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

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.

Most pancreatic neoplasia 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 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; 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.

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.

1.3 Adjuvant and Neoadjuvant treatment

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 p37.

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:

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

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.

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 p24.

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

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.

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 syn-drome (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 respon-siveness 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 sep-sis 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 transthoracic 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.

1.9 The Jaundiced Patient

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

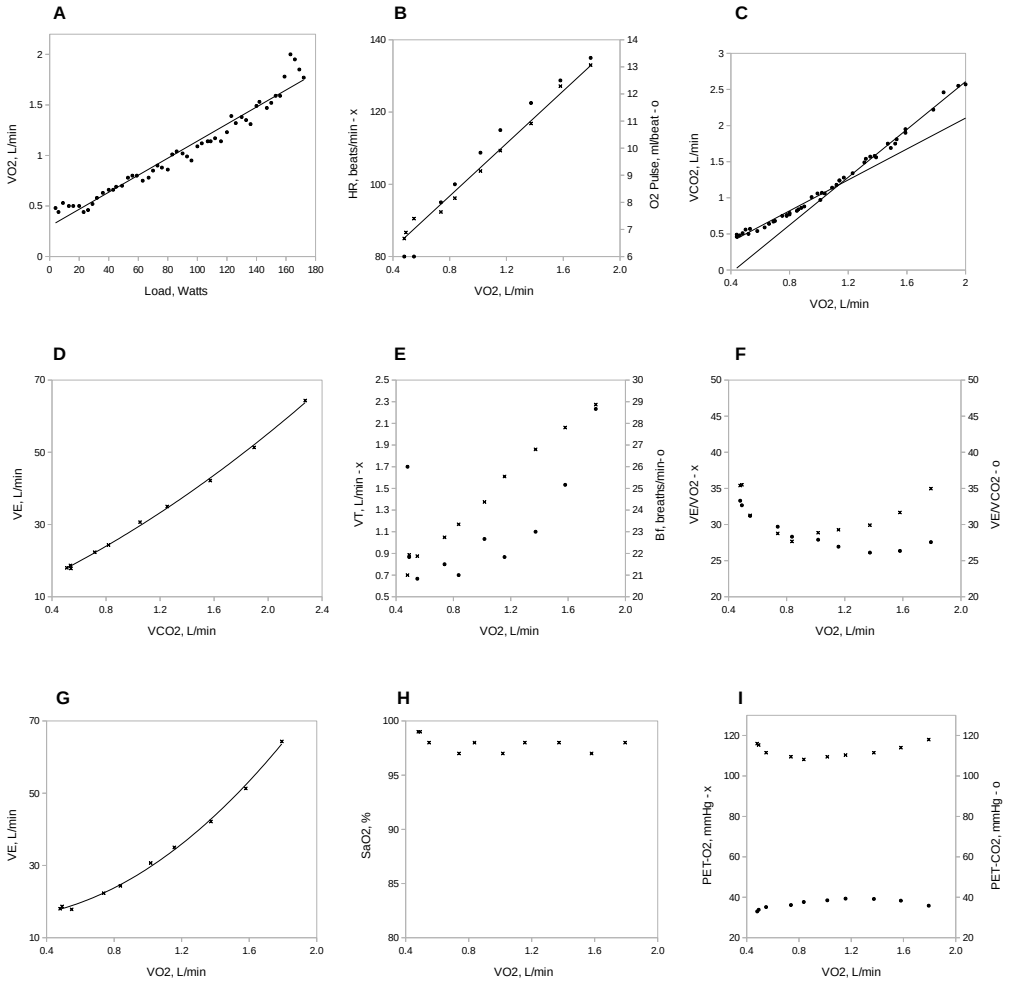

FIGURE 1.1: 9-panel view of trending parameters during incremental cardiopulmonary exercise.

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

Table 1.6: The modified Glasgow Prognostic Score

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

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