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

by

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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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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

Nearly there with this one as well.

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. [*Cancer Research UK* n.d.] The majority of patients (80-85%) with pancreatic cancer present with inoperable disease.[*Cancer Research UK* n.d.; 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 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; 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.

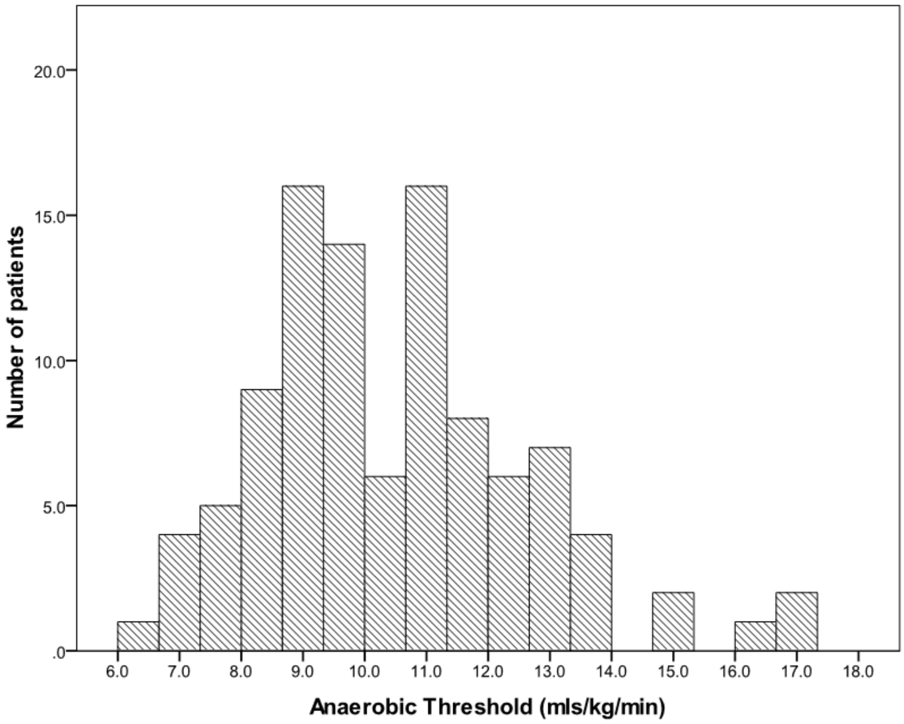


FIGURE 2.1: Distribution of VO_2AT across the study population.

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)				
≤ 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)				
≤ 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)				
≥ 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)				
≤ 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.

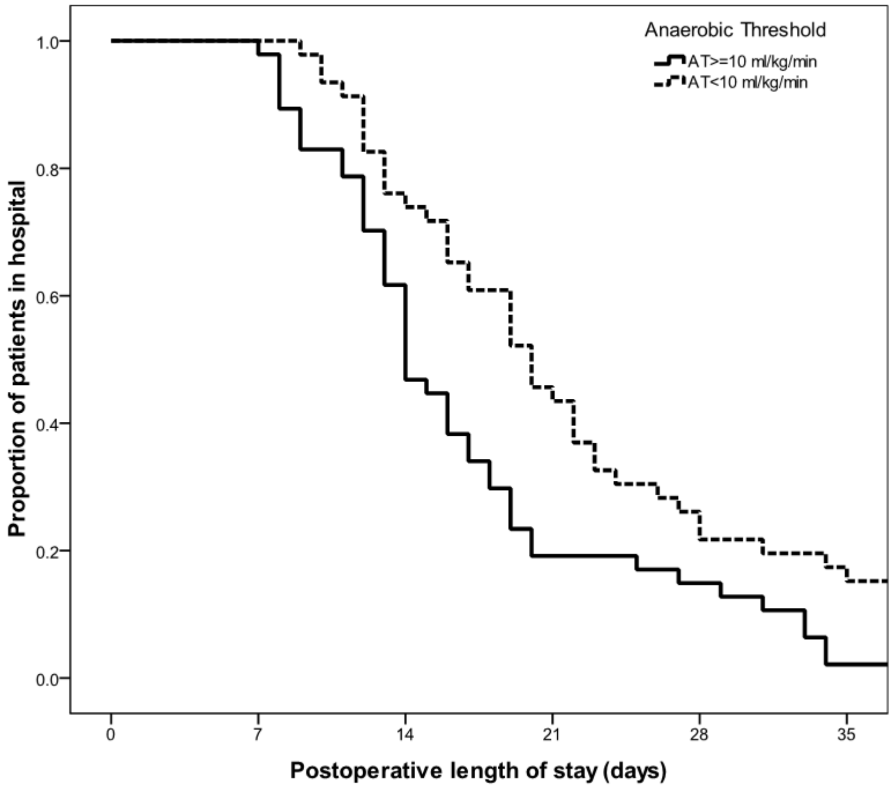
The median length of postoperative stay was 17 days (IQR 13 - 26). The median cumulative length of stay in critical care was 7 days (IQR 6 - 12). Twenty-six patients were admitted to critical care more than once. The relationship between preoperative clinico-pathological characteristics and length of 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 $VO_2AT >= 10ml/kg/min$ 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; Pratt et al. 2008; Winter 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 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 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 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 pre-operative 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 preoperative 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.

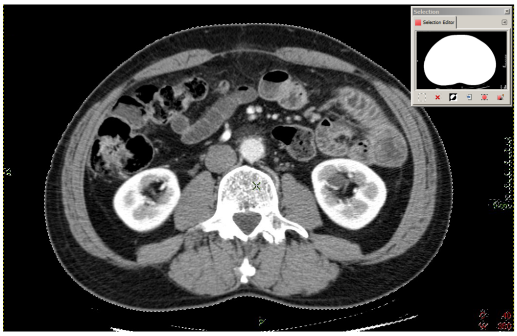
The Fuzzy Select (Magic Wand) tool was used to select contiguous areas of similar colour while simultaneously using visual confirmation that the correct anatomical structures had been selected without overspill into unwanted areas. The number of pixels within the selection was obtained using the 'Histogram' 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:

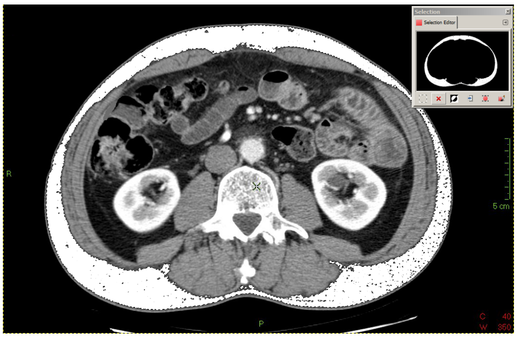
The sequence of steps is depicted in Fig. 4.1 on p 53. The total cross-sectional area of the abdomen at the level of L3/L4 was calculated by first selecting all the empty space outside the image followed by inverting this selection. This is depicted in Fig. 4.1a. Subcutaneous fat in the image was selected 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.

4.2.3 Cardiopulmonary exercise testing

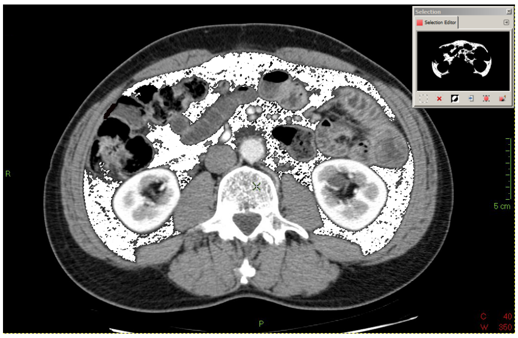
All patients performed cardiopulmonary exercise testing on a cycle ergometer as described in chapterx. Raw data of all breath-by-breath parameters averaged every 10 seconds was collected for analysis. The first three minutes of the recorded data were during the rest period when the patients were on the 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.



(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.)

4.2.4 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 56. 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 57. 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	

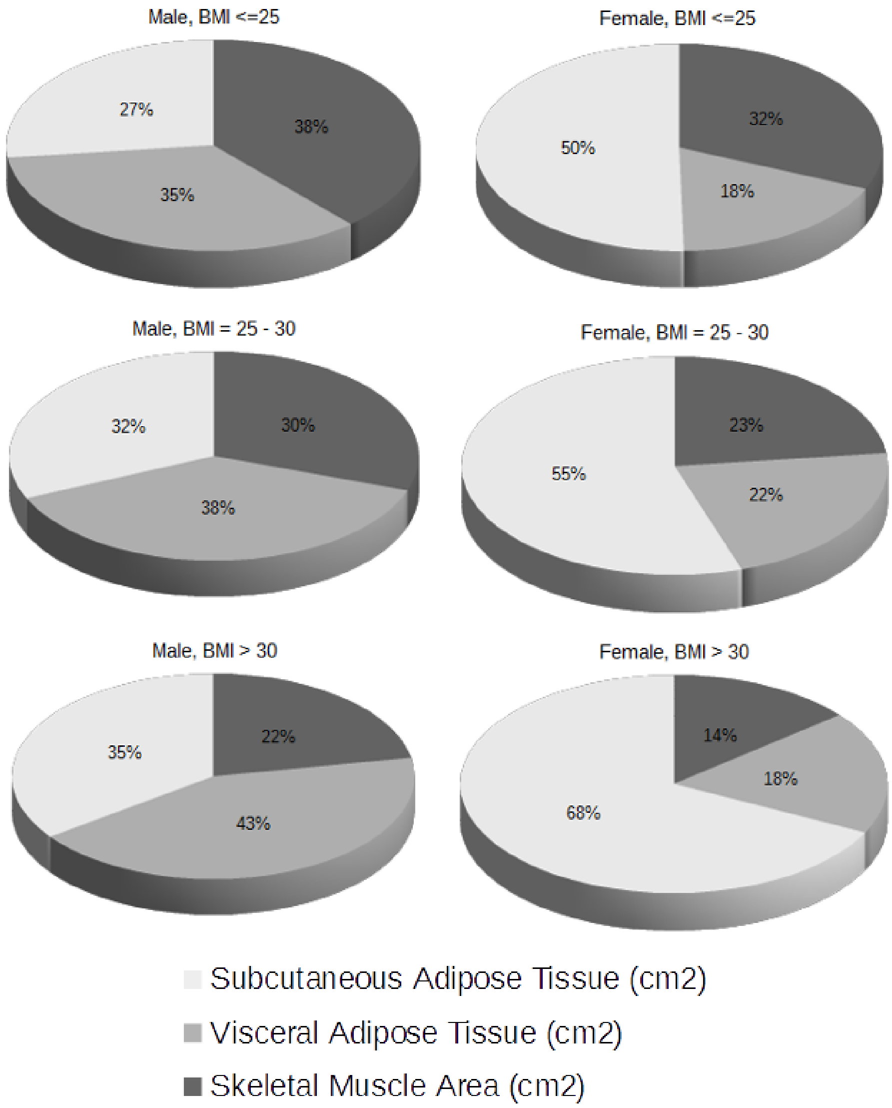


Figure 4.2: Differences in body composition according to gender and body mass index.

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 59.

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, p60. 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.

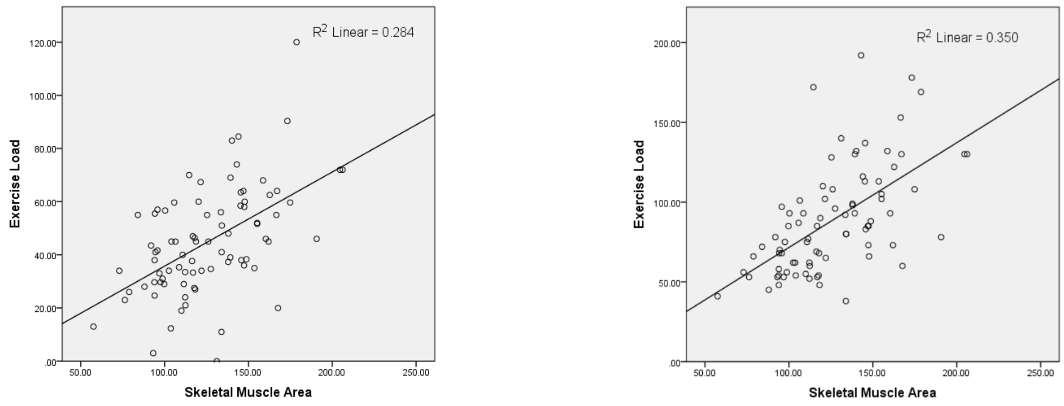
	CSA		TAT		SM	
Variable	ρ	p	ρ	p	ρ	p
Pulmonary Function Tests[a]						
FVC	-0.026	0.823	-0.112	0.325	0.303	0.007
FEV1	0.083	0.468	-0.012	0.919	0.350	0.002
FEV1/FVC	0.096	0.398	0.101	0.374	0.003	978
At Rest[b]						
Minute Ventilation	0.104	0.358	0.116	0.307	0.136	0.230
Tidal Volume	0.234	0.037	0.116	0.305	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 ($r^2 = 0.020, p = 0.206$).



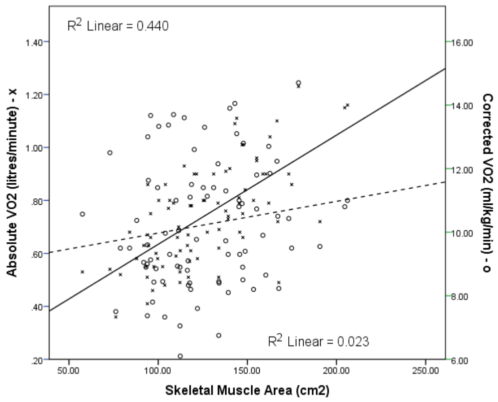
(A) Anaerobic Threshold (B) Peak Exercise

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

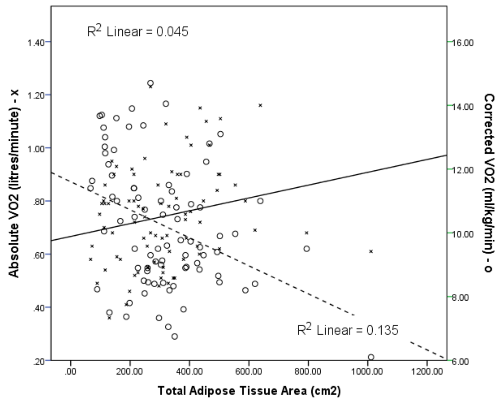
4.3.5 Correlation with Oxygen consumption

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 (p59).

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, postoperative adverse events and survival after pancreaticoduodenectomy for cancer.

Nearly there with this one as well - as soon as I have updated the survival data

Chapter 6

Conclusion

This is the easy bit

Bibliography

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