Cardiopulmonary exercise testing for high-risk South African surgical patients

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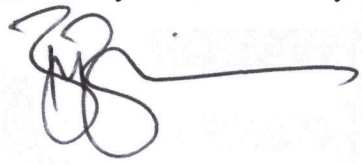
Declaration

This is my original, unaided work. This work has not been previously submitted to this or any other University.



Bruce M Biccard

Dedication

To my wife, Penny who has always given me the freedom and time to follow my thought.

Without her support, work of this nature would not be possible.

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Abstract

Aim: To determine the prognostic value of cardiopulmonary exercise testing (CPET) for major vascular surgery in South African patients.

Methods: CPET has been used in Durban since October 2004 to predict cardiac risk for high-risk patients undergoing major vascular surgery. A submaximal 'anaerobic threshold' (AT) test was conducted on all high-risk patients. Patients were classified into two groups: 'low AT' where the oxygen consumption at the AT was $<11 ml.kg^{-1}.min^{-1}$ for cycling or $< 9 ml.kg^{-1}.min^{-1}$ for arm cranking and 'high AT' when the patient surpassed these targets. Analysis of all in-hospital deaths following surgery was conducted by two independent assessors blinded to the CPET test result. Deaths classified as primarily 'cardiac in origin' have been used in this retrospective cohort analysis.

Results: The AT measured during CPET was not a statistically significant pre-operative prognostic marker of cardiac mortality. However, the survivors of the patients with a 'low AT' may be identified by their response to increasing metabolic demand between 5 and 7 $ml.kg^{-1}.min^{-1}$. Survivors were more dependent on increasing heart rate, while non-survivors were more dependent on oxygen extraction. When this information is added to the AT, CPET was the only test statistically associated with cardiac mortality, in comparison to Lee's Revised Cardiac Risk Index and the resting left ventricular ejection fraction which were not statistically associated with cardiac death. A hundred percent of patients with a positive test died of cardiac causes, while 11% of the patients with a negative test had cardiac deaths. The risk ratio associated with cardiac death following a positive test was 8.00 [95% CI 3.8-16.9]. The sensitivity was 0.25 [95% CI 0.04-0.64], the specificity was 1.00 [95% CI 0.90-1.00], the positive predictive value was 1.00 [95% CI 0.20-0.95] and the negative predictive value was 0.88 [95% CI 0.74-0.95].

Conclusions: CPET provides valuable prognostic information in our surgical population.

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Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
AMI	Acute myocardial infarction
ACC/ AHA	American College of Cardiology/ American Heart Association
AT	Anaerobic threshold
BMI	Body mass index
$CaCO_2$	Oxygen carrying capacity
CI	Confidence interval
CO	Cardiac output
CPET	Cardiopulmonary exercise testing
CVS	Cardiovascular
DO_2	Oxygen delivery
ECG	Electrocardiogaphy
Echo	Echocardiography
EVAR	Endovascular aneurysm repair
FN	False positive
FP	False negative
Hb	Haemoglobin concentration
HIV	Human Immunodeficiency Virus
HR	Heart rate
IALCH	Inkosi Albert Luthuli Central Hospital
LR	Likelihood ratio
NCEPOD	National Confidential Enquiry into Perioperative Deaths
METs	Metabolic equivalents

MI	Myocardial infarction
NPV	Negative predictive value
OR	Odds ratio
$P_{ET}CO_2$	End tidal carbon dioxide concentration
$P_{ET}O_2$	End tidal oxygen concentration)
PPV	Positive predictive value
RCRI	Lee's Revised Cardiac Risk Index
RER	Respiratory exchange ratio
RPM	Revolutions per minute
SaO_2	Haemoglobin oxygen saturation
SD	Standard deviation
SV	Stroke volume
TN	True negative
TP	True positive
VCO_2	Carbon dioxide production
$V\dot{E}$	Minute ventilation
VO_2	Oxygen consumption
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen consumption

Chapter 1

Introduction

Although in the non-surgical population Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) is now probably the leading cause of morbidity and mortality in South Africa (Dougan, 2005, Bradshaw et al., 2005), it has not had the same impact on peri-operative morbidity and mortality in South Africa (Cacala et al., 2006).

Cardiovascular complications are an important cause of morbidity and mortality following major surgery in the developed world (Devereaux et al., 2005c). Major cardiovascular complications following abdominal aortic surgery have an incidence of over 20% (Nishimori et al., 2006). Myocardial infarction within 30 days of elective aortic aneurysm repairs was reported in 7% of the cases in the United Kingdom's recent National Confidential Enquiry into Perioperative Deaths (NCEPOD, 2005). Peri-operative myocardial infarction is associated with an increased risk of in-hospital mortality (Devereaux et al., 2005b) which is borne out in the NCEPOD study where 45% of the patients who sustained a peri-operative myocardial infarct died within 30 days of surgery (NCEPOD, 2005). Peri-operative ischaemia and myocardial infarction (MI) also decrease longterm survival (Devereaux et al., 2005b) and significantly increases consumption of health resources (Devereaux et al., 2005c). It is likely that major cardiovascular complications are the leading cause of peri-operative mortality in South Africa as well, although there is unfortunately no literature to confirm this statement. However, the subsequent discussion will add credence to this statement.

There is no consensus on which special investigation is preferable in pre-operative cardiac risk assessment (Auerbach and Goldman, 2006, Eagle et al., 2002). However, a test of dynamic function is preferable, in comparison to a test of static ventricular function (Kertai et al., 2003). Theoretically, an ideal test would assess both ventricular function and myocardial ischaemia. In addition, an ideal test should allow for risk stratification based on whether limitation is secondary to ventricular function, myocardial ischaemia or both. Cardiopulmonary exercise testing (CPET) has the capacity to separate these physiological determinants of peri-operative outcome (Older et al., 1993, Older et al., 1999). In addition, CPET allows for determination of limited physical performance by analysis of the various physiological markers of oxygen delivery (Wasserman et al., 2005).

The aim of this study was to conduct a retrospective analysis of the use of CPET at Inkosi Albert Luthuli Central Hospital (IALCH) and to compare the prognostic value of CPET with other pre-operative indicators of cardiac mortality.

Chapter 2

Peri-operative cardiac risk

2.1. Determinants of peri-operative cardiovascular risk

2.1.1. Clinical risk indices

The original index of peri-operative cardiovascular risk was described by Goldman (Goldman et al., 1977), with subsequent modification (Detsky et al., 1986). The recent publication of Lee's Revised Cardiac Risk Index (RCRI) (Lee et al., 1999) has been found to be significantly better than previous risk indices at predicting cardiovascular complications (Gilbert et al., 2000) and it has also been validated outside of its derivation population (Boersma et al., 2005). (Table 2.1) The predictive power of Lee's RCRI could be further improved by including age and more specific characteristics of surgical risk (Boersma et al., 2005).

Table 2.1 Cardiovascular outcomes associated with Lee's Revised Cardiac Risk Index

Number of CVS risk factors	Major CVS complications (95% CI) (Lee et al., 1999)	Cardiovascular death (Boersma et al., 2005)
0	0.5 % (0.2-1.1)	
1	1.3 % (0.7-2.1)	0.3 %
2	3.6 % (2.1-5.6)	0.7 %
≥3	9.1 % (5.5-13.8)	1.7 %
4		3.6 %

CVS: (cardiovascular). Clinical risk factors include high-risk surgery, ischaemic heart disease, history of congestive cardiac failure, history of cerebrovascular disease, insulin therapy for diabetes, and a preoperative serum creatinine of >177μmol/L (Lee et al., 1999)

Although, Lee's RCRI and Kertai's revised customised probability index had similar predictive values for the derivation and validation cohorts (Lee et al., 1999, Kertai et al., 2005), this is not surprising as the populations from which these risk indices were derived and then validated were the same. Thus, there is a fundamental flaw in believing that these

clinical risk indices will be of similar prognostic value in South Africa, as these risk indices were derived and/or validated in North American and European patients. For these risk indices to be applicable in South Africa they would have to fulfil two criteria. Firstly, South Africans should be of similar cardiovascular risk to North American and European patients. Secondly, the 'weighting' of the clinical risk factors associated with peri-operative cardiovascular complications needs to be similar to that reported in the international literature. Unfortunately neither of these criteria are met, and thus the applicability of Lee's RCRI (Lee et al., 1999) in South Africa is therefore contentious.

Indeed, it appears that South Africans are now at higher cardiovascular risk than North American and European populations. A process of epidemiological transition has been described to illustrate the progression of cardiovascular risk in a population (Opie and Mayosi, 2005). Exposure to 'Western civilisation' is integral to increasing cardiovascular risk. This may be first identified by a deviation from a steady blood pressure despite increasing age, to one of an increasing blood pressure associated with increasing age (Opie and Mayosi, 2005). Indeed, the lack of an increase in blood pressure with age has been shown in isolated socio-economic groups including Khoisan people and early East African tribal groups. Cardiovascular disease is now the leading cause of death in all developing countries, with the exception of sub-Saharan Africa, where it is displaced by HIV/AIDS (Opie and Mayosi, 2005). The process of epidemiological transition with respect to cardiovascular disease from these healthy isolated tribal units is first characterised by a transition phase associated with disease and famine. However, as pandemics decrease, cardiovascular disease increases, followed by a phase of degenerative and man-made disease with cardiovascular disease being prominent, (Opie and Mayosi, 2005) and finally (possibly) a phase of a partial decrease in risk with health awareness and appropriate

surveillance and management of cardiovascular risk factors. South Africans are probably now at the point of degenerative and man-made cardiovascular disease, while developed countries (from which these clinical risk indices are derived) are probably now in the phase of decreasing cardiovascular risk associated with health awareness and surveillance. South Africans must therefore be considered to be at a higher cardiovascular risk than what the published clinical risk indices predict (Lee et al., 1999, Kertai et al., 2005). This process of epidemiological transition would also suggest that within South Africa the various population groups comprising our population are potentially at different phases of cardiovascular risk, due to differences in socio-economic status (Steyn et al., 2005).

It also appears that the risk factors associated with myocardial infarction in South Africans are not necessarily the same as that of the North American and European populations. Five risk factors in the INTERHEART study were shown to be associated with first-time acute myocardial infarction (AMI) in sub-Saharan Africans. These include a history of smoking, diabetes, and hypertension, abdominal obesity and the ratio of apolipoprotein B to apolipoprotein A-1 (Steyn et al., 2005). These five risk factors can account for 89.2% for the risk of MI (Steyn et al., 2005).

Hypertension and diabetes were significantly more important risk factors for AMI in the African INTERHEART study in comparison to the global INTERHEART study (odds ratio (OR) 3.44 versus 2.49 and OR 3.55 versus 3.07 respectively). Abdominal obesity is also a significantly stronger risk factor in the African INTERHEART study than the global study. Smoking status and permanent stress are also significant predictors of AMI in the African group. Indeed as the OR of a number of these risk factors is higher than that of the overall INTERHEART study, the cardiovascular burden in Africa may well be larger, due

to uncontrolled/ undiagnosed/ poorly managed major cardiovascular risk factors (Steyn et al., 2005), (which is what we would expect from our understanding of epidemiological transition) (Opie and Mayosi, 2005).

Although these risk factors appear to be consistent across ethnic groups in sub-Saharan Africa; the following differences are noted when looking at black, coloured and European/ or other ethnic groups. Hypertension and abdominal obesity in black Africans result in a significantly higher risk of AMI than the overall INTERHEART results (Steyn et al., 2005). Black Africans have a significantly higher risk associated with hypertension and a lower risk associated with current smoking or atherogenic lipid profile (Steyn et al., 2005).

The risk of AMI increases in black Africans with higher income and education (Steyn et al., 2005). This is higher than white patients of a high income bracket, probably again as a result of epidemiological transition (Opie and Mayosi, 2005). Currently, high income black South Africans are probably in the phase of degenerative and man-made disease (Opie and Mayosi, 2005) while high income white South Africans are in a phase of increased health awareness and surveillance. The history of stroke suggests a particularly high risk group of black South Africans (Joubert et al., 2000).

In South African Asian Indians, the older patients (>65 years) frequently have hypertension, diabetes and a history of coronary artery disease as risk factors for acute coronary disease. Younger patients (<45 years) however present with a stronger smoking history and obesity, and a familial history of vascular disease as risk factors for acute coronary syndrome. All groups had associated elevated cholesterol levels as a risk factor (Ranjith et al., 2005), in contrast to black South Africans (Steyn et al., 2005).

Sub-Saharan individuals of European / other African descent have a lower cardiovascular risk associated with the tertiary education and the highest income group (Steyn et al., 2005), suggesting increased surveillance and management of cardiovascular risk factor (Opie and Mayosi, 2005).

The variance of risk factors associated with myocardial infarction between Sub-Saharan Africans and the globally accepted risk factors, and the inter-ethnic differences in risk factors, suggest that the clinical risk indices of peri-operative cardiovascular risk that are not derived in South Africa, are probably of limited value to South Africans.

2.1.2 Surgical risk

The type of operation is a strong determinant of cardiovascular risk. This has been highlighted in Lee's RCRI (Lee et al., 1999), where high-risk surgery included intraperitoneal, intrathoracic and supra-inguinal vascular surgery. Vascular surgical patients have the highest prevalence of cardiovascular disease in the noncardiac surgical population, and hence it is this group that is often investigated when studying peri-operative cardiovascular risk. When further classifying vascular surgical procedures, Kertai et al have improved the predictive power of the RCRI (Kertai et al., 2005, Lee et al., 1999). They defined the following risk groups in vascular surgical patients: High-risk (ruptured abdominal aortic aneurysm), high-intermediate risk (thoraco-abdominal and abdominal aortic surgery), low-intermediate risk (infra-inguinal bypass) and low risk (carotid endarterectomy) (Kertai et al., 2005). In addition, they also considered concurrent medications (beta-blockers and statins) which may be cardioprotective in the peri-operative period. The development of the subsequent customised probability model improved the positive predictive value of the original Lee model (Kertai et al., 2005).

2.1.3. Functional capacity and aerobic metabolic capacity

Major surgery has been equated to a physical endurance event (Biccard, 2005). Surgery initiates a postoperative stress response of approximately 48 to 72 hours in duration (Davies and Wilson, 2004), which is associated with an increase in oxygen consumption and metabolic rate (Older and Smith, 1988, Davies and Wilson, 2004). Hence the aerobic metabolic capacity of an individual is of fundamental importance in determining postoperative survival. The similarity between the surgical stress response and endurance exercise, is that the aerobic capacity an individual can sustain decreases with time. Thus the aerobic work measured in the same individual over a shorter duration of time is higher than that recorded during endurance exercise or following major surgery (Biccard, 2004).

The discrepancy between the analogy of endurance exercise and the postoperative surgical stress response is firstly that a poor functional capacity assessment is not necessary secondary to poor aerobic function, but rather a function of comorbidity (Biccard, 2005, Reilly et al., 1999) and secondly, the oxygen extraction ratio decreases postoperatively (Older and Smith, 1988, Davies and Wilson, 2004), while it increases with exercise (Wasserman et al., 2005).

The aetiology of peri-operative cardiovascular complications is multifactorial. Patients have been found to have fatal myocardial infarctions both at the site of critical lesions and at noncritical sites not traditionally associated with myocardial infarction (Dawood et al., 1996, Cohen and Aretz, 1999). It is this latter group that is almost certainly a consequence of the prolonged postoperative increase in myocardial oxygen demand (Le Manach et al., 2005). The surgical stress response is associated with an increase in oxygen demand from 110 to 170 $ml.min^{-1}m^{-2}$ (5 $ml.kg^{-1}.min^{-1}$) postoperatively, which is equivalent to 1.4

metabolic equivalents (METs) (Davies and Wilson, 2004, Older and Smith, 1988). A MET is the basal metabolic rate assumed to be equivalent to an oxygen consumption of 3.5 $ml.kg^{-1}.min^{-1}$ (Eagle et al., 2002). Metabolic rates as high as 7 $ml.kg^{-1}.min^{-1}$ (240 $ml.kg^{-1}.m^2$) (or 2 METS) have been recorded postoperatively (Older et al., 1993, Older and Smith, 1988, Shoemaker et al., 1988).

Another important recent development is the increasing importance of heart failure as an adverse peri-operative predictor (Hernandez et al., 2004). Although heart failure has always been an adverse peri-operative prognostic marker (Goldman et al., 1977, Detsky et al., 1986, Lee et al., 1999), it has only recently been shown to be a significantly more important risk factor than coronary artery disease in predicting death within 30 days of major noncardiac surgery (Hernandez et al., 2004).

The pre-operative assessment of functional capacity is therefore an important determinant of both coronary and cardiovascular failure risk. Peri-operative cardiac risk is significantly increased if a patient is unable to function at 4 METs (Eagle et al., 2002). In patients over 60 years of age undergoing major abdominal surgery, an anaerobic threshold (AT) measured during cardiopulmonary exercise testing of less than 11 $ml.kg^{-1}.min^{-1}$ was found to be an independent predictor of peri-operative mortality (Older et al., 1993). A pre-operative AT above 14 $ml.kg^{-1}.min^{-1}$ was associated with a good outcome (Older et al., 1993) which is equivalent to approximately 4 METs. Importantly, all the patients in this study underwent high or intermediate risk surgery as classified by the American College of Cardiology/ American Heart Association (ACC/AHA) algorithm (Eagle et al., 2002). (Table 2.2) Myocardial ischaemia in patients with poor functional capacity (Older et al., 1993) (Table 2.3) or symptoms of ischaemia limiting functional capacity (Reilly et al.,

1999), significantly increased adverse peri-operative cardiac events during major or intermediate risk surgery. It is the patients with positive Lee's Revised Cardiac Index risk factors who are most likely to have peri-operative myocardial ischaemia (Lee et al., 1999).

Table 2.2. Peri-operative mortality and anaerobic threshold (Older et al., 1999, Older et al., 1993, Biccard, 2005)

First author (year)	AT < 11 $ml.kg^{-1}.min^{-1}$	AT ≥ 11 $ml.kg^{-1}.min^{-1}$	Risk ratio (95 % CI)
Older et al (1993)	18 % (10 of 55 patients)	0.8 % (1 of 132 patients)	24 (3.1-183)
Older et al (1999)	4.6 % (7 of 153 patients)	0.5 % (2 of 395 patients)	9 (1.9-43)

AT anaerobic threshold

Table 2.3. Peri-operative cardiovascular mortality associated with the anaerobic threshold in patients undergoing major abdominal surgery (Older et al., 1993)

	AT < 11 $ml.kg^{-1}.min^{-1}$	AT > 11 $ml.kg^{-1}.min^{-1}$
Without ischaemia (%)	18	0.8
With ischaemia (%)	42	4

AT anaerobic threshold

Stair climbing capacity also has peri-operative prognostic importance, where the inability to climb two flights of stairs is a predictor of serious peri-operative complications (Reilly et al., 1999, Girish et al., 2001). Climbing a flight of stairs is a 5.5 METs equivalent according to the Duke Activity Status Index (Hlatky et al., 1989) and thus these findings are in agreement with the original work on pre-operative AT testing (Older et al., 1993). However, unlike the AT, the inability to climb two flights of stairs is not a predictor of increased risk of peri-operative mortality (Biccard, 2005). (Table 2.4) This confirms the reservations of using the Duke Activity Status Index in the peri-operative period, which has never been evaluated in the peri-operative setting (Ridley, 2003).

Table 2.4. Peri-operative mortality in all major noncardiac surgery associated with flights of stairs climbed (Biccard, 2005)

Number of flights	Fatalities	Survivors
> 2 flights	4	332
≤ 2 flights	2	357

Risk ratio (95% CI) 0.47 (0.09-2.5)

This discrepancy between the prognostic power of stair climbing and the AT is probably related to the metabolic pathways measured with each test. Two factors have limited the ability of pre-operative field tests of functional capacity to accurately predict postoperative complications secondary to poor aerobic capacity. Firstly, some tests have been of too short a duration and thus measure the oxygen-independent metabolism characteristic on initiation of exercise, as opposed to oxidative phosphorylation which takes a few minutes before it becomes dominant (Biccard, 2005). This is further aggravated by the delay in VO_2-on-kinetics of patients with heart failure, pulmonary and peripheral vascular disease (Biccard, 2005, Grassi, 2000, Grassi, 2001, Hughson et al., 2001), which are clinical conditions commonly associated with patients requiring pre-operative assessment of functional capacity. Secondly, there is an inconsistent relationship between the anaerobic threshold and the peak oxygen consumption (VO_{2peak}) (Biccard, 2005) and the majority of field tests estimate the VO_{2peak} and not the anaerobic threshold. It is the anaerobic threshold however which has been shown to be a more sensitive predictor of outcome in patients with heart failure than the VO_{2peak} (Gitt et al., 2002).

A pre-operative functional capacity should therefore allow for VO_2-on-kinetics and accurately measure aerobic or oxygen-dependent metabolism. Anaerobic threshold testing measured during cardiopulmonary exercise testing meets these requirements. Three minutes of unloaded exercise at the beginning of the test,(York, 2005) should allow adequate time for VO_2-on-kinetics (Hughson et al., 2001) even in patients with heart

failure, pulmonary and peripheral vascular disease(Grassi, 2001). The measurement of the AT is a marker of the point at which there is increased flux of pyruvate to lactate resulting in an imbalance of production and removal lactate from the circulation, with increased exercise intensity (Biccard, 2005, Wasserman et al., 2005). The result is an increased reliance on oxygen-independent metabolism to supplement exercise performance above the AT (Wasserman et al., 2005). Work up to the AT is predominantly oxygen-dependent in incremental work, and thus of prognostic value in patients dependent on aerobic metabolic performance (Older et al., 1993, Older et al., 1999, Gitt et al., 2002).

The AT measured during CPET reflects aerobic metabolic capacity, while stair climbing reflects both aerobic and anaerobic metabolic pathways, and thus stair climbing performance is a closer estimate of VO_{2peak} than AT, thus overestimating the aerobic functional capacity necessary to sustain the peri-operative stress response (Biccard, 2005). Conversely, weight bearing may lead to underperformance during stair climbing (Biccard, 2005). Thus stair climbing may incorrectly classify patients as either good or poor functional capacity, decreasing its prognostic performance (Biccard, 2005).

The inability to walk four blocks or more is used as a screening test of exercise capacity (Reilly et al., 1999). Patients unable to exercise, especially in patients without cardiopulmonary exercise limitation results in the poor positive predictive power of exercise capacity as a screening tool for pre-operative evaluation (Auerbach and Goldman, 2006).

Although approximately 4 METs of pre-operative aerobic metabolic capacity is necessary to predict postoperative survival (Older et al., 1993, Older et al., 1999) (which probably

never requires more than 2 METs) (Davies and Wilson, 2004), some patients still survive major surgery even if 4 METs is not achieved aerobically pre-operatively (Table 2.2).

There has been no attempt to identify the physiological determinants that identify this group of patients. Patients with a poor aerobic capacity do not have the ability to increase oxygen extraction postoperatively. Although, elderly patients have an oxygen extraction ratio of approximately 50% when working near the AT (Weber and Janicki, 1985), postoperatively the oxygen extraction ratio falls to about 30%, meaning that the cardiac output has to rise further to compensate for the decrease in oxygen extraction (Older et al., 1993). This would result in the cardiac output measured at 1.4 METs postoperatively, exceeding the cardiac output at the same metabolic rate and in the same patient recorded during exercise testing pre-operatively. This suggests that in this group of patients with a limited aerobic capacity, there is a subset of patients with the capacity to increase oxygen delivery (DO_2) in the postoperative period, as we know they cannot compensate for the increased oxygen consumption (VO_2) by increasing oxygen extraction.

$$DO_2 = CO \times CaCO_2 \quad (1)$$

$$DO_2 = (HR \times SV) \times (Hb \times \text{Huffner's constant} \times SaO_2) \quad (2)$$

Where CO = cardiac output

$CaCO_2$ = oxygen carrying capacity

DO_2 = oxygen delivery

HR = heart rate

SV = stroke volume

Hb = haemoglobin concentration

SaO_2 = Haemoglobin oxygen saturation

Assuming that high-risk surgical patients are appropriately managed postoperatively, then haemoglobin and oxygen saturation should be adequate. The result is that in order to increase the DO_2 postoperatively, the patient is dependent on the ability to increase the cardiac output. Cardiac output increases by increasing stroke volume and heart rate up to 40% maximal oxygen consumption (VO_{2peak}), and then any further increase in cardiac output is a function of the heart rate (Astrand et al., 1964). It is possible that patients with a poor pre-operatively aerobic capacity who survive the surgical stress response have an aerobic heart rate reserve, hereafter referred to as a 'aerobic surgical heart rate reserve', while non-survivors have no or minimal 'aerobic surgical heart rate reserve'. It is possible that if there is a necessity for a further increase in DO_2 postoperatively (for example secondary to acute haemorrhage or infection) patients who can further increase their cardiac output by a further increase in heart rate, while maintaining aerobic metabolism, may be the group constituting the survivors. Due to the nature of CPET, it may be possible to identify this group when analysing the pre-operative test results.

In non-surgical heart failure patients, CPET markers other than the AT or VO_{2peak} have had prognostic importance in predicting long term survival. These have included cardiac power (systolic arterial pressure x VO_{2peak}) (Cohen-Solal et al., 2002), or (mean arterial pressure x VO_{2peak}) (Williams et al., 2001). However, the VO_{2peak} is a marker of both aerobic and oxygen-independent work, whereas the surgical stress response is dependent on aerobic metabolic demand and hence the evaluation of an aerobic marker such as the AT may be more appropriate (Biccard, 2005). In addition, the AT has recently been shown to more predictive of survival in non-surgical heart failure patients than the VO_{2peak} (Gitt et al.,

2002). Importantly, the safety of measuring the AT is that it is a submaximal test in comparison to the VO_{2peak} (Biccard, 2005). In summary, it would appear inappropriate to evaluate these markers of maximal circulatory power in surgical patients at present. It may be more appropriate to evaluate mechanisms of increasing DO_2 at metabolic rates commensurate with the stress response of the postoperative period.

2.2. Pre-operative investigation for the high-risk surgical patient

2.2.1. Statistical principles and Bayesian theory of pre-operative investigation

Pre-operative investigation is undertaken when patients of indeterminate cardiovascular risk present for surgery, that is, they are not in an obviously low or high-risk group. One can increase the prevalence of a condition (or outcome) in the population being studied by sequential screening and thus combining tests. The post-test prevalence thus becomes the pretest prevalence for a subsequent test (Ridley, 2003). Sequential screening is the basis of clinical management algorithms (Ridley, 2003). By sequential investigation, the prevalence of an uncommon disease may be increased (Ridley, 2003). This is the principle of application of Bayesian theory, where the pre-test probability of an event is further modified by associated clinical risk indices and subsequent findings on pre-operative investigation (Goldman, 1996). It is this subsequent result which is most likely to result in a change in practice or management. Although a number of pre-operative investigations have been reported in the literature, an understanding of the limitations (and strengths) of the statistical methods used is essential in interpreting their clinical importance.

The commonly reported statistical terms associated with pre-operative investigation include sensitivity, specificity, positive and negative predictive value and likelihood ratios.

The definitions (Table 2.5) and the advantages/ disadvantages of these statistical terms (Table 2.6) are tabulated.

Table 2.5. Definition of statistical terms (Ridley, 2003, Coetzee, 2004)

	Positive	Negative
Sensitivity / specificity	TP / TP + FN	TN / TN + FP
PPV / NPV	(TP / TP + FP) x 100	(TN / TN + FN) x 100
Likelihood ratio	Sensitivity / (1 - specificity)	(1 - sensitivity) / specificity

TP true positive; TN true negative; FP false negative; FN false positive; PPV positive predictive value; NPV negative predictive value

Table 2.6. Advantages and disadvantages of statistical terms (Ridley, 2003, Coetzee, 2004)

Statistical terms	Advantages	Disadvantages
Sensitivity / specificity	Independent of disease prevalence	Assumes the disease status of the patients is known
PPV / NPV	Calculates the post-test probability Disease status need not be known	PPV markedly affected by the prevalence of the disease in the population
Likelihood ratios	Independent of disease prevalence Independent of pre-test probabilities	Post-test probabilities require large ratios

PPV positive predictive value; NPV negative predictive value

Considering the limitations of these statistical terms is necessary if one is to compare our local findings with reports in the international literature. While the advantage of the sensitivity and specificity is that they are not influenced by the pre-test prevalence or pre-test probability (Ridley, 2003), the disadvantage of using the sensitivity and specificity to describe findings is that they may not be reproducible when populations are not matched (Ridley, 2003). This would be an important consideration in comparing our findings in South African vascular surgical patients, to other vascular patients reported in the international literature.

Similarly, the use of predictive values has limitations. The pre-test prevalence is the prevalence of the disease prior to performing the investigation (Ridley, 2003). The post-

test prevalence is the likelihood of the patient still having the disease after the test has been performed (Ridley, 2003). This revised pre-test prevalence is known as the positive predictive value or negative predictive value (Ridley, 2003). The advantage of the predictive values is that the denominator is a function of the test results, and not the prevalence of the disease in the population (as is the case with the sensitivity and specificity) (Ridley, 2003) and hence this may be clinically useful. However, the predictive values are influenced by the prevalence of the disease in the population being tested (Ridley, 2003). For example, if a test has a sensitivity and specificity of 95%, only when the prevalence of the event in the population is 20%, is the PPV > 80% (Ridley, 2003).

The likelihood ratio (LR) as an alternative statistical analysis of a pre-operative test is clinically useful for a number of reasons. Firstly, it is independent of the population prevalence(Coetzee, 2004). Likelihood ratio is either the probability of a diseased person having an event (positive) or not having event (negative) compared to a non-diseased person with the same test result (Coetzee, 2004). Secondly, it can be used with a prior probability (or prevalence) to create a posterior probability for the patient being investigated, which would further influence clinical management (Beattie et al., 2006, Fagan, 1975). Thirdly, it allows for the use of continuous data (and not necessarily dichomotous as in the previous statistical definitions) (Grimes and Schulz, 2005).

2.2.2. The statistical performance of clinical risk indices and special investigations in predicting peri-operative major cardiac complications

Tabulation of the current evidence concerning clinical risk indices and pre-operative investigations generally shows a high specificity and a low sensitivity.(Table 2.7)

Table 2.7. The current statistical robustness of clinical risk indices and pre-operative investigations

Pre-operative test	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	LR (neg)	LR (pos)
Goldman's Class IV						57[a]
Detsky Class III						10.6[a]
Lee's RCRI 0 or 1 point					0.16[a]	
Inability to walk 4 blocks[b,c]¶			10	95		
<2 flights of stairs[d]‡	33[b]	48[b]	0.6	99	1.58	0.63
Radionuclide ventriculography	50 (32-69)	91 (87-96)			0.81-0.96[a]	1.41-6.24[a]
Ambulatory ECG	52 (21-84)[e]** 68[f]	70 (57-83)[e]** 66[f]	25[f] 4-15[g]	1-16[g]	1.6[e]**	1.7[e]**
Exercise ECG	74 (60-88)[e]** 69[f]	69 (60-78)[e]** 73[f]	20[f]		0.17-0.89[a]	1.3-2.56[a]
Dipyridamole stress echo	74 (53-94)[e]** 85[f]	86 (80-93)[e]** 80[f]	23[f]		0.19[f]	4.25[f]
Myocardial perfusion scintigraphy	83 (77-89)[e]**	49 (41-57)[e]**	4-20[g]†	95-100[g]†	0-1.06[a] 0.44[h]	1.3-2.56[a] 1.83[h]
Dobutamine stress echo	85 (74-97)[e]** 90[f]	70 (62-79)[e]** 30[f]	38[e] 7-25[g]	93-100[g]	0[a] 0.23[h]	4.76[a] 4.09[h]
Pre-operative exercise testing†			0-81[g]	90-100[g]		
CPET[d,i,j]*	85	71.7	8	99	0.21	4.64

ECG electrocardiogaphy; echo echocardiography; ¶ All complications during hospitalisation; ‡ All cause mortality; † Vascular surgical patients; * In hospital CVS mortality; ** 30 day CVS mortality or myocardial infarction

a (Ridley, 2003), b (Auerbach and Goldman, 2006), c (Reilly et al., 1999), d (Biccard, 2005), e (Kertai et al., 2003), f (Chassot et al., 2002), g (Eagle et al., 2002), h (Beattie et al., 2006), i (Older et al., 1993), j (Older et al., 1999)

If likelihood ratios are calculated and a likelihood ratio of <0.2 (for a negative LR) and >5 (for a positive LR) is considered acceptable performance (Coetzee, 2004), then only 6 results are clinically useful (Table 2.8), and probably in reality only four, as the high risk Goldman (Goldman et al., 1977) and Detsky (Detsky et al., 1986) groups are probably identified routinely today in the 'Major clinical predictors' group of the ACC/AHA algorithm (Eagle et al., 2002). Unfortunately, all these tests only exhibit high specificity (the ability to predict true negatives), as opposed to a high sensitivity (which is the ability to predict true positives).

Table 2.8. Clinically useful pre-operative risk indices or investigations based on reported likelihood ratios

Clinical risk index or Pre-operative investigation	Criterion
Goldman's Risk Index	Class III (Goldman et al., 1977, Ridley, 2003)
Detsky Modified Risk Index	Class IV (Detsky et al., 1986, Ridley, 2003)
Lee's RCRI	0 or 1 clinical risk factors (Lee et al., 1999, Ridley, 2003)
Dipyridamole stress ECG	Negative test (Chassot et al., 2002)
Dobutamine stress echocardiography	Negative test (Kertai et al., 2003)
Cardiopulmonary exercise testing	Negative test (Biccard, 2005)

Cardiovascular complications fall broadly into two groups: that is sudden cardiac events (sudden cardiac death, myocardial infarction and arrhythmias) or cardiac failure.

The commonly reported pre-operative special investigations either identify myocardial ischaemia as a marker of coronary artery disease and/or ventricular dysfunction as a marker of heart failure (Chassot et al., 2002). Myocardial ischaemia is identified either by ST segment depression using ambulatory or stress electrocardiography; or by detection of fixed or reversible myocardial perfusion defects using a vasodilator such as dipyridamole and an isotope such as thallium for imaging during myocardial perfusion scintigraphy; or by detection of new regional wall motion abnormalities of the left ventricle by echocardiography during dipyridamole stress echocardiography and dobutamine stress echocardiography (Chassot et al., 2002, Kertai et al., 2003). Poor ventricular function as a marker of heart failure determined by a low resting ejection fraction (usually accepted as less than 35%) measured with ventriculography (Kertai et al., 2003, Chassot et al., 2002).

A meta-analysis of these pre-operative tests, showed that the tests with the lowest sensitivity were ambulatory and stress electrocardiography of ST depression and ventriculography measuring resting ejection fraction (Kertai et al., 2003). Tests which rely

solely on ECG changes (such as the ambulatory and stress ECG) are limited by existing ECG abnormalities. This has resulted in an unreliable analysis of the ST segment in up to 40% of patients using the ambulatory ECG test (Rose et al., 1993). An additional problem with the exercise ECG test is the necessity for the patient to be able to exercise on a treadmill (Kertai et al., 2003).

The problem with a static test of ventricular function, such as measuring the resting left ejection fraction, is that it does not reveal how the ventricle responds to exercise or increased cardiovascular demand associated with the stress response following surgery. The sensitivity of this test was the lowest of the six reported (Kertai et al., 2003). The reason for this is that firstly, there is a poor correlation between the resting and stress echocardiography in patients with cardiac failure (Lee et al., 2006), secondly there is a poor correlation between ejection fraction and maximal oxygen uptake in patients with coronary artery disease which is not limited by myocardial ischaemia (Older and Hall, 2004) and thirdly dynamic tests of ventricular function may illicit myocardial ischaemia (which is not evident at rest) which would further compromise ventricular function.

Pre-operative tests which identify myocardial ischaemia, whether by fixed or reversible deficits on imaging, or by regional ventricular wall motion abnormalities have a higher sensitivity, than ECG tests of ST depression or resting ventriculography (Kertai et al., 2003). A further meta-analysis showed that dobutamine stress echocardiography had a statistically better negative predictive power than thallium scanning (Beattie et al., 2006). Stress echocardiography was significantly better at predicting cardiac events in positive patients, as stress echocardiography had less false negatives than thallium scanning (Beattie et al., 2006).

Cardiopulmonary exercise testing has never been compared in a meta-analysis to other pre-operative investigations. There are a number of reasons to suggest that it would perform well if compared to other investigations. Firstly, it is specific as are the other desirable tests. (Tables 2.7 and 2.8) Secondly, although it measures ECG ST segment changes, it is not entirely depend on the ST segment for test interpretation. Thirdly, it is a test of dynamic ventricular function and not a static test. Fourthly, although it is exercise dependent, it is traditionally performed on a cycle ergometer, which is preferable to a treadmill as it eliminates weight bearing (Biccard, 2005).

2.3. The requirements for an ideal pre-operative investigation of cardiac risk

A pre-operative investigation conducted to estimate peri-operative cardiovascular risk associated with major surgery should be able to distinguish four groups of patients; patients who require no further intervention prior to surgery, patients requiring acute peri-operative medical therapy (beta-blockade (Devereaux et al., 2005a, Biccard et al., 2006) and/ or statins (Biccard et al., 2005b, Biccard et al., 2005a)) peri-operatively, patients requiring peri-operative haemodynamic optimization (Kern and Shoemaker, 2002) and patients requiring coronary angiography and possible coronary revascularization (Eagle et al., 2002).

The indications for coronary revascularisation in the surgical patient are the same as the non-surgical patient (Eagle et al., 2002). These include left main stem coronary artery stenosis, left main stem equivalent (significant stenosis of the proximal left anterior descending and left circumflex) or 3-vessel disease and disease associated with significant ischaemia on non-invasive testing or left ventricular dysfunction (Eagle et al., 2004).

The indications for pre-operative coronary angiography are listed in Table 2.9 (Eagle et al., 2002).

Table 2.9. The ACC/AHA Class I indications for coronary angiography in the pre-operative evaluation for noncardiac surgery (Eagle et al., 2002).

Evidence for high risk of adverse outcome based on non-invasive test results
Angina unresponsive to adequate medical therapy
Unstable angina, particularly when facing intermediate or high-risk surgery
Equivocal non-invasive test results in patients at high-clinical risk undergoing high-risk surgery

ACC/AHA, American College of Cardiology/ American Heart Association

Pre-operative revascularisation significantly decreases the risk of death and MI associated with intermediate and high-risk noncardiac surgery in patients where coronary revascularisation is indicated (Eagle et al., 1997). As pre-operative coronary revascularisation is associated with cardiovascular risk (Table 2.10), it is suggested that pre-operative revascularisation should only be considered where the expected mortality of the noncardiac procedure exceeds 5% and the combined mortality of the coronary angiography and revascularisation is less than 3% (Rihal, 1998). Patients with a peri-operative cardiac mortality risk of less than 5% and an adverse peri-operative cardiovascular event rate risk of >10% probably would benefit from acute peri-operative beta-blockade (Biccard et al., 2006), and possibly peri-operative statin therapy(Biccard et al., 2005a). No studies have shown that prophylactic coronary revascularisation improves outcome when the complications of the revascularisation procedure are also considered (Bodenheimer, 1996, McFalls et al., 2004).

Table 2.10. The risks of pre-operative coronary revascularisation

Consideration	Risk
Exercise stress testing	MI or death 0.04% (Stuart and Ellestad, 1980)
Coronary angiography	Major complications <2% (Scanlon et al., 1999) Mortality 0.03-0.25% (Mason et al., 1995)
Coronary artery bypass grafting	Mortality 2.3% (Foster et al., 1986) Increased risk death, MI, CVA, renal failure in vascular patients (Lustik et al., 2002)
Percutaneous coronary intervention	Mortality 1-2% (Eagle et al., 2004)
Delay of noncardiac surgery	Morbidity associated with delay of noncardiac surgery
Pathology of subsequent peri-operative MI	45% are not associated with plaque disruption (Dawood et al., 1996), but rather prolonged periods of myocardial oxygen supply-demand imbalance (Landesberg et al., 1993, Rapp et al., 1999) 26% do not occur in the territory identified by non-invasive testing (Poldermans et al., 2001)

Where the risk of peri-operative mortality is expected to exceed 20%, haemodynamic optimisation may be of benefit when it is instituted within 12 hours of surgery and before established organ failure (Kern and Shoemaker, 2002).

Based on these management decisions the following peri-operative management algorithm can be instituted. (Table 2.11)

Table 2.11. Proposed management algorithm of high-risk surgical patients

Predicted peri-operative event rate	Suggested management
Major CVS complications >10%	Acute peri-operative beta-blockade (Biccard et al., 2006)
CVS mortality > 5%	Coronary angiography (Bodenheimer, 1996) and revascularisation
All cause mortality > 20%	Haemodynamic optimization (Kern and Shoemaker, 2002)

Based on the original work by Older and colleagues presented in Table 2.3 (Older et al., 1993), it is possible to identify appropriate peri-operative management according to the

CPET result. (Table 2.12) This is the approach which has been followed in Durban since October 2004.

Table 2.12. Peri-operative management of high-risk patients according to CPET result

CPET result	Peri-operative management
Adequate AT, no early ischaemia	Consider acute peri-operative beta-blockade
Adequate AT without early ischaemia	Acute peri-operative beta-blockade
Poor AT without early ischaemia	Haemodynamic optimisation
Poor AT with early ischaemia	Coronary revascularisation, with repeat CPET once recovered prior to noncardiac surgery

Chapter 3

A literature review of cardiopulmonary exercise testing for noncardiac, non thoracic surgery

3.1. Methods

In order to review the literature on peri-operative cardiopulmonary exercise testing, a Medline search from 1966 to November 2005 was conducted. The terms used in the search were: cardiopulmonary, exercise, anaerobic, ventilatory, threshold and surgery. The search used the text words 'cardiopulmonary exercise' or 'anaerobic threshold' or 'anerobic threshold' or 'ventilatory threshold' and 'surgery'.

All prospective trials were identified which reported the peri-operative outcome associated with documented pre-operative cardiopulmonary exercise test results. The reference lists of eligible trials (and systematic reviews) were also examined for further relevant trials.

Trials were excluded where postoperative outcomes were not reported in the either the control or treatment groups. Where data publication was replicated, we used the publication which contained the largest number of subjects.

Only data from human studies, published in the English language, are included in this review. The data abstracted from the trials included: the type of cardiopulmonary exercise test (treadmill, cycle ergometer or arm cranking), the endpoint measured in the test, the type of surgery scheduled for the patient, the peri-operative outcome in terms of all-cause and cardiovascular mortality.

3.2. Results

Literature searching revealed 440 publications. Four-hundred and twenty-six publications were excluded for the following reasons; 198 trials reported on cardiac surgery and/ or interventional cardiology, 16 studies only used cardiopulmonary exercise testing postoperatively, 87 studies used cardiopulmonary exercise testing for other non surgical assessments, 71 studies were not English publications and 31 other exclusions including lung transplant and lung reduction surgery, pectus excavatum, reviews and where cardiopulmonary exercise testing was not done. Twenty-three papers describing the utility of CPET in thoracic resection were also not reviewed.

The remaining 14 publications have been reviewed. These include four general surgical papers (Older et al., 1999, Older et al., 1993, Gerson et al., 1985, Gerson et al., 1990), one trial for aortic aneurysmal surgery (Nugent et al., 1998), one trial for oesophagectomy (Nagamatsu et al., 2001), two for hepatic transplant (Epstein et al., 2004, Wiesinger et al., 2001), two for obesity surgery (Kanoupakis et al., 2001, Dolfing et al., 2005), three trials for major joint arthroplasty (Philbin et al., 1995, Ries et al., 1995, Ries et al., 1996) and one trial for obstructive sleep apnoea surgery (Lin et al., 2005).

3.3. Discussion

3.3.1. The type of CPET performed and the format of data reporting

The CPET performed either included a maximal symptom limited exercise test (VO_{2peak}) (Philbin et al., 1995, Nugent et al., 1998, Ries et al., 1995, Ries et al., 1996, Nagamatsu et al., 2001, Epstein et al., 2004, Lin et al., 2005, Dolfing et al., 2005, Kanoupakis et al., 2001), or an AT test (Older et al., 1993, Older et al., 1999, Wiesinger et al., 2001), or the ability to cycle for two minutes to a heart rate exceeding 99 beats per minute (in patients

who were not beta-blocked) (Gerson et al., 1985, Gerson et al., 1990). A cycle ergometer was used exclusively in eleven studies, one study used arm cranking (Philbin et al., 1995) in addition to cycling and two studies used a treadmill (Nugent et al., 1998, Kanoupakis et al., 2001). The reporting of exercise capacity varied between studies and included VO_2 as a percentage of predicted (Epstein et al., 2004, Dolfing et al., 2005, Wiesinger et al., 2001, Ries et al., 1995, Ries et al., 1996), VO_2 in $ml.min^{-1}$ (Dolfing et al., 2005, Wiesinger et al., 2001, Philbin et al., 1995, Lin et al., 2005), $ml.kg^{-1}.min^{-1}$ (Philbin et al., 1995, Older et al., 1999, Older et al., 1993, Nugent et al., 1998, Kanoupakis et al., 2001, Ries et al., 1995, Ries et al., 1996, Lin et al., 2005) or $ml.min^{-1}.m^{-2}$ (Nagamatsu et al., 2001).

The great variation in the test used (arm cranking, cycling or treadmill) will all affect the time of onset of the AT, due to different muscle volumes and recruitment (Biccard, 2005) with a lower AT associated with smaller muscle groups, such as arm cranking in comparison to cycling. The reporting of either AT, VO_{2peak} or both means that comparison between studies is not always possible. The inconsistent units used for reporting of VO_2 makes it difficult to compare outcomes between studies, in particular where the VO_2 data are only reported as $ml.min^{-1}$ (Lin et al., 2005).

3.3.2. The ability of an individual to complete a cardiopulmonary exercise test

If cardiopulmonary exercise testing is to become more commonly applied, the majority of patients should be able to perform the test (it should have a low drop out rate). The noncardiac, non-thoracic surgical literature has a drop out rate of 2.2% (32 patients out of 1459 included in studies for testing) (Older et al., 1999, Dolfing et al., 2005, Kanoupakis et al., 2001, Older et al., 1993, Ries et al., 1996, Ries et al., 1995, Philbin et al., 1995, Wiesinger et al., 2001, Epstein et al., 2004, Nugent et al., 1998, Lin et al., 2005, Gerson et

al., 1990, Gerson et al., 1985). However, seven of these 32 patients did not fail to complete the test, but rather were excluded for other reasons (Wiesinger et al., 2001). The actual drop out rate is then 1.7%. One study did not record the drop out rate (Nagamatsu et al., 2001). Looking at specific groups: all 72 morbidly obese patients (defined as a body mass index (BMI) > 40 $kg.m^{-2}$) had reached the AT, on both treadmill and cycle ergometer tests (Dolfing et al., 2005, Kanoupakis et al., 2001). In patients undergoing knee arthroplasty, severe osteoarthritis did not prevent these patients from achieving the AT during testing (Ries et al., 1996, Ries et al., 1995). In patients with either severe rheumatoid arthritis and osteoarthritis for hip and knee replacements, only a single patient (2%) with rheumatoid arthritis could not sustain 60 repetitions per minute (RPM) with either arm cranking or cycling (Philbin et al., 1995). It appears therefore that osteoarthritis is not a limiting factor in cardiopulmonary exercise testing.

All the patients scheduled for hepatic transplantation who have been reported in the literature have also successfully completed exercise testing to AT (Wiesinger et al., 2001) and to $VO_{2\ peak}$ (Epstein et al., 2004). However, exclusion criteria had included hepatic encephalopathy, intrinsic cardiac and/ or pulmonary disease (Wiesinger et al., 2001). These exclusion criteria account for the seven of the 32 drop outs recorded (Wiesinger et al., 2001).

The inability to exercise is not necessarily a limitation associated with CPET as a pre-operative investigation. Indeed, it is an important prognostic marker. In 100 patients undergoing abdominal or noncardiac thoracic surgery, all 5 cardiac deaths were found in the group unable to cycle for 2 minutes to a heart rate of >99 beats per minute (Gerson et al., 1985). This approach which is partly based on a heart rate target is now inappropriate

with the increased utilisation of beta-blockade for managing patients with a history of ischaemic heart disease (Freemantle et al., 1999) and congestive cardiac failure (Metra et al., 2004).

3.3.3. Cardiopulmonary exercise testing for major abdominal surgery

The original work on this group of patients described by Older and colleagues (Older et al., 1993, Older et al., 1999) has already been discussed in Chapter 2 in the section titled; 'Determinants of peri-operative cardiac risk 2.1.3. Functional capacity and aerobic metabolic capacity.' Importantly, even when Older and colleagues triaged and managed the patients with poor cardiopulmonary test results more aggressively, the cardiac mortality was still significantly higher in the patients with a low AT (Older et al., 1999). It appears therefore that a poor aerobic capacity remains a significant cardiovascular risk factor despite intervention. However, an aggressive management approach does decrease mortality in this group (Older et al., 1999, Older et al., 1993).

3.3.4. Cardiopulmonary exercise testing for major vascular surgery

There is a single report in the peer-reviewed literature of cardiopulmonary exercise testing for the pre-operative assessment of abdominal aortic aneurysms (Nugent et al., 1998). Unfortunately, this is a small series of 30 patients having abdominal aortic aneurysmectomy. Patient cardiovascular risk was quantified by the presence of a $VO_{2\ peak}$ less than 83% of predicted, an AT less than the predicted 95% confidence interval, an oxygen pulse less than the predicted 95% confidence interval and ischaemic ST depression of greater than -1 mm. Not surprisingly this paper could not show utility associated with cardiopulmonary exercise testing as the patients were of extremely low cardiovascular risk and the corresponding event rate was thus low. Twenty-six of the 30 patients had less than

two of these risk factors and there was a single peri-operative cardiac death (Nugent et al., 1998). There was a trend however to increased peri-operative complications associated with a poorer CPET result. Their conclusion was that cardiopulmonary exercise testing may be helpful in identifying patients at risk of more postoperative complications, although it should not be used in isolation without thorough clinical assessement (Nugent et al., 1998). Hence, this again suggests that the philosophy of combining clinical risk factors, results of specific investigations and surgical risk may improve peri-operative prognostication.

An abstract reports on CPET for aortic aneurysm surgery in York, United Kingdom (McEnroe and Wilson, 2005). The mortality in the group with an AT < 11 $ml.kg^{-1}.min^{-1}$ was 11% and 6% for the patients with an AT above 11 $ml.kg^{-1}.min^{-1}$. However, the authors did not distinguish between cardiac deaths and other deaths. Patients who had a low AT and a history of ischaemic heart disease had an all-cause mortality of 19%. It was concluded that CPET is useful in stratifying patients for vascular surgery (McEnroe and Wilson, 2005).

3.3.5. The prognostic importance of the time of onset of myocardial ischaemia during cardiopulmonary exercise testing

It has been shown that early myocardial ischaemia (that is within two minutes of the onset of unloaded exercise) during cardiopulmonary exercise testing is a predictor of a worse outcome (Older et al., 1999). This may be because myocardial ischaemia is present at an oxygen consumption equivalent to that expected in the postoperative period (about 1.4 METs) (Biccard, 2005). During unloaded cycling, the predicted METs expended is equivalent to 2.5 to 2.6 METS for men and women respectively, using the following

nomogram (VO_2 unloaded cycling ($ml.min^{-1}$) = 150 + (6 x weight (kg)), at a cadence of 50 to 60 RPM (York, 2005). It is possible therefore that ischaemia during the early period of unloaded cycling may indeed be at an oxygen consumption equivalent to that of the cardiovascular stress associated with the surgical stress response.

3.3.6. The potential utility of the oxygen pulse for peri-operative prognostication

The oxygen pulse is determined by stroke volume and peripheral uptake of oxygen (Wasserman et al., 2005). It is known that peripheral oxygen extraction falls postoperatively (Older and Smith, 1988, Older et al., 1993, Davies and Wilson, 2004). It is possible that patients who increase their oxygen pulse (and hence possibly their oxygen extraction) during CPET, over a metabolic range commensurate with postoperative requirements may be at increased postoperative risk. It would be reasonable to examine the oxygen pulse response between a VO_2 of 5 $ml.kg^{-1}.min^{-1}$ (the expected oxygen consumption following major surgery (Older and Smith, 1988, Davies and Wilson, 2004)) and 7 $ml.kg^{-1}.min^{-1}$ (the maximum expected oxygen consumption postoperatively (Davies and Wilson, 2004)). This has not been previously investigated.

3.4. Recommendations

The methodology and reporting used in the studies reviewed were not standardised. It is therefore difficult to compare outcomes in a meta-analytical fashion. The need for a standardised pre-operative CPET is needed, where surgical and patient clinical risk factors are reported, as well as the AT, the VO_2 peak, and the units used to present the data. The time and definition of onset of significant myocardial ischaemia and the heart rate and oxygen pulse response to exercise also need to be standardised.

Chapter 4

Cardiopulmonary exercise testing in Durban

Methods

CPET was started as a clinical service at IALCH in October 2004, to investigate high-risk surgical patients prior to surgery. Prognostication was based on the original data published by Older and colleagues (Older et al., 1993). All patients undergoing major vascular surgery were referred pre-operatively for CPET. In addition, all patients with clinical risk factors suggestive of high cardiac risk irrespective of the surgery were also referred for CPET. Between October 2004 and June 2006, 95 patients were referred for CPET at IALCH.

Ethics approval was granted by the Ethics Committee of the Nelson R Mandela School of Medicine to abstract data retrospectively for patients who had undergone CPET. The letter of ethical approval and data abstraction sheet is shown in the appendix.

4.1. The cardiopulmonary exercise test

4.1.1. Equipment and calibration

Test equipment included a Monark® 970 cycle ergometer (Monark Exercise AB, Vansbro, Sweden), an online 12 lead ECG and a metabolic cart. For arm cranking the cycle ergometer is mounted on a table, as we do not have an arm crank. The 12 lead ECG was able to show ST segment changes in all leads. The Schiller CS-200® metabolic cart (Schiller AG, Baar, Switzerland) has an oxygen fuel cell (paramagnetic) (Schiller, 2003)

and a carbon dioxide (ultrasound density) (Schiller, 2003) analyser capable of breath-by-breath gas analysis measurement.

Calibrations of flow and volume measurements and gas analysers were made prior to testing according to the manufacturer's instructions on each day of CPET. The flow measurement device was calibrated using a syringe of known volume (2L) (Schiller, 2003) over various flow rates. The gas analyser's calibration uses a two point calibration corresponding to the equivalent of normal gas concentrations at sea level and exhaled gas concentrations (from the calibration gas cylinder containing a gas mix of 5.2% carbon dioxide in nitrogen). In addition, the gas calibration includes a measure of the delay between the change in gas concentration at the distal end of the sample line and the time it takes for this change to be measured by the gas analysers, in order to align gas analyser data with flow meter measurements (York, 2005).

4.1.2. Preparation of the cardiopulmonary exercise test

We have followed the Consensus Protocol for Pre-operative CPX Testing for York, Torbay and UCLH (York, 2005). In addition, we added arm cranking to our testing procedure. All patients for major vascular surgery were routinely referred for pre-operative CPET. In addition, any patients deemed to be of a high-cardiovascular risk and with a confusing clinical picture presenting for elective surgery, were also referred.

Basic demographic and clinical risk factors associated with cardiac risk were recorded. Patients with absolute contra-indications for CPET were excluded. (Table 4.1) In patients referred with aortic aneurysms, the CT angiograms were reviewed to ensure that there was no evidence of leaking of the aortic aneurysm.

Table 4.1. Absolute contra-indication for CPET (York, 2005, ATS/ACCP, 2003)

Contra-indication	Definition
Acute myocardial infarction	Within 7-10 days of transmural infarct or within 5 days if minor and uncomplicated
Uncontrolled arrhythmias	Symptomatic or haemodynamically compromise
Left main stem coronary artery disease	> 50% stenosis
Malignant hypertension	
Pulmonary oedema	
Desaturation at rest	< 85% while breathing room air
Acute inflammatory conditions (pericarditis, myocarditis)	
Unstable angina	Pain free for < 4 days
Dissecting or ruptured aneurysm	
Acute or recent pyrexial illness	
Thyrotoxicosis	
Syncope	
Thrombosis of limbs	Limbs required to perform exercise test

The test was conducted by myself or Dr N. Kalafatis, with the assistance of a respiratory technologist. Full resuscitation equipment and emergency drugs were readily available. All patients gave informed consent for CPET.

Patients were allocated on their ability to perform cycle ergometry. Only patients with peripheral vascular disease and claudication, who were unable to cycle were allocated to arm cranking. Patients were either positioned on the bike or at a table with the cycle ergometer on the table for arm cranking. The knee had 5 degrees of flexion, with the foot in the neutral position on the pedal at the bottom of the cycle stroke. A Hans Rudolph® 8900 Series nasal and mouthbreathing mask was connected to the respiratory gas analysis lines and held in position with a Hans Rudolph® head cap. The patients were requested to

give their 'best effort', although they could stop if they felt uncomfortable or faint. The patients were instructed in the importance of maintaining 60 RPM during the test, as the power calibration is dependent on both the revolutions and the resistance applied to the flywheel.

The objective was to conduct a ramp test of 10 minutes duration. As our ergometer is not mechanically ramped, the increment in work was adjusted every minute, which is acceptable for measuring the anaerobic threshold (Wasserman et al., 2005). The rate of increment in work was predetermined by the formulae shown in Table 4.2. (York, 2005). Although, the calculation used for unloaded VO_2 is specifically for cycling, we used it in our calculations for arm cranking as well. As 10 $ml.min^{-1}$ VO_2 is approximately equivalent to an increase in 1 watt of power (Wasserman et al., 2005), the expected difference in VO_2 between unloaded and peak VO_2 can be converted into watts per minute over a 10 minute period.

Table 4.2 Calculations for predicted oxygen consumption (York, 2005)

Definition	Calculation
Unloaded VO_2	VO_2 unloaded ($ml.min^{-1}$) = 150 + (6 x weight (kg))
Peak VO_2 female	Peak VO_2 ($ml.min^{-1}$) Women = height (cm) – age (years) x 14
Peak VO_2 male	Peak VO_2 ($ml.min^{-1}$) Men = height (cm) – age (years) x 20
Increment in work rate per minute	($Watts.min^{-1}$) = (Peak VO_2 – Unloaded VO_2) / 100

4.1.3. The stages of the cardiopulmonary exercise test

The test consists of four stages: rest, unloaded cycling, ramp and recovery. The patient sits for approximately three minutes during the rest phase when rest data are collected. This

includes resting ECG, blood pressure, peripheral oxygen saturation, baseline ST analysis and respiratory gas analysis. This also allows the respiratory exchange ratio to fall, as some patients are anxious on presentation for the test. This is followed by three minutes of unloaded cycling. This stage, by providing minimal resistance to exercise, allows for oxygen-dependent enzyme induction (VO_2-on-kinetics) prior to ramping (Biccard, 2005). Ramping then starts, with a ramp in wattage according to the predetermined calculations, effected every minute until the anaerobic threshold was believed to be exceeded.

Monitoring during the test included the 12 lead ECG with ST analysis and breath to breath analysis of VO_2, carbon dioxide production (VCO_2), minute ventilation and the respiratory exchange ratio (RER).

The blood pressure and peripheral oxygen saturation was measured on termination of the test. The ECG was measured until any dysrhythmia or ST changes have reverted to pre test levels or alternatively until heart rate was within 10 beats per minute of the pre test rate (York, 2005).

4.1.4. Termination of the cardiopulmonary exercise test

The test was terminated if the anaerobic threshold was attained (Table 4.3), if myocardial complications compromised patient safety (Table 4.4) or the patient terminated the test. The test was deemed terminated by the patient if he or she stopped pedalling before the other criteria were obtained (Tables 4.3 and 4.4) or the patient failed to maintain more than 30 revolutions per minute for more than 1 minute, despite encouragement (York, 2005).

Table 4.3. Determination of the Anaerobic Threshold (York, 2005, Wasserman et al., 2005)

Using a combination of the following:
Rising ventilatory efficiency for oxygen, despite a plateau for carbon dioxide
RER >1
Rising End Tidal Oxygen, which precedes a fall in end tidal carbon dioxide
Cross over of VCO_2 and VO_2 when plotted on same axis
Increase in gradient of VCO_2 vs VO_2, which exceeds 1

Table 4.4. Myocardial complications demanding termination of the CEPT (Older et al., 1999, York, 2005)

New S-T segment changes exceeding –2.0 mm (depression) or +3.0 mm (elevation)
New dysrythmia occurs

The AT is usually measured using the modified V-Slope method and is confirmed by changes in other variables such as the respiratory exchange ratio, ventilatory efficiency and end tidal values for oxygen. The V-slope method is based on the assumption that the slope of a VCO_2-VO_2 graph cannot exceed one. However, with increased glycolytic metabolism and lactate production, the associated bicarbonate buffering of protons results in an increase in VCO_2 and the slope of the VCO_2-VO_2 graph exceeds one. The point at which this occurs is the AT determined by the V-slope method (Wasserman et al., 2005).

Other methods of confirming the anaerobic threshold are the ventilatory equivalent method. Here with buffering of protons, there is a period of isocapnic buffering following the anaerobic threshold, where the ratio of minute ventilation ($V\dot{E}$) to VO_2 increases without an increase in VO_2/VCO_2 (Wasserman et al., 2005). Because of the relative hyperventilation with respect to oxygen consumption at the anaerobic threshold, the end tidal oxygen concentration ($P_{ET}O_2$) increases while the end tidal carbon dioxide

concentration ($P_{ET}CO_2$) only starts to decrease approximately 2 minutes later (Wasserman et al., 2005).

4.2. Interpretation of the cardiopulmonary exercise test results

4.2.1. Anaerobic threshold

A low anaerobic threshold was defined as a positive test result. For cycling, an AT < 11 $ml.kg^{-1}.min^{-1}$ was considered a positive test result (Older et al., 1993, Older et al., 1999).

As far as arm cranking was concerned, the definition of a low AT which is prognostic for major surgery is not defined. As the muscle mass of arms is smaller than that of the legs, more work is done by the smaller muscle mass in order to maintain the workload and hence the AT is reached at a lower level. The AT relative to the $VO_{2\ peak}$ has been shown to be 46.5 (± 8.9)% for arm cranking and 63.8 (± 9.0)% for cycling (Davis et al., 1976). Therefore the AT of arm cranking was approximately 73% of that recorded during cycling.

However, this is complicated by the fact that the more severe the pathology of the legs, the more an individual will depend on the arms during activities, resulting in a relative increase in the aerobic capacity of the arms. Hence one would expect these patients to have a relative increase in AT for arm cranking in comparison to cycling. This is borne out in research of orthopaedic patients scheduled for major joint replacement of knees and hips, with a mean AT of 10.6 (± 2.4) $ml.kg^{-1}.min^{-1}$ in the cycle group and an AT in the arm cranking of 8 (± 1.7) $ml.kg^{-1}.min^{-1}$ (Philbin et al., 1995). The AT of arm cranking is thus 75% of the AT of cycling in this study. The arm cranking and leg cycling groups were not statistically compared, although cycling mean age and weight were 67.7 (± 1 SD 9.3) years

and 82.8 ((± 1 SD 20.1) kg and arm cranking mean age and weight were 67.4 ((± 1 SD 7.4) years and 86.4 ((± 1 SD 15.8) kg respectively (Philbin et al., 1995).

Paraplegic patients have an AT 18% higher than able-bodied people when arm cranking, probably secondary to metabolic and muscle adaptations associated with an increased reliance on arm exercise (Schneider et al., 1999).

There appears to be no work on the effect of peripheral vascular disease on subsequent arm power (JV Robbs, personal communication). However, with less pedal mobility, a similar increase in aerobic arm functional performance is assumed, in keeping with changes seen with paraplegic patients (Schneider et al., 1999). However, the increase in aerobic capacity of the arms could not be considered to be equivalent to that of paraplegics, as patients with peripheral vascular disease still have pedal mobility. Hence it was assumed that the increase in arm aerobic capacity to be approximately 50% of that seen in paraplegics, hence approximately 9% higher than that routinely observed (Philbin et al., 1995, Davis et al., 1976). Therefore the equivalent to 11 $ml.kg^{-1}.min^{-1}$ for cycling, was 9 $ml.kg^{-1}.min^{-1}$ for arm cranking, based on an expected AT of with arm cranking of 73% of that recorded with cycling (Philbin et al., 1995), plus 9% for improved aerobic arm function, resulting in a predicted AT for arm cranking of 82% of that recorded for cycling.

4.2.2. The time of onset of significant myocardial ischaemia

Early myocardial ischaemia was defined as myocardial ischaemia occurring within two minutes of unloaded exercise (Older et al., 1999), and was considered a positive result for myocardial ischaemia.

4.3. Classification of cardiac outcome

All in-hospital deaths in patients who had undergone CPET were analysed by two independent assessors. One was a surgeon (Professor D. Muckhart) and the other an anaesthetist (Dr S. Bechan), both working in postoperative intensive care. Both were blinded to the patients' CPET results. They were asked to determine if a death was primarily cardiac in origin or not. To fulfil these criteria, the cardiac event had to be deemed the primary precipitant leading to death. Cardiac deaths were classified as 'sudden cardiac death' (AMI or cardiac arrest) and cardiac failure (increasing inotropic requirements without an obvious precipitant cause). The assessors had access to all clinical notes and investigations conducted on the patients. They independently determined the cause of death. The assessors then conferred and if there were any discrepancies regarding the cause of death these were resolved through discussion and consensus was reached.

4.4. Statistical methods

SPSS 13.0 for Windows (1 Sept 2004) was used for data analysis. The distribution of demographic variables was analysed. Levene's test for equality of variances was conducted, when comparing independent data using a two tailed Student's T-test. The two tailed Fisher's Exact Test was performed when analysing categorical data. Alpha was set at 5%. Receiver operating curves were constructed for analysis of the AT and cardiac mortality data.

Chapter 5

Results

5.1. The outcome of all patients referred for CPET

Ninety-five patients were referred for CPET. The subsequent management following referral for CPET, as of the middle of November 2006, is reported in Table 5.1.

Table 5.1. Management of patients referred for CPET

Outcome	Number of patients (percentage)
CPET done and vascular surgery completed	58 (61 %)
CPET done and awaiting surgery	18 (19 %)
Excluded from analysis	19 (20 %)

The reasons for excluding nineteen patients from analysis is listed in Table 5.2.

Table 5.2. Exclusion criteria of patients referred for CPET

Exclusion criteria	Number of patients (percentage)
CPET contra-indicated	3 (16 %)
CPET done and patient absconded	2 (10 %)
CPET done and surgical pathology managed conservatively	10 (53 %)
CPET done and died prior to surgery	1 (5 %)
CPET done and survived nonvascular surgery	3 (16 %)

Of the three patients in whom CPET was contra-indicated; one had a dissection of the common iliac artery and two had evidence of rupture of abdominal aortic aneurysms.

5.2. Patient demographics

The demographics of the patients are shown in Table 5.3. Height and weight were normally distributed, while age was skewed to the right, with a skewness of -1.416. The median age (range) was 68 years (15 to 90) with an interquartile range of 58; 72 years.

There was no difference in the demographics between the patients included in this analysis and the excluded patients from Table 5.2. Levene's Test for Equality of Variances was not significant for age, height or weight and hence equal variances are assumed.

Table 5.3. Demographics of patients included and excluded in this analysis

Patient demographic	Included patients	Excluded patients	P value
Gender (Male/Female)	46 (79 %) / 12 (21 %)	15 (79 %) / 4 (21 %)	
Age (years)	63 ± 13.4 †	67 ± 12.5 †	0.189
Weight (kg)	69.1 ± 13.0 †	65.5 ± 18.3 †	0.356
Height (cm)	168.20 ± 7.4 †	165.8 ± 7.2 †	0.243

† Mean ± 1SD

5.3. Cardiopulmonary exercise test results

Twenty-seven patients performed arm cranking and 31 patients underwent cycle ergometry. Levene's test for equality of variances was not significant (p=0.679). The two tailed t-test for independent variables found the AT to not be significantly different between the arm cranking and cycling groups (p=0.069). The AT results are shown in Table 5.4.

Table 5.4. Group anaerobic threshold results expressed in $ml.kg^{-1}.min^{-1}$

Test	Mean ± 1SD	95% CI	T value	P value
Arm cranking	11.7 ± 3.8	10.1 - 13.3	-1.862	0.069
Cycle ergometer	13.7 ± 3.6	12.7 - 14.6		

5.4. Cardiac outcome according to surgical procedure

The cardiac deaths classified according to surgical procedures are shown in Table 5.5. Cardiac deaths only followed aortic surgery. This included both open and endovascular procedures.

Table 5.5. Outcomes related to specific vascular surgical procedures

Vascular surgical procedure	N subjects	N (percentage) cardiac deaths
Emergency abdominal/ thoracic	1	1 (100 %)
Elective abdominal/ thoracic	40	6 (15 %)
EVAR	10	2 (20 %)
Extra-anatomic shunts	3	0 (0 %)
Infra-inguinal bypass	4	0 (0 %)

N = number of; EVAR = endovascular aortic aneurysm repair

5.5. Subgroup analysis of patients undergoing surgery associated with reported cardiac mortality

An analysis of the subgroup of the 50 patients undergoing the elective vascular surgical procedures with reported cardiac mortality (abdominal / thoracic and EVAR) was conducted. This group had a cardiac mortality of 16%. As this is an analysis of outcome following major elective vascular surgery, the single emergency procedure is excluded.

5.5.1. Anaerobic threshold

Using a positive test result of an AT < 11 $ml.kg^{-1}.min^{-1}$ for the cycle ergometer and an AT < 9$ml.kg^{-1}.min^{-1}$ for the arm cranking, this test was found to not be significantly associated with cardiac death. (Table 5.6)

Table 5.6. Anaerobic threshold and cardiac outcome

Anaerobic threshold	Cardiac deaths	Survivors	Total
Low	3 (33 %)	6	9
High	5 (12 %)	36	41

Fisher's Exact Test 2-tailed p=0.144.

As this study design is a retrospective cohort, the relative risk is used (as opposed to the odds ratio). The risk ratio associated with cardiac death following a low AT was 2.73 [95% CI 0.79-9.41]. The sensitivity was 0.38 [95% CI 0.10-0.74], the specificity was 0.86 [95% CI 0.71-0.94], the positive predictive value was 0.33 [95% CI 0.09-0.69] and the negative

predictive value was 0.88 [95% CI 0.73-0.95]. The positive likelihood ratio is 2.7 and the negative likelihood ratio is 0.7.

The area under the curve for receiver operating curves for arm cranking and cycle ergometry were both insignificant (p=0.50 and p=0.61 respectively) and thus the sample size was too small to determine cut points.

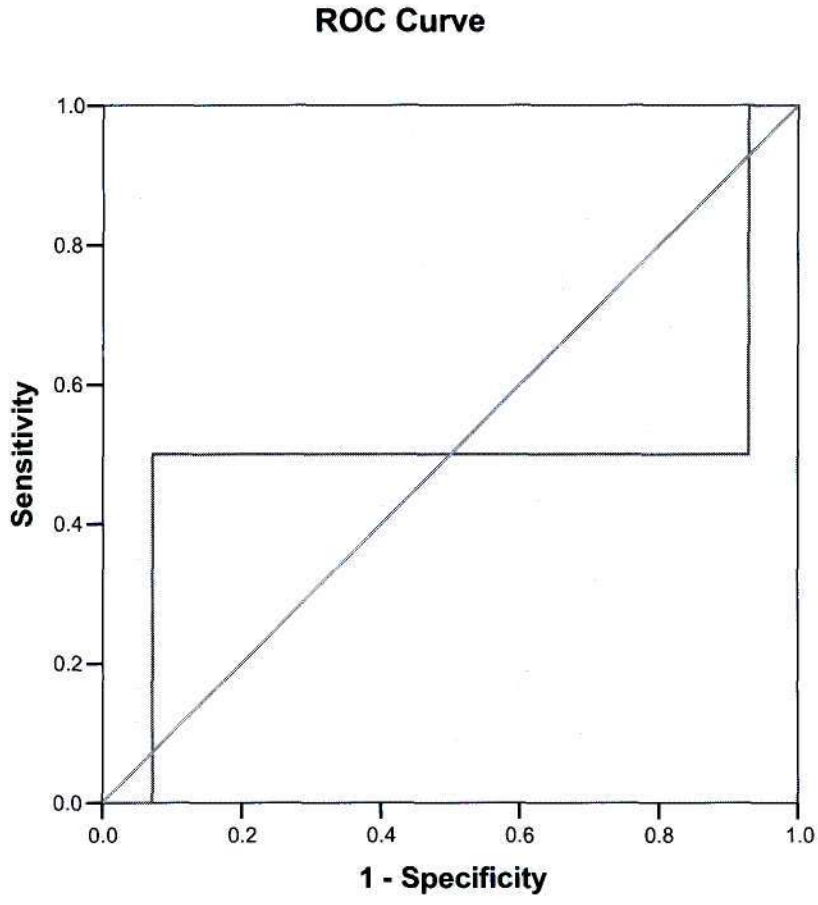

Figure 5.1. ROC for AT measured during arm cranking and cardiac mortality

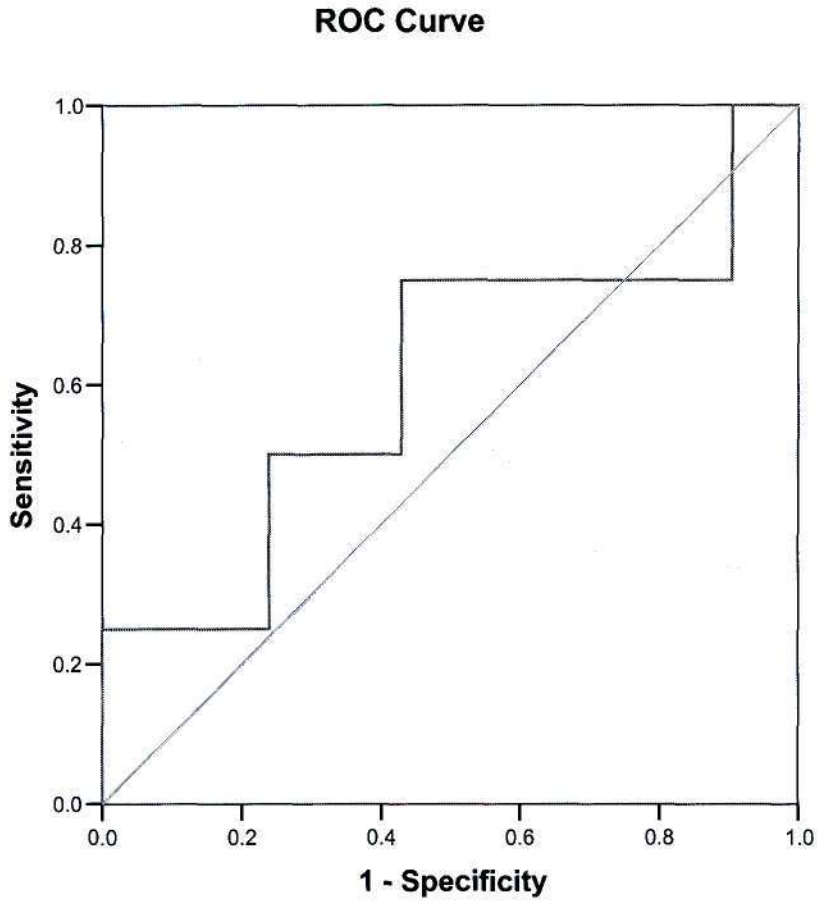

Figure 5.2. ROC for AT measured during cycling and cardiac mortality

5.5.2. The change in oxygen pulse and heart rate between a VO_2 of 5 and 7 ml.kg^{-1}.min^{-1}

Analysis of the heart rate difference between 5 and 7 ml.kg^{-1}.min^{-1} (the expected and maximum expected oxygen consumption following surgery respectively) and the percentage change in oxygen pulse between 5 and 7 ml.kg^{-1}.min^{-1} revealed no statistical difference between the high and low anaerobic threshold groups (Table 5.7).

Table 5.7 The change in oxygen pulse and heart rate between 5 and 7 $ml.kg^{-1}.min^{-1}$ during CPET for low and high anaerobic threshold groups

Anaerobic threshold	Difference between 5 and 7 $ml.kg^{-1}.min^{-1}$	Mean ± 1SD	T value	P value
Low	Oxygen pulse (%)	16.7 ± 10.1	-0.399	0.694
High		18.5 ± 18.0		
Low	Heart rate (bpm)	13 ± 8	0.536	0.595
High		12 ± 9		

The nine low anaerobic thresholds reported are shown in Table 5.8. None of these patients had early myocardial ischaemia. Using the decision analysis flow diagram of Wasserman et al all the patients were shown to be limited primarily by cardiac function (as opposed to respiratory or pulmonary vascular disease).

Table 5.8. Details of the nine patients with a low AT.

Patient	AT	Arm/ Cycle	Outcome	Oxygen pulse at specified VO_2 ($ml.kg^{-1}.min^{-1}$)			HR at specified VO_2 ($ml.kg^{-1}.min^{-1}$)		
				5	7	% change in oxygen pulse	5	7	Increase in HR
48	9.38	Cycle	Survived	4.4	4.8	9	110	126	16
54*	9.18	Cycle	Survived	6.6	7.8	18	47	60	13
74	6.60	Arm	Survived	3.3	3.6	9	98	123	25
80	9.90	Cycle	Survived	4.6	5.2	13	103	108	5
86*	10.10	Cycle	Survived	Indeterminate as VO_2 at rest > $7ml.kg^{-1}.min^{-1}$					
88*	9.30	Cycle	Survived	6.1	6.6	8	64	81	17
14	8.63	Arm	Died†	4.2	4.7	12	84	105	21
24*	5.00	Cycle	Died†	4.8	6.5	35	73	76	3
22*	10.80	Cycle	Died‡	4.6	5.9	28	77	84	7

* Patients on chronic beta-blockade; †cardiac failure; ‡ sudden cardiac death following postoperative myocardial ischaemia

The mean difference (± 1SD) in the increase in the oxygen pulse between a VO_2 of 5 and 7 $ml.kg^{-1}.min^{-1}$ for the survivors and non-survivors respectively was 11.5 ± 4.2 and 25.2 ± 12.1 percent. This approached significance with a t-value of 2.417 and a p value of 0.052.

The mean difference (± 1SD) in heart rate (HR) between a VO_2 of 5 and 7 $ml.kg^{-1}.min^{-1}$ for the survivors and non-survivors respectively was 15.2 ± 7.2 and 10.3 ± 9.5 beats per minute. This was not significant with a t-value of 0.829 and a p value of 0.439.

Analysis of the patients with a high AT, showed that the mean difference (± 1SD) in the increase in the oxygen pulse between a VO_2 of 5 and 7 $ml.kg^{-1}.min^{-1}$ for the survivors and non-survivors respectively was 18.5 ± 18.8 and 18.7 ± 13.2 percent. This was not significant with a t-value of -0.16 and a p value of 0.987.

5.5.3. Early myocardial ischaemia during CPET

Three of the patients out of the 95 patients referred for CPET had early myocardial ischaemia during CPET. The first and third patients had an acceptable AT and the second patient had a low AT. Based on the reported cardiovascular mortality by Older and colleagues in elderly patients undergoing major abdominal surgery, the expected mortality was 4% for the first patient and 42% for the second patient (Older et al., 1993). As a result, the first patient was acutely beta-blocked for the peri-operative period and underwent endovascular aneurysm repair (EVAR). This patient had an early postoperative cardiac death. The second patient was referred for coronary angiography, which found three vessel coronary artery disease with tight ostial stenosis of the left mainstem requiring coronary artery bypass grafting. Based on the outcomes of the first two patients, the third patient

was referred to the cardiologists. The outcome of the cardiological assessment is still awaited.

5.5.4. Clinical risk factors

Lee's Revised Cardiac Risk Index (Lee et al., 1999) was found to be non predictive of cardiac death (Table 5.9).

Table 5.9. Lee's RCRI and cardiac outcome

Lee's RCRI	Cardiac deaths	Survivors	Total
0 or 1 risk factors	5 (14%)	31	36
> 1 risk factors	3 (21%)	11	14

Fisher's Exact Test 2-tailed p=0.67

5.5.5. Left ventricular ejection fraction

A traditional cut-off of an ejection fraction of ≤ 35% was used as a predictor of a high-risk patient previously in Durban. This was also non predictive of cardiac mortality. (Table 5.10)

Table 5.10. Ejection fraction and cardiac outcome

Ejection fraction	Cardiac deaths	Survivors	Total
≤ 35%	0 (0%)	1	1
> 35%	7 (17%)	34	41

Fisher's Exact Test 2-tailed p=1.00

5.5.6. Chronic medical therapy

The cardiac outcome associated with chronic statin and beta-blocker therapy is shown in Tables 5.11 and 5.12.

Table 5.11. Pre-operative statin therapy and cardiac outcome

Statin therapy	Cardiac deaths	Survivors	Total
No therapy	6 (15%)	33	39
On therapy	2 (18%)	9	11

Fisher's Exact Test 2-tailed p=1.00

Table 5.12. Pre-operative chronic beta-blocker therapy and cardiac outcome

Chronic beta-blocker therapy	Cardiac deaths	Survivors	Total
No therapy	4 (11%)	31	35
On therapy	4 (37%)	11	15

Fisher's Exact Test 2-tailed p=0.22

Chapter 6

Discussion

Due to the small sample size (despite nearly two years of a CPET clinical service), a number of important clinical issues cannot be statistically verified. In addition, the findings which are statistically significant have such small numbers in the contingency tables that a type one error cannot be excluded. However, the importance of the data presented here, cannot be ignored.

6.1. Surgical risk

Cardiac deaths were only recorded in patients undergoing surgery involving the abdominal and/ or thoracic aorta (both open and closed procedures). The most striking characteristic of the data presented is that the cardiac mortality is high; 18% for the group as a whole and 60% in patients with a low anaerobic threshold and 12% with an acceptable anaerobic threshold. This is higher than the cardiac mortality expected from the international literature of aortic surgery (NCEPOD, 2005, Le Manach et al., 2005). The all-cause 30-day mortality for elective abdominal aneurysm repairs was 6.2% in the NCEPOD report on 2004 practice in the United Kingdom (NCEPOD, 2005). In addition, the mortality in both high and low AT groups was higher than similar groups for aortic surgery in the United Kingdom (McEnroe and Wilson, 2005). The reasons for our high cardiac mortality could include higher cardiovascular risk associated with epidemiological transition (Opie and Mayosi, 2005), associated with suboptimal primary medical care in our population (MRC/BHF, 2002, Biccard et al., 2005b).

The numbers presently are too small in this study to stratify patients statistically according to procedures of different surgical risk. However, clinically all the cardiac deaths are in the aortic surgery group. This is consistent with the published literature (Kertai et al., 2005), where aortic surgery is the most important elective surgery cardiovascular risk subgroup. Compared to carotid endarterectomy (as a reference procedure) which is considered the lowest cardiovascular risk group associated with vascular surgery, the odds ratio associated with thoraco-abdominal or abdominal aortic surgery was 13.1 (95% CI 3.6-47.7) (Kertai et al., 2005). This clearly has an important clinical application, as the alternative surgical option of an 'extra-anatomic' shunt had no mortality in this cohort, even when the anaerobic threshold was poor. This is consistent with other reports of surgical risk. Surgical risk is more reliable at identifying the true negatives (Ridley, 2003), that is patients undergoing low or intermediate risk surgery are unlikely to have an adverse cardiac outcome (Ali et al., 2000). Surgical risk is specific (Ali et al., 2000) (and thus an adverse outcome would be unlikely in low risk surgery).

6.2. The cardiopulmonary exercise test result

A low AT was not statistically associated with peri-operative cardiac death in this study, as some of these patients still survived despite a low anaerobic threshold. (Table 5.6) The question is whether these patients could be predicted.

6.2.1. The low anaerobic threshold without early myocardial ischaemia

It may be possible to predict survivors with a low AT, if one examines the cardiovascular response during CPET to increasing VO_2 from 5 $ml.kg^{-1}.min^{-1}$ (the expected oxygen consumption following major surgery (Older and Smith, 1988, Davies and Wilson, 2004)) to 7 $ml.kg^{-1}.min^{-1}$ (the maximum expected oxygen consumption postoperatively (Davies

and Wilson, 2004)). (Table 5.7) The survivors increase their heart rate more than non-survivors, while the non-survivors increase their oxygen pulse more than survivors. The latter response is approaching statistical significance. (Table 5.8) Conversely, beta-blocked patients who died, could not increase their heart rate by 10 bpm and simultaneously increased their oxygen pulse by > $1ml.kg^{-1}.min^{-1}$.

This response is in physiological agreement with what we understand about the postoperative period. Patients who rely more on increasing their oxygen pulse (non-survivors) than their heart rate (survivors) are at risk postoperatively. The oxygen pulse is a function of the increasing stroke volume and peripheral uptake of oxygen (Wasserman et al., 2005). The dependence on increasing oxygen extraction peripherally, is compromised postoperatively with the oxygen extraction ratio falling to 30% (Older and Smith, 1988, Older et al., 1993, Davies and Wilson, 2004). As stroke volume should be maximal postoperatively (Biccard, 2004) and haemoglobin should be optimally managed, the only two physiological determinants of increasing oxygen delivery are the heart rate response and the fraction of inspired oxygen. Thus patients able to increase their heart rate, are at a physiological advantage postoperatively over patients who are reliant on increasing peripheral oxygen uptake during increasing exercise.

This prognostic marker has not been previously described. It suggests an 'aerobic surgical metabolic reserve' identifiable in potential survivors with a low AT. However, in order to confirm a statistically significant difference in the oxygen pulse and heart rate response between survivors and non-survivors, a sample size of 24 patients (12 patients per group) and 28 patients (14 patients per group) respectively would be required. This is based on the

results shown in Table 5.8 and calculated for a power of 80% and an alpha error of 5% (EpiCalc 2000, Joe Gilman and Mark Myatt 1998, Brixton Books).

If one was to use the oxygen pulse response to increasing exercise intensity between 5 and 7 $ml.kg^{-1}.min^{-1}$ to further discriminate patients, the sensitivity and specificity of the test would be further improved. A negative test result could be considered a 'high' AT or a 'low' AT with an oxygen pulse increase of < 20% between 5 and 7 $ml.kg^{-1}.min^{-1}$, and a positive test result could be considered a 'low' AT with an oxygen pulse increase of > 20% between 5 and 7 $ml.kg^{-1}.min^{-1}$. Using 20% as a cut-off is based on a 2SD from the mean of the change oxygen pulse in the survivors (mean $\pm$ 1SD for survivors of 11.5% $\pm$ 4.2).

Table 6.1. The effect of incorporating oxygen pulse into the test result for CPET

Anaerobic threshold and change in oxygen pulse	Cardiac deaths	Survivors	Total
Low with increase in oxygen pulse >20%	2 (100%)	0	2
High or Low with increase in oxygen pulse < 20%	6 (11%)	42	48

Fisher's Exact Test 2-tailed p=0.02.

The risk ratio associated with cardiac death following a low AT coupled with an increase in oxygen pulse of >20% between 5 and 7 $ml.kg^{-1}.min^{-1}$ was 8.00 [95% CI 3.8-16.9]. The sensitivity was 0.25 [95% CI 0.04-0.64], the specificity was 1.00 [95% CI 0.90-1.00], the positive predictive value was 1.00 [95% CI 0.20-0.95] and the negative predictive value was 0.88 [95% CI 0.74-0.95]. The positive likelihood ratio is ∞ and the negative likelihood ratio is 0.75.

6.2.2. The presence of early myocardial ischaemia

It is impossible to statistically evaluate early myocardial ischaemia as a clinical risk factor. As our patients were vascular surgical patients, the finding of early myocardial ischaemia on unloaded exercise may be an important prognosticator of significant coronary artery disease independent of the AT, in the presence of major vascular surgery. This is contrary to the case mix of major abdominal surgery as presented by Older's group where patients with a good anaerobic threshold and early myocardial ischaemia had a cardiovascular mortality of 4% with a low anaerobic threshold and early myocardial ischaemia had a cardiovascular mortality of 42% (Older et al., 1993). It therefore appears that medical therapy may be even inadequate in patients with a good AT, and I would recommend that all vascular surgical patients with early myocardial ischaemia on CPET, should be referred for coronary angiography.

6.3. Clinical risk indices

Lee's RCRI is the most predictive clinical risk index for major cardiac complications following surgery (Lee et al., 1999). However, when using a discriminator of less than 2 clinical risk factors (which theoretically should be associated with a good clinical outcome) with acute peri-operative beta-blockade alone (Boersma et al., 2001), and more than 2 clinical risk factors (a high risk group), no difference could be shown in the low risk and high risk group. There are two possible reasons for this. Firstly, the sample size is too small to show a difference. The second possibility is that the weighting of clinical risk factors for peri-operative cardiac events in our population (Steyn et al., 2005) is different to that reported in the international literature. It is important to continue to attempt to identify low-risk patients based on the presence or absence of clinical risk factors. This would

prevent inappropriate use of CPET (Grimes and Schulz, 2005), with resultant false positive test results and consumption of resources.

6.4. Medical therapy

It is likely that chronic beta-blockade may not be protective in the peri-operative period (Giles et al., 2004), as opposed to acute peri-operative beta-blockade (Devereaux et al., 2005a). Conversely, statin therapy may provide peri-operative cardioprotection for high-risk patients presenting for noncardiac surgery (Biccard et al., 2005b). Although neither drug was statistical associated with a specific cardiac outcome, the trends seen with chronic beta-blockade were consistent with the literature; there were more cardiac deaths in the chronically beta-blocked group (37% versus 11%). The real concern is despite the exceptionally high cardiac mortality in our patients, only 22% of these patients were on statin therapy prior to surgery. This is similar to what the incidence was between 1991 and 2001 in Holland (Kertai et al., 2004). It is suggested that all vascular patients should receive statin therapy (MRC/BHF, 2002), and clearly the high mortality in this group suggests that this is appropriate, especially as statins positively affect the outcomes associated with acute coronary events (Biccard et al., 2005b). In the NCEPOD study of abdominal aneurysm surgery in the United Kingdom conducted over a two month period in 2004, the incidence of statin therapy in elective patients was 53% (NCEPOD, 2005). Thus our figures are approximately a quarter of the desirable therapeutic intervention (MRC/BHF, 2002), and about a half of the 'real' figures of a first world country (NCEPOD, 2005).

6.5. Recommendations

CPET has been shown to be the only special investigation to provide valuable prognostic information in high-risk vascular patients in this study. It is for this reason that it is imperative that CPET continues in Durban.

We now have pretest probabilities (Grimes and Schulz, 2005) associated with cardiovascular mortality and CPET. With continued auditing of our management and outcomes, we can apply likelihood ratios to our own work and with the use of Fagan's nomogram (Fagan, 1975) accurately prognosticate for both patient and surgeon.

6.5.1. Future study recommendations

There are three areas of research that should be immediately implemented. Firstly, the high cardiovascular mortality in these patients would suggest that there is a further subgroup in this population who sustain undiagnosed peri-operative myocardial infarctions. It is well-known that postoperative myocardial infarctions increase adverse cardiac events twenty-fold within two years of surgery (Mangano et al., 1992) and result in a fourfold increase in mortality within three to five years of surgery (Charlson et al., 1994). There is therefore a strong indication to study troponin levels in all the patients who are being referred for CPET to identify the incidence of myocardial infarction in this group, identify and manage peri-operative myocardial infarctions appropriately (which are currently been missed) and to identify those patients who are at increased long-term risk secondary to peri-operative myocardial infarction.

Secondly, it is necessary to continue to study both the traditional clinical risk indices associated with postoperative cardiac complications (Lee et al., 1999), as well as follow

other clinical risk factors associated with AMI in Sub-Saharan Africans following the INTERHEART study (Steyn et al., 2005). It is vital that a clinical risk index is established which is specific for our patient population.

Finally, the 'surgical heart rate reserve' needs to be clarified. Indeed, an appropriate approach would be to pool data from various centres currently performing CPET and analyse the findings. This would either confirm or refute the proposal made in this thesis. Similarly, the 'so-called' non-responders of haemodynamic optimisation studies may have thus been identified by the fact that they have a low 'surgical heart rate reserve'.

6.5.2. Revision of the peri-operative management protocol of patients for elective abdominal or thoracic vascular surgery

Based on the outcomes reported here, the following revised peri-operative management protocol of that listed in Table 2.12 is presented in Figure 6.1. The suggested revision of our peri-operative management protocol for elective major vascular surgery is based on the following principles. As the cardiovascular mortality of the group with a good AT without early myocardial ischaemia exceeds 10%, it is therefore appropriate to recommend that all these patients are acutely beta-blocked (Biccard et al., 2006), provided that there is no contra-indication.

Some of the patients with a poor AT appear to still have the capacity to survive the surgical stress response. As it is likely that an adequate 'surgical heart rate reserve' is necessary to increase oxygen delivery postoperatively, should it be required (for example following acute haemorrhage or anaemia), beta-blockade cannot be recommended in these patients. However, as these patients are at major peri-operative cardiovascular risk they should all

receive peri-operative statin therapy (Biccard et al., 2005a) and be haemodynamically optimised (Kern and Shoemaker, 2002). Postoperatively, serial troponin levels should be monitored to identify if any of these patients are at risk of a late myocardial infarction secondary to myocardial oxygen-supply demand imbalance (Le Manach et al., 2005). If this is suggested, then late initiation of acute peri-operative beta-blockade may be considered once the stress response is starting to tail off.

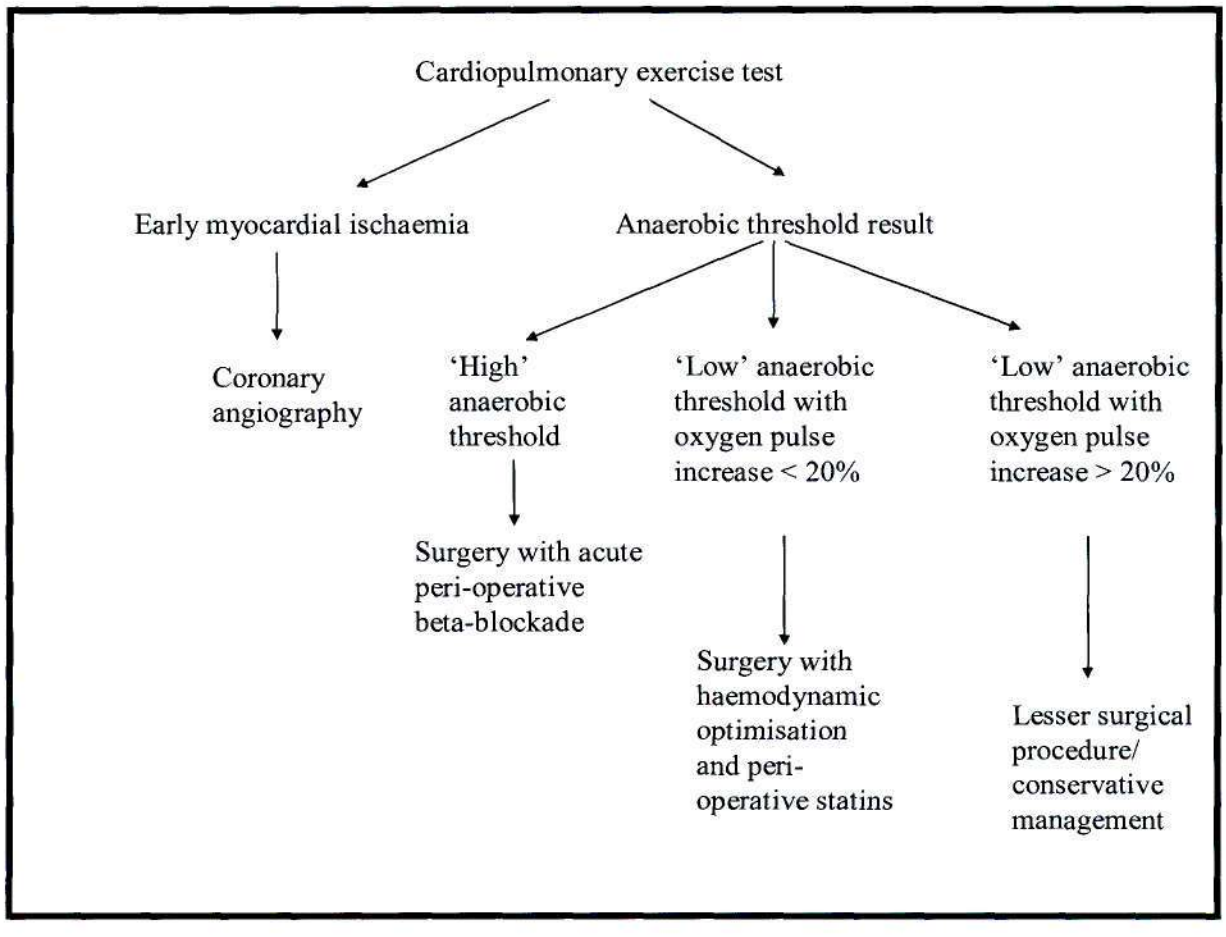

Figure 6.1. Flow diagram of proposed peri-operative management based on CPET result

The patients without a 'surgical heart rate reserve' are unlikely to be able to tolerate any acute short-term increase in aerobic metabolic demand and hence oxygen delivery. In these

patients, conservative management or 'lesser' surgical procedures should be seriously considered.

All patients experiencing early myocardial ischaemia on CPET, should be referred for coronary angiography to exclude patients with lesions warranting coronary revascularisation pre-operatively. This approach would not over-extend resources, as in a nearly two year period, this would have resulted in three patients been referred to cardiology for angiography. Indeed, it could be argued that the use of CPET pre-operatively significantly decreases unnecessary cardiological referrals.

Based on the angiographic result, two management options can be considered. In the patients with coronary artery disease warranting revascularisation, this should proceed prior to the noncardiac surgery. These patients should then return for a repeat CPET prior to the noncardiac surgery. Peri-operative management decisions should be determined by this second CPET.

Patients referred for coronary angiography, who are found not to have an indication for coronary revascularisation should be managed with acute intense peri-operative beta-blockade. As myocardial ischaemia is almost certainly present at the metabolic demand associated with the postoperative stress response, a lesser procedure with a commensurate lesser stress response would be preferable.

6.6. Limitations of this work

This work is retrospective. The sample size is small and hence a number of questions can not yet be answered. The clinicians were not blinded to the results. In addition, the AT cut-

off for arm cranking was estimated. It has not been prospectively evaluated. As only two individuals died following arm cranking (one in the 'low' group and one in the 'high' group), it is impossible to assess the validity of 9 $ml.kg^{-1}.min^{-1}$ as a predictor of peri-operative cardiac outcome. In this study, a cutoff value of 8.9 $ml.kg^{-1}.min^{-1}$ performed best with a sensitivity of 50% and a specificity of 93%. A larger sample size is needed in order to further define an appropriate cutoff value for arm cranking.

6.7 Conclusion

Pre-operative CPET at IALCH for high-risk South African surgical patients provides clinically useful peri-operative prognostic information. The CPET result allows for appropriate patient risk stratification and peri-operative management. Further investigation is required to confirm the importance of a 'high oxygen extraction' between 5 and 7 $ml.kg^{-1}.min^{-1}$ and 'early myocardial ischaemia' measured during CPET as determinants of patient survival. It is recommended that CPET continues as a clinical service for high-risk surgical patients at IALCH.

Appendices

1. Letter of ethical approval

24 February 2006

Mr B Biccard
Department of Physiology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

PROTOCOL: CARDIOPULMONARY EXERCISE TESTING FOR HIGH RISK - SOUTH AFRICAN SURGICAL PATIENTS. B BICCARD, PHYSIOLOGY. REF: H331/05

Dear Mr Biccard

A sub-committee of the Biomedical Research Ethics Committee considered the abovementioned application and the protocol was approved. The study is given full ethics approval and may begin as at today's date: 24 February 2006.

This approval is valid for one year from 24 February 2006. To ensure continuous approval, an application for recertification should be submitted a couple of months before the expiry date. In addition, when consent is a requirement, the consent process will need to be repeated annually.

I take this opportunity to wish you everything of the best with your study. Please send the Biomedical Research Ethics Committee a copy of your report once completed.

Yours sincerely

PROFESSOR J MOODLEY
Chair: Biomedical Research Ethics Committee

2. Data extraction sheet

1. Demographics
    a. Gender
    b. Age
    c. Weight
    d. Height
2. Clinical risk factors
    a. Ischaemic heart disease- history
    b. Ischaemic heart disease- ECG
    c. History of congestive cardiac failure
    d. History of stroke
    e. Diabetes mellitus
    f. Serum creatinine
    g. Hypertension
    h. Left ventricular ejection fraction
    i. Chronic beta-blockade
    j. Statin therapy
3. Cardiopulmonary exercise test
    a. Type of test
    b. Anaerobic threshold
    c. Presence and time of myocardial ischaemia during CPET
    d. Heart rate between 5 and 7 $ml.kg^{-1}.min^{-1}$
    e. Oxygen pulse between 5 and 7 $ml.kg^{-1}.min^{-1}$
4. Surgical procedure
5. Postoperative outcome until discharge

a. Death

b. Myocardial infarction

c. Inotrope requirements

d. Postoperative haemorrhage

e. Postoperative anaemia

f. Postoperative blood pressure

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