**The effects of neoadjuvant chemoradiotherapy on physical fitness and morbidity in rectal cancer surgery patients**

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**Abstract**

**Background:** Neoadjuvant chemoradiotherapy (NACRT) followed by surgery for resectable locally advanced rectal cancer improves outcome compared with surgery alone. Our primary hypothesis was that NACRT impairs objectively-measured physical fitness. We also wished to explore the relationship between fitness and postoperative outcome.

**Method**: In an observational study, we prospectively studied 27 consecutive patients, of whom 25 undertook cardiopulmonary exercise testing (CPET) 2 weeks before and 7 weeks after standardized NACRT, then underwent surgery. In-hospital post-operative morbidity and mortality were recorded. Patients were followed up to 1 year for mortality. Data was analysed blind to clinical details. Receiver-operating curve (ROC) analysis defined the predictive value of CPET for in-hospital morbidity at day 5.

**Results**: Oxygen uptake (o2 in ml.kg-1.min-1) at estimated lactate threshold (L) and at Peak exercise (o2 atPeak in ml.kg-1.min-1) both significantly decreased post-NACRT: o2 at L 12.1 (pre-NACRT) vs. 10.6 (post-NACRT), p<0.001 (95%CI -1.7,-1.2); o2 at Peak 18.1 vs. 16.7, p<0.001 (95%CI -3.1,-1.0). Optimal o2 at L and Peak pre-NACRT for predicting postoperative morbidity were 12.0 and 18.1 (o2 at L - AUC = 0.71, 77% sensitive and 75% specific; o2 at Peak – AUC = 0.75, 78% sensitive and 76% specific). Optimal o2 at L and Peak post-NACRT for predicting postoperative morbidity were 10.7 and 16.7 (o2 at L - AUC = 0.72, 77% sensitive and 83% specific; o2 at Peak – AUC = 0.80, 85% sensitive and 83% specific).

**Conclusion**: NACRT before major rectal cancer surgery significantly decreased physical fitness as assessed by CPET.

**Key Words**

Neoadjuvant chemoradiotherapy; cardiopulmonary exercise testing; cancer surgery; morbidity; rectal cancer; physical fitness.

**Trials Registry Number:** NCT01334593

**INTRODUCTION**

In the United Kingdom colorectal cancer is the third commonest cause of cancer death[1]. In 2009, 33 600 new cases were registered in England (~1/3 rectal), with ~13 000 deaths in 2010 [2]. In 2012, of ~9000 diagnosed with rectal cancer (35% over 75 years), 75% underwent major resection, 76% of whom had no worse than mild systemic disease (American Society of Anaesthesiologists (ASA) score of 1 or 2), with 90-day post-operative mortality of 3.2% [3]. The 2012 UK National Bowel Cancer Audit reported ASA score (a categorical descriptor of fitness for surgery) as the strongest predictor of death within 30 days of surgery [3]. Twenty-five per cent of rectal cancers are locally advanced (T3/T4 N+), and these are considered for neoadjuvant chemoradiotherapy (NACRT) to control local disease, improve operability, achieve tumour downsizing and negative resection margins [4,5]. However, standard NACRT based on external beam radiation and oral or intravenous fluoropyrimidines causes dose-limiting toxicity (most commonly diarrhoea, hand-foot syndrome, cardiotoxicity and haematological toxicity) reaching Grade 3–5 in ~20% (Common Terminology Criteria for Adverse Events, Version 3.0) [6]. It is less clear whether there are further metabolic adverse effects from cancer therapies which could impact outcome after surgery.

Cardiorespiratory fitness, assessed by cardiopulmonary exercise testing (CPET), reliably predicts outcome following major surgery [7,8] . CPET provides an integrated quantitative assessment of the cardiorespiratory system at rest and under the stress of maximal exercise, testing the physiological reserve required to withstand the stress of surgery. Knowledge of the effects of cancer and cancer therapies on physical fitness is critical to develop interventions targeted at improving fitness prior to surgery. Subjective assessment tools have been used to predict surgical outcomes, but there is little evidence linking objectively-measured physical fitness and surgical outcome in this group. Only two trials suggest that rectal cancer patients with a lower subjective performance status or physical fitness (WHO Score >1) have worse post-operative outcome after combined chemotherapy or chemo-radiation and surgery [6, 9].

We hypothesised that standardised NACRT prior to elective surgery for locally advanced rectal cancer would impair objectively-measured physical fitness; specifically oxygen uptake (o2) measured at estimated lactate threshold (L) and at Peak exercise. We also explored the relationship of o2 at L and o2 at Peak in predicting in-hospital post-operative morbidity.

**PATIENTS AND METHODS**

**Patients and Study Design**

This single-centre, prospective, observational cohort study, based in a tertiary referral NHS University Teaching Hospital, was approved by the Northwest Research Ethics Committee (11/H1002/12) and registered with ClinicalTrials.gov (NCT01334593). Written informed consent was obtained from all patients. We recruited consecutive patients between August 2011 and July 2012 referred to the Colorectal Multi-Disciplinary Team (MDT), age ≥18 years, with locally advanced (circumferential resection margin threatened) resectable rectal cancer, who were scheduled for standardised NACRT (see below) on the basis of Tumour, Node, Metastasis (TNM) classification >T2/N+ with no metastasis [10] and WHO Performance Status < 2 [11]. Predefined exclusion criteria were: non-resectable disease, inability to perform CPET due to lower limb dysfunction, patients who declined surgery or NACRT, patients who received non-standard NACRT or were unable to give informed consent. CPET was performed 2 weeks before and 7 weeks post-NACRT (prior to surgery at 9 weeks post-NACRT). TNM staging investigations involved flexible sigmoidoscopy for histological diagnosis, colonoscopy, chest, abdomen and pelvis computer-aided tomography (CT) and a 1.5 tesla pelvic magnetic resonance imaging (MRI). Eligible patients then underwent standardised NACRT for 5 weeks. Preoperative radiotherapy consisted of 45 Gy in 25 fractions on weekdays using a three-dimensional conformal technique with CT guidance. Patients were treated prone (on a belly-board) to spare small bowel, with a comfortably full bladder. The clinical target volume included the primary tumour, the mesorectum and the mesorectal lymph nodes, including the perirectal, presacral and internal iliac nodes. The upper radiation extent was 3 cm above the tumour but no further than the sacral promontory. The perineum was included if an abdomino-perineal resection (APR) was planned, while for low anterior resection (LAR) the lower radiation border was 3 cm below the tumour. A boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. Oral capecitabine (825 mg.m-2) was given twice daily on radiotherapy days. No patients received brachytherapy. Acute toxicity and adverse events were discussed at the weekly colorectal multidisciplinary meeting (MDT). Adverse events were graded on the National Cancer Institute Common Terminology Criteria (version 3.0), and acute radiation-induced skin toxicity using the Radiation Therapy Oncology Group scoring system.

All patients completed NACRT and went on to have CPET, spirometry and restaging chest, abdomen and pelvic CT and pelvic MRI at 7 weeks post-NACRT. The colorectal MDT, anaesthetists and medical staff collecting outcome data were blind to CPET results. All patients underwent total mesorectal excision (TME) surgery [12] after completing NACRT. A defunctioning stoma was constructed at the discretion of the surgeon.

Patients were assessed pre- and post-operatively using the Colorectal Physiologic and Operative Severity Score for the Enumeration of Mortality and Morbidity (CR-POSSUM) [13]. In-hospital surgical outcome was assessed using the Post-Operative Morbidity Survey (POMS) at Day 5 [14] (patients score 1 for each complication) and Clavien-Dindo Classification of Surgical Complications [15] (highest grade recorded for the most serious sustained complication over the whole hospital stay). Surgical outcome was collected by staff blind to CPET data. All patients were followed for medium-term surgical outcome assessed using 180-day radiological documented loco-regional recurrence, Clavien-Dindo Classification (highest grade recorded for the most serious sustained in-hospital complication upon readmission during the 180-day follow-up) and 1 year mortality.

**Measurements**

In accordance with the American Thoracic Society/American College of Chest Physicians recommendations[16], CPET was performed on an electromagnetically-braked cycle ergometer (Ergoline 2000) for 3 min at rest, 3 min freewheel pedalling, ramped incremental exercise (10-25 W/min based on height, age and predicted o2 at unloaded and Peak exercise) [17] until volitional termination, then 5 min recovery. Ventilation and gas exchange were measured using a metabolic cart (Geratherm Respiratory GmbH (Love Medical Ltd). Heart rate, 12-lead ECG, blood pressure, and pulse oximetry were monitored throughout. At the initial CPET age, gender, height, weight, tumour staging, surgical procedure, WHO classification and ASA-PS [18] were recorded. At the second CPET, weight was reassessed. Resting flow-volume loops recorded at each CPET were used to derive Forced Expiratory Volume over 1 second (FEV1) and Forced Vital Capacity (FVC). A venous sample was obtained a median of 7 days before each CPET and analysed for haemoglobin. Ventilation and gas exchange variables derived from CPET included the amount of oxygen extracted from the inspired gas in a given period of time, expressed as o2 (measured in absolute terms (ml.min-1) and also calculated relative to body weight (ml.kg-1.min-1)). The highest o2 achieved during a CPET session is termed o2 at Peak. Ventilatory equivalents for oxygen and carbon dioxide (E/o2 and E/co2) are measurements of the ventilatory requirement for a given metabolic rate. Oxygen (O2) pulse is o2 divided by heart rate, hence represents the amount of O2 extracted by the tissues of the whole body from the O2 carried in each stroke volume (ml/beat). Work rate (W) is defined as the rate at which work is performed on the ramp incremental test. All these variables are measured both at estimated lactate threshold (L) and at Peak exercise [17]. Estimation of L was performed using a conventional cluster of variables (breakpoint in the o2 and co2 relationship) [19], with increases in E/o2 and end-tidal oxygen partial pressure (PET O2) but no increase in E/co2 or fall in end-tidal carbon dioxide partial pressure (PET CO2) [20]. Evaluation of L was undertaken by two independent assessors and a final third, blinded to clinical data and CPET time points, who also resolved any disagreement between the first two assessors.

**Statistical Analysis**

Continuous variables are presented as mean and standard deviation (SD) or as median and interquartile range (IQR), depending on the distribution. Categorical variables are presented as a frequency and/or proportion. Pre- and post-NACRT data were compared using paired t-tests. Relationships between the change in haemoglobin concentration and the change in o2 at L and o2 at Peak were assessed using the Pearson correlation coefficient. Statistical significance was accepted at p<0.05. Descriptive analysis was used to compare baseline characteristics of patients pre- and post-NACRT (Table 1), to document in-hospital complications using POMS day 5 and Clavien-Dindo classification, together with 180-day morbidity using Clavien-Dindo classification, loco-regional recurrence rates (Table 4) and 1 year mortality.

The primary variables of interest were o2 at L and o2 at Peak exercise (ml.kg-1.min-1). Exploratory variables included other CPET variables namely, baseline and peak heart rate, Oxygen pulse, E/co2 and Work rates both at L and at Peak exercise. Our primary aim was to assess the effect of NACRT on patient fitness by comparing the pre- and post-NACRT values for each CPET variable. We also aimed to explore the relationship between the two primary variables and post-operative in-hospital morbidity.

Receiver operator characteristic (ROC) curves were constructed for o2 at L and o2 at Peak exercise pre- and post-NACRT. From these the optimal cut-point was identified by minimising the distance to the top-left corner. Logistic regression models were used to further explore the relationship between o2 at L and o2 at Peak exercise pre- and post-NACRT and in-hospital complications. We dichotomised complication episodes around the ROC cut-off values for pre- and post-NACRT values of o2 at L and o2 at Peak.

Our aim was to recruit 22 patients who would undergo standardised long-course chemoradiotherapy and elective rectal surgery as an intention to treat for rectal cancer. This estimate was based on a two-sample t-test with 90% power to detect an estimated mean (SD) minimum clinically relevant difference in o2 at L of 1.5 (1.0) ml.kg-1.min-1). A drop-out rate of 10% was assumed (based on a previous pilot study).

**RESULTS**

**Patient flow and demographics**

Thirty-five patients were eligible for surgery, of whom 5 did not consent and 3 were recruited into a different trial; 27 patients were recruited and underwent CPET prior to NACRT; 2 withdrew their consent before post-NACRT CPET, the remaining 25 (17 males and 8 females) completed NACRT and underwent elective rectal cancer surgery (Figure 1-online).

Table 1 describes patient characteristics and table 2 describes tumour and treatment characteristics. There were no significant changes in WHO performance status, haemoglobin or lung function following NACRT. CPET was performed at 2.0 ± 0.8 weeks pre-NACRT and at 7.0 ± 1.0 weeks post-NACRT. 84% of diagnosed rectal cancers were T3 with threatened circumferential resection margins. 52% had a good response to NACRT determined by MRI. All patients underwent total mesorectal excision (TME) surgery at a median of 63 days (range 51-78) post-NACRT. The circumferential resection margin (CRM) was >5mm in all cases. No patients had complete pathological response.

**Chemoradiotherapy and acute toxicity**

The mean cumulative dose of capecitabine was 96% (range 84-100%) of the planned treatment dose; 3 patients needed dose reduction. All but 1 patient received at least 45Gy radiotherapy, and all completed the full 25 fractions. 7 patients (including 3 receiving a diverting stoma because of obstructive symptoms prior to starting NACRT) experienced grade 3 toxicity, notably diarrhoea and radiation dermatitis, but no grade 4 toxicity. No hepatic toxicity was encountered.

**The effect of NACRT on physical fitness**

Table 3 shows CPET-derived variables pre- and post-NACRT. Post-NACRT, both absolute (ml.min-1) and relative (ml.kg-1.min-1)o2 at L and o2 at Peak exercise were significantly decreased (p<0.001): Figure 2 and 3 (online) show pair-plots of individual patients’ relative o2 at L and relative o2 at Peak pre- and post-NACRT. Oxygen pulse at L and at Peak (ml.beat-1) were also significantly decreased (p=0.005 and p=0.002 respectively). E/co2 did not change. There was no significant change in median work rate at L (p=0.055), but a significant decrease in work rate at Peak (p=0.005). There were no significant changes in resting or peak heart rate, spirometry and haemoglobin between pre- and post-NACRT. No significant relationship was found between the change in o2 at L and change in haemoglobin (r=0.18; p>0.05).

**Relationship between physical fitness and surgical outcome**

The median WHO performance status of 1 (0-2) pre-NACRT did not change post-NACRT. Mean operative severity score of 11.2 (1.2), physiological score of 9 (1.8) and predicted mortality of 7.8% (4.5%) was calculated using CR-POSSUM. No in-hospital mortality was observed.

ROC curves were constructed to discriminate between patients with and without post-operative in-hospital complications based on their pre- and post-NACRT o2 at L and o2 at Peak. First, using pre-NACRT data, an optimal o2 at L of 12.0 ml.kg-1.min-1 (Area under curve (AUC) = 0.71, 95% CI 0.50-0.93; 77% sensitive and 75% specific) and o2 at Peak of 18.1 ml.kg-1.min-1 (AUC = 0.75, 95% CI 0.55-0.95; 78% sensitive and 76% specific) predicted those at risk of postoperative complications (Figure 4 - online). Second, using post-NACRT data, an optimal o2 at L of 10.7 ml.kg-1.min-1 (AUC = 0.72, 95%CI 0.50-0.94; 77% sensitive and 83% specific) and o2 at Peak of 16.7 ml.kg-1.min-1 (AUC = 0.80, 95% CI 0.60-1.00; 85% sensitive and 83% specific) also predicted risk of postoperative complications (Figure 5 - online).

Two patients were dead at 1 year due to distant metastases (radiologically documented in liver and brain). Both patients had o2 at L of ≤10.7 ml.kg-1.min-1 post-NACRT and suffered a post-operative anastomotic leak (Grade IIIb). A third patient had radiologically documented liver and lung metastasis at 1 year, also with an o2 at L of ≤10.7 ml.kg-1.min-1 post-NACRT. 15 of 25 patients experienced ≥1 post-operative complications (Grade ≥1). 10 of 15 patients with an in-hospital complication had o2 at L ≤10.7 ml.kg-1.min-1. Table 4 shows in-hospital complication graded by Clavien-Dindo classification and POMS at day 5, as well as 180-day morbidity graded by Clavien-Dindo classification.

To further explore the association of o2 at L ando2 at Peak with in-hospital morbidity, we dichotomised complication episodes (observed throughout the whole of the patients in-hospital stay) around the ROC cut-off values of 12.0 ml.kg.-1.min-1 for pre-NACRT and 10.7 ml.kg-1.min-1 for post-NACRT o2 at L. The odds of complications decreased by 90% for patients above these cut-off values (pre-NACRT – OR 0.10, 95% CI 0.16-0.63; p=0.014 and post-NACRT – OR 0.09, 95% CI 0.01-0.61; p=0.014). Fitting the same model for pre- and post- o2 at Peak (Cut-off 18.1 ml.kg-1.min-1 pre-NACRT and 16.7 ml.kg-1.min-1 post-NACRT), the odds of complications decreased by 85% and 94% respectively for patients above these cut-off values (pre-NACRT – OR 0.15, 95% CI 0.03-0.87; p=0.035 and post-NACRT – OR 0.06, 95% CI 0-0.44; p=0.006).

**DISCUSSION**

This is the first study to demonstrate that in patients with locally advanced resectable rectal cancer, NACRT prior to surgery is associated with a clinically significant reduction in objectively-measured physical fitness (decreasing o2 and oxygen pulse at L, o2 at Peak exercise, and peak work rates). This reduction in fitness following NACRT is consistent across a broad range of levels of prior fitness (Figures 2 and 3). Our analyses also suggest that cut-off values derived from ROC analysis of o2 at L and o2 at Peak exercise may have utility in the prediction of post-operative in-hospital morbidity. Taken together these findings suggest that physiological reserve (the ability to increase o2 in response to a stressor) is important for rectal cancer patients exposed to the dual challenges of NACRT and major surgery, and that the decline in objectively measured physical fitness in this cohort may be associated with post-operative clinical outcome (complications).

The benefits of NACRT for locally advanced rectal cancer are improved local disease control [5] and possibly overall and cancer-specific survival [21], however the effects of NACRT on objectively measured physical fitness have not previously been explored. Only Swellengrebel and colleagues [6] clearly link poor performance status (or poor fitness) at diagnosis and the extent of surgery to post-operative morbidity.

The mechanism of this decline in physical fitness has not been explored in this cohort. However, we know that cancer-induced cachexia can cause loss of up to 75% of skeletal muscle [22], resulting in fatigue and higher mortality [23]. In our cohort cancer progression is not a contributing factor as tumours were on average downstaged (Table 1). Equally haemoglobin, BMI and weight remained stable on NACRT in our patients. Chemotherapy, particularly capecitabine, may also directly contribute [24], by mechanisms which are not fully understood. We know that oxidative damage [25] resulting from doxorubicin-based chemotherapy in haematological malignancies causes loss of muscle mass [26], up-regulation of E3 ubiquitin-ligase/MAFbx [27] and mitochondrial death [28]. Moreover, drugs with a quinone moiety can directly interact with oxygen to generate reactive oxygen species (ROS) [29], while other chemotherapeutic agents decrease antioxidant levels. The effects of capecitabine in relation to oxidative damage and mitochondrial damage are unknown. Chemotherapy also affects cardiorespiratory and microcirculatory function [30], physical activity [24], and mitochondrial and other cellular metabolism [31], but cellular/physiological mechanisms remain elusive.

Our findings have potentially important clinical implications because reduced physical fitness is known to be associated with increased perioperative morbidity and mortality after major intra-abdominal surgery [7,8]. Our data provides the first direct evidence that the benefits of NACRT in tumour downsizing may be at least partly offset by increased perioperative risk due to reduced physical fitness. Our data further show that standardized and objective measurements of fitness allow an accurate assessment with high predictive power. A detailed understanding of pre-treatment state can be expected to be particularly important in patients with borderline baseline fitness, where further fitness decline may be linked to adverse post-operative outcomes. This relationship merits further investigation, as does the possibility of intervention by exercise training during NACRT or in the pre-operative period to attenuate these deleterious effects of NACRT. This is currently the focus of our pilot study investigating the improvements in physical fitness and quality of life resulting from a 9-week structured responsive endurance training programme (SRETP) following NACRT prior to elective rectal cancer surgery (PB-PG-0711-25093).

This study demonstrates a clear reduction in objectively-measured physical fitness using validated and robust methodology with links to post-operative in-hospital morbidity. Particular strengths of our study are the low risk of confounding by indication [32], the blinded physiological evaluation, the standardization of the NACRT, the homogenous cancer cohort and the comprehensive short- and medium-term follow up. Limitations lie in the observational design and the small sample size. Our study was adequately powered (90%) to detect a 1.5 ml.kg.-1min-1 difference in o2 at L, and we achieved this goal at a confidence level of 1.7 to 1.2 ml.kg.-1min-1. A larger prospective study is in development to quantify the link between the change in physical fitness and post-operative outcome.

In conclusion, NACRT before major rectal cancer surgery significantly reduces physical fitness objectively assessed by CPET. We identify an association between reduced physical fitness and post-operative morbidity which merits further investigation. Our data open the intriguing possibility that a tailored, pre-operative exercise intervention might improve physical fitness and support improved outcome in patients with operable rectal cancer.

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**Conflict of interest statements**

M. West - No interest declared

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**Table 1 –** Patient demographics and clinical characteristics

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **All** | **Pre-NACRT** | **Post-NACRT** | **Mean difference** **(95% CI)** | ***p*-value** |
| Age (years) a | 67.7(9.2) |  |
| Gender M:F (%) a | 17(68) : 8(32) |
| CR-POSSUM- Operative Severity Score b | 11.2(1.2) |
| CR-POSSUM-Physiological Score b | 9(1.8) |
| CR-POSSUM- Predicted Mortality (%) b | 7.8(4.5) |
| Weight (kg) a |  | 75(16.9) | 75.3 (17.4) | 0.30 (-1.2, 0.60) | 0.540 |
| Height (m) a |  | 166.4(8) | 166.6(8.1) | 0.20 (-0.58, 0.10) | 0.161 |
| BMI (kg.m-2) a |  | 27.0 (5.5) | 27.0 (5.6) | 0.01 (-0.32, 0.35) | 0.942 |
| WHO Performance Status c |  | 1 (0-2) | 1 (0-2) | N/A | 1.000 |
| FEV1 (l) a |  | 2.5(0.8) | 2.5(0.7) | 0.00 (-1.19,1.18) | 0.929 |
| FVC (l) d |  | 3.7(2.9-4.4) | 3.7(3.0-4.5) | 0.04 (-0.05, 0.14) | 0.361 |
| FEV1/FVC (%) a |  | 67.2(10.5) | 67.0(11.5) | -0.02 (-2.04, 1.56) | 0.786 |
| Haemoglobin (g.dl-1) a |  | 13.6(1.5) | 13.5(1.6) | -0.03 (-0.47, 0.40) | 0.865 |
| Clinical TNM classification e | cT2 |  | 1 | 3 |  |
|  | cT3 |  | 21 | 19 |
|  | cT4 |  | 3 | 3 |
|  | cN0 |  | 7 | 13 |
|  | cN1 |  | 13 | 9 |
|  | cN2 |  | 5 | 3 |
|  | cM0 |  | 25 | 25 |

a Values are mean (SD). b Values are mean (SD) for CR-POSSUM components. c Median (range) for World Health Organisation (WHO) Performance Status. d Values are median (IQR). e International Union against Cancer tumour node metastasis (TNM), values are presented as number of patients.

**Table 2 –** Tumour characteristics and treatment details

|  |  |
| --- | --- |
|  | **Number of patients (n=25)a** |
| **Tumour distance from anal verge** |
| <5 cm | 6  |
| 6-10cm | 14  |
| >10cm | 5  |
| **Operation Type** |
| Open | 14 |
| Laparoscopic | 11 |
| **Surgery** |
| Low anterior resection and diverting stoma | 15 |
| Abdomino-perineal resection and end stoma | 7 |
| Hartmann procedure | 3 |
| **Pathological TNM** |
| pT1 | 4  |
| pT2 | 5 |
| pT3 | 11 |
| pT4 | 5  |
| pN0 | 15  |
| pN1 | 6 |
| pN2 | 4  |
| **Dukes Staging** |
| A | 8  |
| B | 7 |
| C 0/1 | 10  |
| **Resection margins** |
| R0 | 25 |

a Values are presented as number of patients

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Pre-NACRT** | **Post-NACRT** | **Mean Difference** **(95% CI)** | **P-value** |
| o2 at L (ml.kg-1.min-1) a | 12.1 (9.4-13.0) | 10.6 (8.2-12.0) | -1.5 (-1.7, -1.2) | **<0.001** |
| o2 at L (ml.min-1) b | 905.2 (343.4) | 803.0 (323.5) | -102.2 (-75.7,-128.7) | **<0.001** |
| o2 at Peak (ml.kg-1.min-1) a | 18.1 (15.7-20.4) | 16.7 (12.1-19.2) | -1.4 (-3.1, -1.0) | **<0.001** |
| o2 at Peak (ml.min-1) b | 1370 (710) | 1180 (690) | -190 (-86.7, -252.1) | **<0.001** |
| O2 pulse at L (ml.beat-1) b | 8.7 (2.9) | 8.1(2.7) | -0.7 (-1.2, -0.2) | **0.005** |
| O2 pulse at Peak (ml.beat-1) b | 11.2 (3.6) | 10.1 (3.0) | -1.1 (-1.8, -0.4) | **0.002** |
| E/co2 at L b | 33.5 (5.1) | 33.1 (5.1) | -0.4 (-1.7, 0.9) | 0.541 |
| E/co2 at Peak b | 35.8 (5.5) | 35.8 (6.1) | 0 (-1.2, 1.2) | 0.994 |
| Baseline heart rate(beats.min-1) a | 85 (68-91) | 83 (70-88) | -2 (-4.7, 2.1) | 0.426 |
| Peak heart Rate(beats.min-1) a | 124 (103-144) | 122 (110-139) | 2 (-6.4, 10.5) | 0.624 |
| Work load at L (W) a | 46 (35-56) | 46 (24-55) | -5 (-10.0, 0.1) | 0.055 |
| Work load at Peak (W) a | 104 (66-122) | 96 (60-116) | -8 (-13.4, -2.7) | **0.005** |

**Table 3 –** Cardiopulmonary exercise testing variables

a Values presented as median (IQR). b Values presented as mean (SD). o2 at L , Oxygen uptake at estimated lactate threshold; o2 at Peak, Oxygen uptake at peak exercise; O2 pulse at L, Oxygen pulse at estimated lactate threshold; O2 pulse at Peak, Oxygen pulse at peak exercise; E/co2 at L, Ventilatory equivalents for carbon dioxide at estimated lactate threshold; E/co2 at L, Ventilatory equivalents for carbon dioxide at peak exercise; Work load at L, Work load at estimated lactate threshold; Work load at Peak, Work load at peak exercise

**Table 4 –** Total post-operative in-hospital morbidity assessed by Clavien-Dindo (CD) Classification and POMS at Day 5 dichotomized at the ROC cut-off for Oxygen uptake at estimated lactate threshold (o2 at L) post-NACRT\*. 180-day morbidity assessed by Clavien-Dindo Classification (grade and number of observed episodes dichotomized at the ROC cut-off o2 at L post-NACRT).

|  |  |  |
| --- | --- | --- |
| **Complication Type** | **In-Hospital Morbidity** | **180-day Morbidity** |
|  | **CD** | **POMS at Day 5** | **CD** | **Observed Episodes** |
| **L ≤10.7 \*****(n=13)** | **L >10.7 \*****(n=12)** | **L ≤10.7 \*****(n=13)** | **L >10.7 \*****(n=12)** |
| **Pulmonary*** Pneumonia
 | II | 2 | 0 | II | 0 | 2 |
| **Infection*** Febrile requiring antibiotics
* Anastomotic leak requiring re-operation
 | IIIIIb | 32 | 11 | II0 | 10 | 30 |
| **Renal*** Acute kidney injury
 | I | 1 | 0 | 0 | 0 | 0 |
| **Gastrointestinal*** Ileus
* Total parenteral nutrition
* High output stoma
* Abdominal collection
* Bowel obstruction
 | III000 | 45000 | 01000 | 0IIIIIIIaIIIb | 01101 | 00020 |
| **Cardiovascular*** Arrhythmias
 | II | 1 | 0 | 0 | 0 | 0 |
| **Neurological** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Haematological** | II | 1 | 0 | II | 1 | 0 |
| **Pain** | I | 0 | 1 | 0 | 0 | 0 |
| **Wound*** Abdominal
* Perineal
 | IIII | 13 | 02 | 0I | 01 | 02 |

CD, Clavien-Dindo Classification; POMS, Post-Operative Morbidity Survey; L, estimated lactate threshold