**STUDY PROTOCOL**

**Pilot Study and Preoperative Fitness Study assessing**

**High Intensity Interval Training to optimise fitness before major abdominal surgery**

Can High Intensity Interval Training improve preoperative fitness and postoperative outcomes?

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| Principal Investigator | **Doctor John Woodfield**, Senior Lecturer, Department of Surgical Sciences, University of Otago, Dunedin |

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| Co-Investigators | **Kate Thomas**, Vascular Technologist and PhD Candidate, Department of Surgical Sciences and School of Physical Education, Sport and Exercise Sciences, University of Otago, Dunedin |
| **Doctor Chris Baldi,** Senior Research Fellow, Department of Medicine, University of Otago, Dunedin |
| **Doctor Matthew Zacharias,** Senior Lecturer, Department of Surgical Sciences, University of Otago, Dunedin |

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# 1. Synopsis

**Title for Preoperative Fitness Studies:** High Intensity Interval Training (HIIT) to optimise fitness before major abdominal surgery

**Preoperative Fitness study Participants:** 30 patients scheduled for major abdominal surgery

**Overall Sample Size:** After 30 patients have been enrolled the sample size required for the completion of the study will be calculated.

**Planned Study Duration:** September 2015 to December 2017

**Preoperative Fitness study Objectives:**

To assess if a preoperative exercise program using high intensity interval training can improve fitness, as measured by an increase in peak oxygen consumption of >2ml/kg/min

To assess a range of clinical endpoints which may be used to determine if improving fitness can improve clinical outcomes after surgery. To determine which of these clinical endpoints will be the best endpoint to select as the primary endpoint for a subsequent clinical outcomes study

# 2. Background

The ability to predict who will develop perioperative complications remains difficult because the aetiology of adverse events is multifactorial [1]. Many important risk factors, such as the number of pre-existing comorbidities, the extent of the underlying pathology and the magnitude of the required operation cannot be changed prior to surgery. However there is the possibility that one important area that contributes to perioperative morbidity, the ‘overall fitness’ or cardiopulmonary functional reserve of the patient, could be improved preoperatively by an individualised exercise program. The patients’ cardiopulmonary function can be assessed by measuring oxygen consumption during cardiopulmonary exercise testing (CPET). It has also been demonstrated that poor performance on CPET, for example an anaerobic threshold (AT) of <10-11ml/kg/min [2,3,4]; or a Peak oxygen consumption (Peak VO2) of <15-18.6ml/kg/min [5] is associated with a significantly higher rate of postoperative complications.

Studies assessing the impact of exercise on CPET measurements show that the use of High Intensity Interval Training (HIIT) results in a better improvement in Peak VO2 than continuous moderate exercise [6], and have also demonstrated HIIT to be safe in patients with moderate coronary artery disease and cardiac failure [7]. Although the general benefits of exercise have been widely studied, there is a surprisingly limited amount of data, using objective measurements such as Peak VO2 or AT, on the ability of a structured exercise program to improve cardiorespiratory performance before surgery. We identified four prospective studies performed over a four to six week period [8,9,10,11]. Although these all documented an improvement in either Peak VO2 or oxygen consumption at AT, in one study this was considered to be too small to be clinically significant [10]. Other limitations of these studies included a small sample size (12-39 patients), only two studies having a control group [8,10] and only one being randomized [10]. Two assessed patients undergoing thoracic surgery [9,11], one was before rectal surgery [8] and the other assessed patients with abdominal aortic aneurysms [10]. Further randomised studies are therefore indicated. A second problem is that although we know that fitter patients do better [2,3,4,5], no study has demonstrated that improving fitness preoperatively will result in a subsequent reduction in perioperative complications. Although in some reviews this has been assumed to be the case, this assumption needs to be properly tested. This would require not only studying preoperative response to HIIT, but also documenting a range of relevant postoperative clinical outcomes such as hospital stay, postoperative complications, recovery from surgery and quality of life. The overall aim of our study is therefore to assess the impact of a focused short term exercise program on both preoperative fitness and postoperative outcomes. We aim to do this by first performing a preoperative fitness study and then a postoperative outcomes study.

# 3. Objective and Hypothesis

The overall objective of this study is to examine the impact of a focused individualized high intensity interval exercise program over a four to six week period on preoperative fitness and postoperative complications.

The hypotheses to be tested are that:

1) An individualized and supervised preoperative HIIT program will result in a clinically significant increase in Peak VO2  of 2ml/kg/min

2) A clinically significant increase in Peak VO2 will result in clinically relevant improvements in length of hospital stay, complications and time to return to normal level of functioning after surgery.

The objectives of the preoperative exercise study are

1) To examine the optimal individualization and delivery of HIIT to patients who are scheduled for major abdominal surgery. This study population which will include patients with advancing age and medical co-morbidities.

2) To assess if an individualized and supervised preoperative HIIT program will result in a clinically significant increase in Peak VO2  of 2ml/kg/min

3) To explore the best primary outcomes for a subsequent randomised controlled trial examining clinical endpoints. The distribution of measurements for these endpoints will be used to calculate the sample size for the clinical outcomes study

The objective of our planned subsequent clinical outcome study will be to assess if a significant increase in Peak VO2 will result in clinical benefits, such as in length of hospital stay, postoperative complications and time to return to normal level of functioning after surgery. The clinical outcome study will only be performed if the preoperative exercise study shows a significant increase in Peak VO2  of 2ml/kg/min. The protocol and ethics application for this study will be submitted following the completion of the preoperative exercise study.

**4. Overview**

 ENROLMENT

Patient booked for major abdominal surgery in 6 weeks Aged 45-85

**Excluded**

Inability to exercise

Uncontrolled hypertension

Clinical angina or MI in last 3 months

AAA > 6.5 cm

Severe COPD, FEV1 < 1.0

Anaemia <80g/l

Short course radiotherapy

Explanation of study and consent

Routine preoperative testing

Initial data collection including SF 36 and CPET testing

**Excluded**

Inability to perform CPET

Contraindication on CPET

Randomisation

Allocation 1:1

 ALLOCATION

Exercise training

n > 15

Usual Care

n > 15

 INTERVENTION

 4 – 5 weeks

H I I T

14 sessions, 4 to 5 weeks

Preoperative Assessment (CPET and SF 36)

 HOSPITAL STAY

Surgery

Surgery

(Weekly exercise sessions continue if surgery delayed)

Post-operative data collection up to discharge.

Including POMS, SRS, morbidity, mortality and length of stay

 FOLLOW -UP

Post discharge data collection.

6 weeks – final complications, SRS and SF36

3 months – SF 36

(All abbreviations are covered in the text)

# 5. Study Design

### 5.1 Methodology and Study Participants

This is a prospective observational study assessing the impact of a clinical intervention (HIIT). Patients undergoing major abdominal surgery, will be invited to participate if they meet the inclusion criteria. In terms of recruitment there will be two main points of entry into the study. The first will be when the patient is booked for surgery at the outpatient department, where they will be given information about the study and will then be contacted by the research nurse. The second will be when the patient is to be taken off a waiting list for surgery, at which time they will be contacted by the research nurse. Those who are interested will be interviewed by the research nurse. All subjects will be familiarised with the protocol before providing written consent. Participant’s preference for ‘exercise’ training or ‘usual care’ will be documented. They will then be assessed in an anaesthetic clinic for their preoperative workup and the first cardiopulmonary exercise test (CPET) will be performed. After this patients will be randomly allocated 1:1 to the exercise training group or the usual care group. The number of patients approached, those excluded and those who decline to be involved will be documented.

### 5.2 Inclusion / Exclusion Criteria

Inclusion criteria:

1) Patient offered major abdominal surgery

2) Aged 45-85

3) Approximately six weeks to wait until surgery

Exclusion criteria:

 1) Inability to exercise or to perform a CPET

 2) Contraindication found on CPET

 3) Uncontrolled hypertension (BP>180/100)

4) Experiencing clinical angina (Does not include those who are asymptomatic on Rx or those who have had successful revascularization)

 5) Myocardial infarction in the past 3/12

6).Uncontrolled cardiac arrhythmias

7) Intracranial aneurysm

8) Aortic aneurysm >6.5cm

9) Severe obstructive pulmonary disease with a FEV1 < 1.0 litres

10) Inability to provide consent

11) Significant anaemia, Hb <80g/l

12) Short course preoperative radiotherapy

### 5.3 Intervention Protocols

*Cardiopulmonary Exercise Testing (CPET)* will be performed before HIIT and again before surgery (after the completion of 14 sessions of HIIT)

Cardiopulmonary exercise testing will be performed in the cardiology ward in the seventh floor of Dunedin Public Hospital on an electromagnetically braked ergometer using individualised ‘stepped; protocols based on the individual’s fitness levels as described [12]. This will be supervised by a senior researcher with medical staff also being on site. After 3 minutes resting (for resting spirometry and to let gas exchange variables stabilise), the test proceeds with 2 minute stages against an incremental resistance until volitional termination, followed by 5 minutes of recovery. Heart rate, 12-lead ECG, blood pressure and pulse oximetry are monitored throughout the procedure. Reasons for termination include volitional exhaustion, a plateau of VO2 with increasing workload, an RER of >1.1 or changes in the ECG tracing suggestive of ischaemia. Peak oxygen consumption (V˙O2max), respiratory exchange ratio, (RER: V˙CO2 /V˙O2) and heart rate (HR) will be measured using online gas analysis (Quark b2 and Quark C12x systems, Cosmed Cardio Pulmonary Exercise Testing; Cosmed, Rome, Italy), from which the workloads required to elicit 60% and 90% HRmax will be determined for the exercise trials.

*High Intensity Interval Training (HIIT)* – This will include 14 sessions over a 4 to 6 week period, finishing shortly before scheduled surgery. Exercise will be performed with other patients who are enrolled in the same or similar studies under the supervision of a trained exercise physiologist in the School of Physical Education. Exercises will use stationary cycling (Monark cycle ergometers), with monitoring of pulse and blood pressure. For patients on beta blockers the level of perceived exertion, using the 1-20 Borg scale [13] will be monitored as well as the pulse. Each session will begin and end with 5 min of unloaded cycling. Initial sessions will include ten 15-second intervals at a heart rate exceeding 85% of age-predicted maximum heart rate, or a rating of perceived exertion (RPE) score of ≥ 16, with ‘rest’ intervals of 45 seconds at heart rates of 50% maximum heart rate. All training programs will be individualised to meet the capacity of the participant. The duration of exercise will increase and the duration of rest will decrease as the participant gains fitness. The aim of the 14-session format is for participants to achieve five 2-minute intervals of high intensity work with 2-minute active rest durations. The total interval duration will not exceed 10 minutes throughout the training period. Each session will last approximately 30 min or less. For safety reasons, the intensity of exercise and intervals will be adjusted if systolic blood pressure exceeds 180 mm Hg, if the heart rate exceeds 95% of the maximum observed on baseline CPET, or if the perceived exertion on the Borg scale exceeds 18. Pulse (the indicator of ‘high intensity’) will be monitored and recorded from downloadable Polar Heart Rate monitors to assure exercise adherence. Patients who have their surgery delayed will complete one additional HIIT session per week up until surgery to maintain fitness [14]. All adverse events will be recorded.

The feasibility of performing CPET testing at Dunedin Hospital and HIIT in the School of Physical Education is enhanced by Dr Chris Baldi performing a study using a very similar methodology on the impact of HIIT in diabetic patients. The experience gained will assist in the administration of HIIT during this study. During the Pilot study the individualisation of the HIIT will take account age, patient comorbidities and performance during the initial exercise session.

### 5.4 Data collection and Endpoint Measurements

The following endpoint measurements will be assessed.

*Peak oxygen consumption (Peak VO2):* VO2 max is the maximum capacity of an individual’s body to transport and use oxygen during incremental exercise during CPET. This is an important measurement as it is associated with postoperative complications [15,16] and also with medium term mortality data [17]. Peak VO2 will be used to assess if HIIT can improve cardiorespiratory fitness prior to surgery.

*Quality of Life using the Short Form 36 Health Survey (SF 36):* In the context of this study the SF 36 is used for two purposes. The first is as a quality of life measurement tool to assess the impact of HIIT on the patients overall wellbeing. The second is to assess if there is any difference in speed of recovery after surgery, which can be assessed by using the ten questions which make up the physical functioning component of the score. The SF 36 will be performed at six and twelve weeks after surgery.

*Length of Hospital stay (LOS):* The number of post-operative days in hospital will be compared between the two groups.

*Surgical recovery score (SRS*): This assesses 13 items including energy levels, feeling of fatigue and a number of practical physical activities. The SRS has been shown to correlate with major complications and length of hospital stay [18]. This will be used to assess recovery after surgery.

*Post-operative morbidity score (POMS):* Assesses postoperative adverse events in nine different categories according to predefined criteria that are easy to check and to document [19].

*Six week complication rates*: All postoperative complications (morbidity and mortality) will be documented. This will include complications that occur in hospital and those that occur after discharge. At six weeks the patient will either be seen in a surgical clinic, or will be contacted by a member of the research team. Specific complications and overall complication rates will be compared between the two groups.

Data collection will occur at a number of points throughout the study (see overview diagram)

* All patients will be worked up as part of their surgery. This will include medical history including current medications, a physical examination, routine observations, body mass index and routine preoperative bloods. Base-line measurements will be recorded at this time. The patients’ preference for being in the exercise or usual care group will be documented.
* Initial tests performed prior to randomisation will include CPET and the SF-36 questionnaire. Data recorded during CPET will include Peak VO2 and RER.
* During HIIT data on work intensity, intervals of rest and on safety parameters such as pulse and blood pressure will be documented. This data will be used to help plan the next session.
* Following HIIT and prior to surgery CPET and SF 36 testing will be repeated
* Following surgery and during stay in hospital all complications will be documented. In addition to this the POMS and SRS will be recorded on day 5.
* At six weeks the patient will either be reviewed or contacted by phone. At this stage complications will be checked, and both the SF-36 questionnaire and the SRS completed. Subsequent changes in the patients’ attitude to what group they were placed in, and any impact the patients’ attitude may have had on overall results will be documented.
* At three months the SF-36 questionnaire and the SRS will be assessed.

### 5.5 Risk Management

Unexpected myocardial infarction continues to be one of the leading causes of unexpected postoperative mortality, and is the main concern with respect to CPET and HIIT. CPET is an established test for assessing unstable angina, has clearly documented guidelines for safety, for diagnosis of unstable angina and for stopping the test, as outlined in our protocol in section 5.3. The guidelines from the American Heart Association confirm that adverse events are rare during properly supervised tests [20]. In this study CPET tests will be performed in the cardiology ward (seventh floor of Dunedin Public Hospital) under the supervision of a senior researcher with additional medical staff also being on site.

With respect to HIIT this has been used in the rehabilitation of patients with coronary artery disease, and there are reported cases of HIIT being used successfully used in patients with active angina [7]. However in this study a more a cautious approach will be followed. The design of the study includes three steps to minimise cardiac risk: during enrolment, before HIIT and also during HIIT. During enrolment patients with risk factors for a myocardial event are excluded. This includes those with active angina, uncontrolled hypertension and a myocardial infarction in the last three months. Prior to initiation of any HIIT sessions, a formal CPET will be performed and any patient with ischaemic changes diagnosed during the CPET test will be excluded. Performing the CPET test up to Peak VO2 (instead of VO2 at anaerobic threshold) will also increase the chance of identifying problems during CPET. Thirdly the HIIT program will be performed under supervision by an exercise physiologist, in the school of physical education, and has safety criteria built into it. These include a supervised and graduated workload, which is designed according to the target heart rate for the individual (taking into consideration additional factors such as age and comorbidities), with hemodynamic and symptom monitoring during and after exercise. An automated external defibrillator is present on site and there is a phone line to a designated arrest team in case of any cardiac event.

A safety monitoring committee, of three consultants not directly involved in the study will be established. The committee will be drawn from the areas of anaesthesia, surgery, cardiology and/or exercise medicine. Study protocols and any adverse events will be independently reviewed by the committee.

# 6. Statistics

Additional information is needed to calculate the number of patients required to demonstrate differences in the results of the endpoints being studied. The pilot study will provide information on changes in Peak VO2 which will help with the sample size calculation for the preoperative fitness study. The preoperative fitness study will gather data which will help us to calculate the required sample size for the clinical outcomes study.

Patient demographics will be assessed using descriptive statistics. Continuous variables will be reported as mean with range and standard deviation or as median with inter-quartile range depending on the distribution of results. Categorical variables will be reported as frequency (%).

Differences in Peak VO2 (For example Peak VO2 after HIIT v Peak VO2 after usual care) will be recorded as mean results with standard deviations. Assessing the significant differences before and after HIIT and between the two groups will require mixed effects modelling and an analysis of covariance (ANCOVA) analysis, using baseline fitness as the covariate. Differences in the SF 36 subscales scores (these give a score between 0 and 100) between the two groups will be assessed using the student t- test or Mann-Whitney U test depending on the distribution of scores. Statistical significance will be set at p<0.05.

The postoperative morbidity survey generates a percentage of patients with or without morbidity. Differences between groups can be compared using the chi-square test. Differences in complication rates between groups will also be compared using the chi-square test or with Fisher’s exact test. The surgical recovery score generates a score between 17 and 100. As the scores are likely to be non-parametric, distribution differences between the groups will be compared using the Mann-Whitney U test, or by using the student t test after logarithmic transformation. Length of stay data is also likely to be positively skewed. Differences between groups will be compared using the Mann-Whitney U test.

**7 Potential benefit of study**

1. Change in clinical practice: At the moment there is minimal ‘additional clinical input’ to optimise patients before surgery. Usual care involves information about the diagnosis and surgery, sometimes a support person (such as a nurse specialist) who may spend some time with the patient, and the medical correction of any obvious preoperative problems. If HIIT is shown to lead to significant benefits in outcomes, then this would potentially lead to a change in mind-set, resulting in a much more active approach to the preoperative care of patients

2. Improving outcomes: Minimising complications requires a multifactorial approach. This study examines if it is possible to improve cardiorespiratory fitness before surgery, and if this will result in improving clinical outcomes after major surgery. Up to date no other study has quantified the impact of preoperatively improving cardiorespiratory performance on postoperative complications, length of stay, postoperative recovery or on quality of life.

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