxygen consumption to allow more reliable comparison between subjects.

Janz et al studied oxygen consumption and aerobic capacity in adolescents over several years as part of the Muscatine study and reported their findings in 1997[Kathleen F. Janz and Mahoney 1997] and 1998.[KATHLEEN F. Janz et al. 1998] Aerobic capacity in the form of VO_2peak was evaluated annually in 126 children (mean age 10.3 years) for five years. Body composition changes were also tracked over this period. They reported on the changes in body composition that occur over time and the differences in these changes between circum-pubertal boys and girls. They reported on the significant difficulties in normalising VO_2 using total body mass and suggested that fat-free mass was the most appropriate variable for normalising VO_2. They found that VO_2 normalised using total body mass underestimated aerobic fitness levels of heavier boys and girls. However, this underestimation was greater in girls than in boys.

Goran et al reported that total body fat did not affect maximal aerobic capacity.[Goran et al. 2000] They reported on VO_2max in obese women before and after weight loss. VO_2max corrected for total body weight was significantly lower in the obese state while VO_2max corrected for fat-free mass did not change significantly after weight loss. They also reported that the limiting factor in the obese state was not the cardio-respiratory system but the fact that it was more difficult for obese individuals to do the same amount of work as a normal weight person in weight-bearing activities. This is likely due to the extra fat mass in these individuals that did not contribute to aerobic capacity but instead may increase the exercise load.

These findings have been replicated by several other authors in different subject groups.[Loftin et al. 2001; Lemaitre et al. 2006; Savonen et al. 2012; Krachler et al. 2014] Several of the above studies also recommend using allometric scaling to avoid the confounding effects of total body weight. However, this has not gained widespread clinical use.

In a study aimed at determining the optimal method of expressing VO_2max, Maciejczyk and coworkers analysed the differing influence of body fat and lean body mass on aerobic performance in a two groups of physically fit men categorised based on their body fat percentage.[Maciejczyk et al. 2014] They reported that high body mass regardless of composition was correlated negatively with VO_2 when it was corrected for total body weight penalising otherwise fit men purely based on the proportion of body weight that was contributed by body fat. However, when VO_2 was corrected for lean body mass, they found that the results were similar between the low body fat and high fat body groups. They, similar to Goran et al[Goran et al. 2000], recommend that VO_2 be normalised to lean body mass rather than total body weight.

The conclusion from the above studies would be that oxygen consumption normalised for total body weight unfairly penalises obese patients in the absence of true impairment of cardio-respiratory function. This has significant clinical implications as outlined below.

4.4.3 Clinical implications of spurious correlation

Older et al in their pioneering study in 1993 reported that VO_2AT ¡ 11mls/kg/min was associated with increased mortality in elderly patients undergoing major abdominal surgery.[P Older, Smith, et al. 1993] While they did not provide any data on other preoperative or intra-operative factors, they concluded that cardiopulmonary exercise testing was useful in predicting postoperative outcome. However, this first report on the use of cardiopulmonary exercise testing as a preoperative risk assessment tools repeatedly states that a VO_2AT ¡ 11mls/kg/min represented cardiac failure. This association is repeated in their later work on 548 patients which also showed a clear association between VO_2AT ¡ 11mls/kg/min and mortality due to cardiovascular causes. [P Older, A Hall, and Hader 1999] The concepts of *'surgical anaerobic threshold'* and *'postoperative cardiac failure'* were introduced later and were described as the *'inability of the heart to meet the demand of postoperative stress.'*[Society and Physicians 2003]

Swart and Carlisle reported that VO_2AT ¡ 11mls/kg/min in patients undergoing open colorectal surgery was associated with adverse outcomes.[M. Swart and J. B. Carlisle 2012] However, the proportion of females in the low VO_2AT group was significantly greater than that in the normal VO_2AT groups (24% vs 51%). The average VO_2AT in men calculated from the data presented in their paper was 11.02 mls/kg/min while in women it was 9.81 mls/kg/min. In a study by Wilson et al that reported cardiopulmonary exercise testing predicted outcome in major elective intra-abdominal surgery, the proportion of females in the low VO_2AT group was 51% while it was 28% in the group with normal AT.[Wilson et al. 2010] There was no data presented on body mass index in this study.

This is similar to the findings in our cohort of patients. This may have been due to the increased incidence of obesity especially in the subcutaneous plane as we have found in our cohort of patients as shown in Fig. **??**.

It is clear from the review presented in Chapter 1, that cardiopulmonary exercise testing is useful in predicting risk after major surgery. Cardiopulmonary exercise testing has become ubiquitous in the preoperative workup of complex surgical patients. However, the results of the present study suggest that the results especially in the obese, female patient must be interpreted with caution, especially when used to select patients who may be declined surgery based on their cardiopulmonary exercise test results.

4.4.4 Measuring impact of Prehabilitation

Where time to surgery is not critical, prehabilitation has gained an increasingly important role in optimising patients for surgery and mitigating the effects of neoadjuvant oncological therapy. Cardiopulmonary exercise testing has been reported to be a useful objective measure of the impact of prehabilitation in surgical patients.[West et al. 2015]

The design of such prehabilitation programs must not depend solely on body weight adjusted parameters of cardiopulmonary exercise testing when assessing the success of the interventions in these programs. Instead, improvement in the absolute values of VO_2AT and VO_2Peak in conjunction with other parameters that are not affected by body composition such as O2Pulse, tidal volume[L. W. Jones et al. 2007] or maximal exercise load may provide more reliable evidence of improvement in aerobic capacity.

Chapter 5

An investigation into the relationship between cardiopulmonary exercise testing, comorbidity, systemic inflammation and survival after pancreaticoduodenectomy for cancer.

5.1 Introduction

Median survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma varies from approximately 18 months to 24 months.[Winter, Cameron, Campbell, et al. 2006; John P Neoptolemos, Stocken, Bassi, et al. 2010]

Selecting patients who will benefit from the survival advantage that a pancreaticoduodnectomy offers is important to maximise the usefulness of this morbid procedure.

Comorbidity is not only associated with postoperative morbidity and mortality (Section 1.4) but has also been reported to be associated with poor long-term survival in patients undergoing surgery several different cancers including colorectal cancer [] and breast cancer.[] With 10-year survival rates approaching 60% and 80% in these patients, it is not surprising that some patients with significant comorbidity may die from their comorbid disease rather than from cancer recurrence. However, cancer-specific survival is also shorter in patients with significant comorbidities.

Systemic inflammation has been proposed as one of the intermediary mechanism in these patients that increases rates of recurrence and decreases disease free survival. The modified Glasgow Prognostic Score, a measure of preoperative systemic inflammation in cancer patients, is associated with poor survival regardless of the site or stage of cancer. This is discussed in detail in Section 1.8.

However, an objective method to measure comorbidity itself remains elusive and various scores have been used for this purpose. The Charlson Comorbidity Index is one such score and has been reported to predict long-term survival in cancer patients. Cardiopulmonary exercise testing is an objective measure of aerobic fitness and of cardiorespiratory comorbidity and has been shown to be useful in predicting complications after major abdominal surgery including pancreatic surgery. ([Ausania et al. 2012] and Chapter 2)

Moreover, cardiopulmonary exercise testing has been used to predict medium term survival after aortic aneurysm surgery [J. Carlisle and M Swart 2007] as well as overall survival in patients with medical diseases such as chronic heart failure or chronic obstructive airways disease. The relationship between cardiopulmonary exercise testing and long-term survival in patients undergoing pancreaticoduodenectomy for cancer has not been reported before.

5.2 Aim

The aim of the present study was to investigate the relationship between cardiopulmonary exercise testing, comorbidity, systemic inflammation and survival in patients undergoing pancreaticoduodenectomy for pancreatic ductal adenocarcinoma.

5.3 Patients and Methods

All patients who underwent pancreaticoduodenectomy for pancreatic ductal adenocarcinoma between August 2008 and July 2012 were included in the study. Data was collected prospectively in a structured database and included demographics, preoperative clinico-pathological characteristics, cardiopulmonary exercise testing, postoperative complications, tumour characteristics and long-term survival. Survival data was collected using the Greater Glasgow and Clyde NHS Clinical Portal and the Scottish National Statutory Register of Deaths. The modified Glasgow Prognostic Score was calculated as described in Table 1.6 on p28. The POSSUM Physiology Score was calculated as described in **??**.

The Scottish Index of Multiple Deprivation (SMID) combines 38 indicators across 7 domains including income, employment, health, education, skills and training, housing, geographic access and crime. All of Scotland's population is placed into 6505 geographical groups ranked in descending order of deprivation. SMID quintiles place these into 5 categories with 1 representing the most deprived areas and 5 representing the least deprived. The SMID quintile for each patient was derived from the postcode of their primary residence.

5.3.1 Statistics

Standard thresholds were used to categorise continuous variables where applicable. Kaplan-Meir survival analysis and Cox-regression analysis were used to study the relationship between preoperative clinico-pathological characteristics and long-term survival. SPSS version 22 statistical software package was used for all analysis.

5.4 Results

5.5 Discussion

This is considerably less than other common cancers such as colorectal cancer or breast cancer where 5-year survivals across all stages are 60% and 90% respectively. However, only 10-20% of pancreatic cancers are suitable for potentially curative surgery and of patients who undergo curative surgery 5-year survival remains low at approximately 20%.[CancerResearchUK 2014]

Chapter 6

Conclusion

This is the easy bit

Appendix A

Breath-by-breath CPET sample data

FIGURE A.1: Breath-by-breath sample data with values averaged every 10 seconds - Part 1.

Time min:sec	%peakVO$_2$	Load W	VE l/min	Vt l	VO$_2$ l/min	VO$_2$/kg ml/(kg*min)	VE/VO$_2$ l/l	VCO$_2$ l/min	VE/VCO$_2$ l/l	RER	PET O$_2$ mmHg	PET CO$_2$ mm Hg	O$_2$Puls ml/beat	HR beats/min	Bf 1/min	Vd/Vt %	O2sat %
00:10	20	-	13	0.74	0.39	4.6	31.3	0.38	31.9	0.98	111	34	5	75	18	34	97
00:20	18	-	12	0.71	0.35	4.2	30.6	0.34	31.3	0.98	110	34	5	74	16	33	97
00:30	18	-	12	0.78	0.37	4.4	29.7	0.36	30.7	0.97	109	35	5	73	15	33	97
00:40	20	-	12	0.77	0.36	4.4	30.4	0.36	30.9	0.98	110	35	5	73	16	33	97
00:50	17	-	12	0.82	0.35	4.2	31.8	0.36	31.3	1.02	111	34	5	73	15	33	97
01:00	18	-	12	0.84	0.34	4.1	33.2	0.35	32	1.04	113	34	5	74	14	34	97
01:10	17	-	11	0.73	0.29	3.5	34.9	0.31	33.3	1.05	114	33	4	75	15	35	98
01:20	13	-	12	0.71	0.29	3.5	38.3	0.31	36.2	1.06	117	31	4	75	17	35	98
01:30	25	-	14	1.03	0.34	4.1	39.5	0.38	35.9	1.1	119	30	5	73	14	33	98
01:40	12	-	14	1.2	0.36	4.3	36.2	0.4	31.9	1.14	119	31	5	74	11	27	98
01:50	15	-	10	0.95	0.28	3.3	35.7	0.31	31.3	1.14	117	33	4	76	11	30	98
02:00	16	-	10	0.81	0.25	3	37.6	0.28	33.4	1.12	117	33	3	76	13	34	98
02:10	9	-	11	0.76	0.29	3.4	35.6	0.31	32.9	1.08	115	33	4	76	15	34	98
02:20	15	-	12	0.57	0.28	3.4	38.5	0.29	36.9	1.04	116	32	4	78	21	38	97
02:30	22	-	15	0.6	0.41	4.9	33.8	0.4	34.5	0.98	113	33	5	84	25	36	97
02:40	28	-	20	0.75	0.55	6.5	33.1	0.55	32.9	1.01	114	34	6	86	26	34	97
02:50	25	-	19	0.73	0.5	5.9	35.9	0.53	33.7	1.06	117	33	6	88	26	35	97
03:00	27	-	20	1	0.51	6	36.7	0.56	33.2	1.11	117	33	6	87	20	34	98
03:10	22	-	18	0.87	0.43	5.2	38.3	0.49	33.9	1.13	117	33	5	86	21	36	98
03:20	24	-	18	0.82	0.47	5.6	35.1	0.51	32.1	1.09	116	34	5	86	22	34	98
03:30	24	-	17	0.95	0.49	5.8	33.6	0.53	30.6	1.1	115	35	6	87	18	32	98
03:40	27	-	18	0.95	0.49	5.8	34.1	0.53	31.1	1.1	115	35	6	86	19	33	98
03:50	25	-	17	0.94	0.47	5.7	34.2	0.52	31.4	1.09	115	35	6	86	18	33	98
04:00	21	-	16	0.73	0.42	5	35.4	0.45	33	1.07	116	33	5	85	22	35	98
04:10	25	4	18	0.7	0.48	5.7	35.4	0.51	33.3	1.06	116	33	6	85	26	34	98
04:20	21	6	17	0.68	0.44	5.3	34.9	0.46	33.3	1.05	115	34	5	86	25	36	98
04:30	29	9	19	0.92	0.53	6.4	33.7	0.57	31.6	1.07	114	34	6	86	21	33	98
04:40	25	13	19	0.91	0.5	6	35.3	0.56	31.7	1.11	116	34	6	87	21	33	98
04:50	25	16	19	0.94	0.5	6	35.2	0.56	31.8	1.11	115	34	6	88	21	34	98
05:00	35	20	20	1.17	0.5	5.9	38.5	0.56	34.3	1.12	116	34	6	88	17	37	98
05:10	18	23	18	0.98	0.44	5.2	38.9	0.49	34.6	1.12	116	34	5	88	19	37	98
05:20	24	26	16	0.74	0.46	5.5	33.2	0.48	31.6	1.05	113	35	5	89	22	34	98
05:30	26	29	17	0.73	0.52	6.2	30.3	0.5	31.2	0.97	111	35	6	92	23	34	98
05:40	31	32	17	0.82	0.58	6.9	27.9	0.54	29.8	0.94	109	36	6	92	21	32	98
05:50	31	36	18	1	0.63	7.5	27.5	0.59	29.2	0.94	109	36	7	91	19	30	97
06:00	35	40	21	0.98	0.66	7.9	29.8	0.64	30.8	0.97	111	35	7	91	21	32	97
06:10	33	43	21	0.88	0.66	7.9	30.1	0.64	31.1	0.97	111	35	7	92	24	33	98
06:20	37	45	21	1.05	0.69	8.3	29.3	0.67	30.2	0.97	110	36	8	91	20	33	98
06:30	34	49	21	0.96	0.7	8.4	28.5	0.68	29.6	0.96	109	36	8	92	22	32	98
06:40	41	53	23	1.08	0.78	9.4	27.4	0.75	28.5	0.96	108	37	8	92	21	30	98
06:50	42	56	23	1.07	0.8	9.5	27.8	0.77	28.8	0.96	109	37	9	93	22	31	98
07:00	40	59	25	1.25	0.8	9.6	29.5	0.79	30	0.98	110	36	8	94	20	33	97

Figure A.2: Breath-by-breath sample data with values averaged every 10 seconds - Part 2.

07:10	39	63	24	1.27	0.75	9	29.9	0.75	29.9	1	110	37	8	94	19	33	97
07:20	40	67	23	0.96	0.78	9.4	28.1	0.76	28.8	0.98	109	37	8	93	24	31	98
07:30	44	70	25	1.11	0.85	10.2	27.5	0.82	28.4	0.97	109	37	9	95	22	31	97
07:40	47	73	25	1.22	0.9	10.8	26.6	0.88	27.4	0.97	108	38	9	97	21	29	97
07:50	46	76	25	1.15	0.88	10.5	27.3	0.86	28	0.97	107	38	9	98	22	32	97
08:00	35	80	24	1.3	0.86	10.3	26.6	0.84	27.4	0.97	106	39	9	100	18	31	97
08:10	56	83	28	1.27	1.01	12	26.4	0.97	27.4	0.97	107	39	10	102	22	30	97
08:20	54	86	31	1.46	1.04	12.5	28.5	1.06	28.1	1.01	109	38	10	103	21	31	97
08:30	52	90	31	1.44	1.02	12.2	28.9	1.07	27.5	1.05	110	39	10	103	22	30	97
08:40	50	93	32	1.58	0.99	11.9	31.4	1.06	29.3	1.07	111	38	10	104	21	33	97
08:50	49	96	30	1.16	0.95	11.4	29.8	1.01	28.2	1.06	111	38	9	105	26	32	98
09:00	56	100	32	1.34	1.09	13	28.2	1.14	26.9	1.05	109	39	10	105	24	30	98
09:10	57	103	33	1.54	1.12	13.3	28.8	1.18	27.2	1.06	110	39	10	107	22	30	97
09:20	63	107	35	1.69	1.14	13.7	29.5	1.24	27.2	1.08	110	39	11	108	21	30	98
09:30	56	109	35	1.5	1.14	13.6	29.7	1.24	27.3	1.09	111	39	11	108	23	30	98
09:40	64	112	36	1.73	1.17	13.9	29.7	1.28	26.9	1.1	111	39	11	110	21	29	98
09:50	55	116	35	1.56	1.14	13.6	29.3	1.24	26.8	1.09	110	40	10	111	22	30	98
10:00	64	120	36	1.64	1.23	14.7	28.7	1.34	26.2	1.09	110	40	11	112	22	29	97
10:10	72	123	43	1.94	1.39	16.5	30.4	1.56	27	1.13	111	39	12	113	22	28	97
10:20	67	126	43	1.65	1.32	15.8	31.4	1.54	26.9	1.17	113	38	12	114	26	28	97
10:30	72	130	42	1.65	1.38	16.5	29.4	1.58	25.7	1.15	112	39	12	116	26	26	98
10:40	68	133	42	1.85	1.35	16.2	30.3	1.57	26.2	1.16	112	39	11	118	23	27	98
10:50	68	136	39	2.08	1.31	15.6	29.3	1.49	25.6	1.14	110	40	11	120	19	26	98
11:00	77	140	44	1.99	1.49	17.8	28.7	1.69	25.3	1.13	111	40	12	120	22	24	98
11:10	79	142	48	1.85	1.53	18.3	30.8	1.81	26	1.18	113	38	13	121	26	25	97
11:20	75	147	47	2.06	1.47	17.6	31	1.75	25.9	1.19	113	39	12	125	23	25	97
11:30	77	150	47	1.96	1.52	18.1	30.2	1.75	26.1	1.15	112	40	12	127	24	26	98
11:40	81	153	51	1.92	1.59	19	31.3	1.9	26.3	1.19	114	38	12	128	27	24	97
11:50	83	156	54	2.02	1.59	18.9	32.9	1.95	26.8	1.23	116	38	12	130	27	24	97
12:00	90	159	61	2.56	1.78	21.2	33.8	2.22	27	1.25	116	37	14	132	24	22	97
12:10	104	163	71	2.65	2	23.8	34.9	2.57	27.1	1.29	119	35	15	134	27	18	97
12:20	98	166	75	2.36	1.95	23.3	37.6	2.55	28.7	1.31	121	34	14	136	32	21	97
12:30	95	169	74	2.13	1.85	22.1	39.3	2.46	29.5	1.33	122	33	13	138	35	23	98
12:40	91	172	73	2.16	1.77	21.2	39.9	2.36	30	1.33	121	34	13	139	34	25	97
12:50	89	-	72	2.15	1.71	20.4	41	2.32	30.1	1.36	122	33	12	140	33	24	98
13:00	81	-	71	2.05	1.58	18.9	43.9	2.23	31.1	1.41	124	32	11	138	35	25	98
13:10	68	-	55	1.91	1.29	15.5	40.9	1.88	28.2	1.45	123	34	10	136	29	20	98
13:20	72	-	56	2.11	1.45	17.3	37.7	2.05	26.6	1.41	122	36	11	130	27	19	98
13:30	65	-	65	1.89	1.28	15.3	49.5	1.97	32.1	1.54	127	31	10	125	34	26	97
13:40	46	-	46	1.69	0.95	11.4	46.6	1.5	29.6	1.57	126	32	8	119	27	23	95
13:50	49	-	50	1.51	0.89	10.6	54.6	1.42	34.1	1.6	128	28	8	117	33	25	96
14:00	36	-	48	1.53	0.74	8.8	63.1	1.24	37.5	1.68	129	29	6	115	32	33	96
14:10	40	-	43	1.22	0.78	9.4	53	1.25	33.3	1.59	127	31	7	110	35	29	97
14:20	39	-	43	1.15	0.77	9.2	52.4	1.18	34.2	1.53	127	30	7	107	37	31	97
14:30	36	-	39	1.14	0.71	8.4	52.6	1.07	34.7	1.52	127	30	7	105	34	31	98
14:40	34	-	39	0.99	0.67	8	54.5	1.02	35.7	1.52	127	29	6	104	39	32	97

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