**Cardiopulmonary exercise testing for the prediction of morbidity risk after rectal cancer surgery**

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**TYPESETTER: THROUGHOUT PLEASE JOIN UP “V” WITH o2(no space)**

**Background:** This study investigated the relationship between objectively measured physical fitness variables derived by cardiopulmonary exercise testing (CPET) and in-hospital morbidity after rectal cancer surgery.

**Methods:** Patients scheduled for rectal cancer surgery underwent preoperative CPET (reported blind to patient characteristics) with recording of morbidity (recorded blind to CPET variables). Non-parametric receiver operating characteristic (ROC) curves and logistic regression were used to assess the relationship between CPET variables and postoperative morbidity.

**Results:** Of 105 patients assessed, 95 (72 men) were included; ten patients had no surgery and were excluded (3 by choice, 7 owing to unresectable metastasis). Sixty-eight patients had received neoadjuvant treatment. ROC curve analysis of oxygen uptake (o2) at estimated lactate threshold (L) and peak o2 gave an area under the ROC curve of 0.87 (95 per cent confidence interval 0.78 to 0.95; *P*< 0.001) and 0.85 (0.77 to 0.93; *P*< 0.001) respectively, indicating that they can help discriminate patients at risk of postoperative morbidity. The optimal cut-off points identified were 10.6 and 18.6 ml per kg per min for o2 at L and peak respectively.

**Conclusion:** CPET can help predict morbidity after rectal cancer surgery.

**+A: Introduction**

Major colorectal surgery is associated with substantial morbidity1 and mortality, particularly in elderly patients and those with co-morbidities2. A recent colorectal cancer audit3 reported a 30-day mortality rate of 2.9 per cent for elective colonic and 1.5 per cent for rectal surgery. Outcome after major surgery depends both on modifiable factors, such as perioperative medical care, and on physiological tolerance of surgical trauma. Accurate risk stratification permits optimization of perioperative management and efficient use of resources, such as intensive care beds. Current approaches to risk prediction include clinical acumen, prediction scores (for example the American Society of Anesthesiologists Physical Status (ASA-PS) classification, Duke’s Activity Scores, the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) and colorectal (CR)-POSSUM)4,5, plasma biomarkers6, measures of cardiac function7 and shuttle walk tests8. Their effectiveness in predicting surgical morbidity is not well established8.

The distance walked in 6 min at preoperative assessment can help predict morbidity following colorectal surgery9. Cardiopulmonary exercise testing (CPET) is the most objective and precise means of evaluating presurgical physical fitness10–12. CPET assesses cardiorespiratory reserve (physical fitness) and has been used for risk stratification before thoracic and abdominal surgery13–15. It is not known whether CPET variables can predict risk in patients with rectal cancer. This study tested the hypothesis that CPET variables are associated with in-hospital morbidity in this patient group.

**+A: Methods**

Between January 2010 and December 2011, consecutive adult patients referred to the CPET service by the colorectal multidisciplinary team (MDT) were assessed for suitability of inclusion. Predefined inclusion criteria were diagnosis of operable rectal cancer and no distant metastasis. Exclusion criteria were inability to perform CPET owing to lower limb dysfunction or inability to give informed consent, or patients who declined neoadjuvant chemoradiotherapy (CRT) or had emergency surgery.

Discussions with Aintree University Hospitals NHS Foundation Trust and subsequently with the North West Research Ethics Committee established that formal ethical approval was not necessary, as the study was deemed to be a service evaluation of consecutively recruited patients. However, Caldicott guidelines16 were adhered to fully. All patients received an information sheet regarding CPET, and written consent was obtained. No patient was refused surgery on the basis of gas exchange measurements, although any electrocardiography (ECG) abnormalities were raised at the colorectal MDT meeting and the patient was referred appropriately.

CPET was performed 2 weeks before starting any neoadjuvant therapy or major surgery. Eligible patients underwent neoadjuvant radiotherapy on the basis of threatened circumferential resection margins on staging magnetic resonance imaging (MRI). A total dose of 45 Gy in 25 fractions was given using a three-dimensional conformal technique with computed tomographic guidance. A further boost dose was given (5.4 Gy in 3 fractions) to the primary tumour only. Oral capecitabine (825 mg/m2) was given twice daily on radiotherapy days. No patients received brachytherapy. Surgery for patients receiving neoadjuvant CRT was performed 9 weeks after the end of their treatment. All patients had total mesorectal excision. A defunctioning stoma was constructed at the discretion of the surgeon.

## *+B: Cardiopulmonary exercise testing*

CPET followed American Thoracic Society–American College of Chest Physicians recommendations17. After resting spirometry (flow–volume loops), CPET on an electromagnetically braked cycle ergometer (Ergoline 200) comprised 3 min resting (to allow gas exchange variables to stabilize), 3 min freewheel pedalling, and then a ramped incremental protocol until volitional termination and 5 min recovery. Ventilation and gas exchange were measured using a metabolic cart (*Fig. 1*). Heart rate, full disclosure 12-lead ECG, blood pressure and pulse oximetry were monitored throughout. Ramp gradient was set to 10–25 W/min based on a calculationusing predicted freewheel oxygen uptake (o2), predicted o2 at peak exercise, height and age18.

## *+B: Patient characteristics and outcome measures*

Patient characteristics recorded at the initial CPET session included age, sex, height, weight, pelvic MRI staging, surgical procedure, planned cancer therapy (straight to surgery, long- or short-course neoadjuvant chemotherapy, or CRT), World Health Organization classification and ASA-PS), as well as diagnosis of diabetes, ischaemic heart disease, cerebrovascular disease or heart failure. Resting flow–volume loops were used to derive values for forced expiratory volume in 1 s and forced vital capacity. Ventilation and gas exchange variables derived from CPET included o2, ventilatory equivalents for oxygen and carbon dioxide (E/o2, E/co2), and oxygen pulse (o2/heart rate), all measured at estimated lactate threshold (L) and at peak exercise18. L was estimated conventionally (breakpoint in the co2 – o2 relationship19, with increases in E/o2 and end-tidal (PET) o2 but no increase in E/co2 or decrease in PET co2 20). Peak o2 was averaged over the last 30 s of exercise. CPETs were reported by two experienced assessors, both blinded to patient demographics and outcome data, with resolution of any differences by a third assessor.

Short-term surgical outcome (recorded by medical and nursing staff blinded to CPET data) using the nine domains listed in the Postoperative Morbidity Survey (POMS)21 on day 5, the Dindo–Demartines–Clavien classification22 (highest grade for the most serious sustained in-hospital morbidity) and in-hospital mortality were recorded. Postoperative morbidity is defined as POMS score of 1 or above. Length of hospital stay was also recorded and all patients were followed up to 1 year for mortality. The colorectal MDT (including anaesthetists) was blinded to all CPET data. No perioperative management or decisions were influenced by CPET data.

The variables of primary interest were o2 at L and at peak (ml per kg per min). Exploratory variables included oxygen pulse at L (ml/beat), E/co2 at L,and work rate at L. The primary aim was to establish the relationship between postoperative morbidity (assessed by POMS at day 5) and o2 at L. The study also aimed to explore the multivariable relationship between CPET variables and postoperative in-hospital morbidity.

## *+B: Statistical analysis*

Non-parametric receiver operating characteristic (ROC) curves were constructed for o2 at L and at peak in order to assess their independent ability to discriminate between patients with and without in-hospital postoperative morbidity. Optimal cut-off points were obtained by minimizing the distance between points on the ROC curve and the upper left corner. Five variables (limited to satisfy the ‘10 events per variable’ rule23) were identified as candidates for a multivariable logistic regression model: o2 at L and at peak, sex, operation type (laparoscopic or open) and age. Model fit was assessed using the Hosmer and Lemeshow goodness-of-fit test, and model selection was achieved using backward stepwise selection, minimizing the Akaike information criterion.

The log rank test was used to compare Kaplan–Meier survival (length of stay) curves for patients with and those without postoperative morbidity. Continuous variables are reported as mean (s.d.) or median (i.q.r.), depending on their distribution. Categorical variables are presented as frequencies with percentages. Logistic regression was used to assess the relationship between variables and morbidity on day 5 after surgery. Other categorical comparisons were conducted using the χ2 test, or Fisher’s exact test where expected cell counts were insufficient or in the presence of zero cells. Results were considered to be statistically significant at the 5 per cent level; no corrections were made for multiple comparisons. All analyses were conducted using Stata® release 12 (StataCorp LP, College Station, Texas, USA).

**+A: Results**

One hundred and five consecutive patients were recruited and underwent CPET. Of these, ten had no surgery (patient choice, 3; unresectable metastasis on restaging, 7). Thus, 95 patients (72 men and 23 women) had major elective surgery and complete outcome data.

*+B: Patient characteristics*

*Table 1* shows patients grouped by occurrence of in-hospital postoperative morbidity (defined as POMS score at day 5 of 1 or above). Three patients developed a supraventricular tachycardia at peak exercise, which resolved spontaneously during recovery; after discussion at a MDT meeting and referral to a cardiologist, surgery proceeded as normal. Increased body mass index and a preoperative diagnosis of heart failure were associated with increased odds of in-hospital morbidity.

*Table 2* shows tumour characteristics and oncological treatment received. There was no difference in oncological treatment, clinical or pathological staging between patients with and those without postoperative morbidity.

*Table 3* shows grouped CPET data. Lower o2 at L, peak o2, work rate at L and oxygen pulse at L were independently associated with increased odds of in-hospital morbidity. No major adverse clinical events occurred during CPET. Three patients who were unable to attain L sustained morbidity and their discharge was delayed.

*+B: Postoperative morbidity*

Forty-six patients (48 per cent) experienced in-hospital morbidity. All patients were alive 30 days after surgery. Five patients (5 per cent) developed an anastomotic leak at a median of 6 days (all following low anterior resections); four of these patients had reoperation and one was treated conservatively with radiologically inserted drains and intravenous antibiotics. A further two patients were reoperated on at a median of 5 days (1 patient suffered intestinal obstruction and another developed a pelvic collection). All of these patients experienced further morbidity with delayed hospital discharge.

Using non-parametric ROC curves, o2 at both L and peak was associated with POMS day 5 morbidity (*P*< 0.001). For o2 at L (area under the curve (AUC) 0.87, 95 per cent confidence interval (c.i.) 0.78 to 0.95), the optimal cut-off was 10.6 ml per kg per min, giving 84 per cent sensitivity and 92 per cent specificity (*Fig. 2a*). For peak o2 (AUC 0.85, 95 per cent c.i. 0.77 to 0.93), the optimal cut-off was 18.6 ml per kg per min, giving 82 per cent sensitivity and 80 per cent specificity (*Fig. 2b*).

To satisfy the Hosmer–Lemeshow goodness-of-fit test o2 at both L and peak was dichotomized (at the median value), as no suitable transformation was found that would yield an easily interpretable result. From the five candidate variables, o2 at L and at peak were retained in the final multivariable logistic regression model. However, as neither variable contributed meaningfully to the other (they are highly correlated), univariable models were used instead. Owing to the dichotomization, this resulted in two identical models. As a result, the odds of POMS day 5 surgical morbidity were reduced by 93 per cent for patients above the median *versus* those below the median (odds ratio 0.07, 95 per cent c.i. 0.03 to 0.19; *P*< 0.001). Median values were 11.2 and 18.8 ml per kg per min for o2 at L and peak respectively.

The median number of morbidity events on day 5 (POMS day 5) was 1 (i.q.r. 0–2). *Table 4* shows POMS-defined morbidity at day 5 after surgery dichotomized at the optimal cut-off for o2 at L. Infection, pulmonary, gastrointestinal, cardiovascular and wound morbidity domains differed significantly between groups. *Table 5* showstotal postoperative morbidity grade as assessed by the highest grade of in-hospital morbidity. A significant difference in the distribution of morbidity grade was observed when the patient cohort was dichotomized at the optimal cut-off point for o2 at L, with a significantly higher morbidity (grade 1–4) in patients with o2 at L of less than 10.6 ml per kg per min.

Overall median (i.q.r.) length of stay was 9 (6–16) days. Patients with no POMS-defined morbidity on day 5 had a median length of stay of 7 (6–9) days, compared with 15 (7–24) days in patients with POMS-defined morbidity on day 5 (*P*< 0.001, log rank test). Four patients discharged before day 5 were assumed to have a POMS score of zero. All patients were followed up for 1 year after surgery to determine mortality. Seven patients died within 1 year of operation (liver and lung metastasis, 3; liver and brain metastasis, 2; hospital-acquired pneumonia, 1; out-of-hospital cardiac arrest, 1); all had a o2 at L of less than 10.6 ml per kg per minand experienced postoperative in-hospital morbidity (4 developed hospital-acquired pneumonia, 2 had further surgery for a postoperative collection and 1 for wound dehiscence).

**+A: Discussion**

The findings in this study support the use of CPET as an objective tool for risk assessment before rectal cancer surgery. Patients with lower o2 at L, peak o2, work rate at L and oxygen pulse at L are at increased risk of postoperative morbidity, so these variables may be useful in perioperative risk stratification. Sex, operation type and age were not independently related to postoperative morbidity and did not contribute more information than either o2 at L or peak o2 alone.

This study adds to the literature supporting objective measures of physical fitness derived by CPET for risk assessment in major abdominal surgery4,10–15,25–27. A particular strength of the study is that clinicians were blinded to CPET results (as in previous studies4,15), thereby eliminating ‘confounding by indication’28. The best prognostic markers of postoperative morbidity for this cohort were o2 at L, with an optimal cut-off of 10.6 ml per kg per min, and peak o2, with an optimal cut-off of 18.6 ml per kg per min. These are similar to cut-off values found by others15,25,27,29, although individual variables from patients showed higher sensitivity and specificity than in previous studies. Single-variable endpoints derived from CPET (such as L) may not be associated with 5-year survival30. However, in the present study all patients who died within 1 year of surgery (7 per cent) had an o2 at L of less than 10.6 ml per kg per minand developed postoperative in-hospital morbidity. This might represent an endpoint related to survival in this cohort, although an adequately powered study is needed to explore this.

No difference was found in preoperative physical fitness or postoperative morbidity between patients having neoadjuvant CRT and those going straight to surgery (data not shown). Neither the impact of neoadjuvant CRT on preoperative physical fitness and postoperative morbidity, nor the benefits of improving preoperative fitness by means of exercise interventions are known.

The strengths of this study include the consecutive nature of patient assessment for eligibility, the homogeneous study population, the blinded reporting of objectively measured CPET variables, the blinding to CPET results of both clinicians and outcome data collectors, and use of the POMS21 as a primary outcome measure. Potential limitations include the single-centre design, which limits the generalizability of the data, as well as the ROC curve cut-off points that were optimized and derived for this local cohort as part of service evaluation. Decisions regarding perioperative care or fitness for surgery should be based on the complete clinical and CPET picture, and not on individual CPET variables in isolation. Nonetheless, this study demonstrates that both o2 at L and peak o2 are predictors of short-term outcome in rectal cancer surgery.

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*Disclosure:* The authors declare no other conflict of interest.

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**Fig. 2: Please follow mark-ups for parts a & b. NB: Lengthen vertical axes so that figures are square**

**Fig. 1** Cardiopulmonary exercise testing equipment: static, electromechanically braked exercise bike and metabolic cart (with permission of Geratherm Respiratory GmbH, Love Medical Cardiopulmonary Diagnostics Ltd, Manchester, UK)

**Fig. 2** Receiver operating characteristic (ROC) curves for oxygen uptake at **a** estimated lactate threshold (o2 at L) (A) and **b** peak exercise (peak o2). Open circles indicate optimal cut-off point obtained by minimizing the distance to the upper left corner. Area under ROC curve: **a** 0.87, **b** 0.85

**Table 1** Patient demographics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total (*n* = 95) | No morbidity (*n* = 49) | Morbidity (*n* = 46) | *P* |
| Age (years)\* | 66(10.0) | 65(9.4) | 68(10.5) | 0.122† |
| Sex ratio (M : F) | 72 : 23 | 39 : 10 | 33 : 13 | 0.372‡ |
| Body mass index (kg/m2)\* | 27.7(4.1) | 27.1(3.2) | 28.3(4.8) | 0.003† |
| Haemoglobin (g/dl)\* | 12.5(1.4) | 12.3(1.5) | 12.8(1.5) | 0.890† |
| Co-morbidity |  |  |  |  |
| Ischaemic heart disease | 14 (15) | 9 (18) | 5 (11) | 0.391‡ |
| Heart failure | 6 (6) | 0 (0) | 6 (13) | 0.008§ |
| Cerebrovascular disease | 4 (4) | 1 (2) | 3 (7) | 0.092§ |
| Diabetes | 18 (19) | 8 (16) | 10 (22) | 0.293‡ |
| Surgical procedure |  |  |  | 0.223‡ |
| Anterior resection | 66 (69) | 37 (76) | 29 (63) |  |
| Abdominoperineal resection  | 22 (23) | 11 (22) | 11 (24) |  |
| Hartmann procedure | 4 (4) | 0 (0) | 4 (9) |  |
| Other | 3 (3) | 1 (2) | 2 (4) |  |
| Type of surgery |  |  |  | 0.941‡ |
| Laparoscopic | 43 (45) | 22 (45) | 21 (46) |  |
| Open | 52 (55) | 27 (55) | 25 (54) |  |
| Anastomosis |  |  |  | 0.653‡ |
| Yes | 69 (73) | 38 (78) | 31 (67) |  |
| No | 26 (27) | 11 (22) | 15 (33) |  |

Values in parentheses are percentages unless indicated otherwise; \*values are mean(s.d.). †Univariable logistic regression; ‡χ2 test; §Fisher’s exact test.

**Table 2** Clinical staging and histopathological tumour assessment

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total (*n* = 95) | No morbidity (*n* = 49) | Morbidity (*n* = 46) | *P*‡ |
| Neoadjuvant therapy |  |  |  | 1.000 |
| Yes | 68 (72) | 35 (71) | 33 (72) |  |
| No (straight to surgery) | 27 (28) | 14 (29) | 13 (28) |  |
| MRI tumour category† |  |  |  | 0.088 |
| T1 | 1 (1) | 0 (0) | 1 (2) |  |
| T2 | 25 (26) | 11 (22) | 14 (30) |  |
| T3 | 66 (69) | 38 (78) | 28 (61) |  |
| T4 | 3 (3) | 0 (0) | 3 (7) |  |
| MRI node category† |  |  |  | 0.892 |
| N0 | 10 (11) | 6 (12) | 4 (9) |  |
| ≥ N1 | 85 (89) | 43 (88) | 42 (91) |  |
| Pathological tumour category |  |  |  | 0.325 |
| T0 | 7 (7) | 4 (8) | 3 (7) |  |
| T1 | 11 (12) | 6 (12) | 5 (11) |  |
| T2 | 23 (24) | 11 (22) | 12 (26) |  |
| T3 | 50 (53) | 28 (57) | 22 (48) |  |
| T4 | 4 (4) | 0 (0) | 4 (9) |  |
| Pathological node category |  |  |  | 0.151 |
| N0 | 55 (58) | 32 (65) | 23 (50) |  |
| ≥ N1 | 40 (42) | 17 (35) | 23 (50) |  |
| No. nodes retrieved\* | 14 (10–18) | 12 (8–17) | 15 (11–19) | 0.123§ |
| Resection margin |  |  |  | 0.283 |
| R0 | 84 (88) | 45 (92) | 39 (85) |  |
| R1 | 11 (12) | 4 (8) | 7 (15) |  |

Values in parentheses are percentages unless indicated otherwise; \*values are median (i.q.r.). †Magnetic resonance imaging (MRI) classified according to International Union Against Cancer TNM Classification of Malignant Tumours, seventh edition24. ‡χ2 test, except §univariable logistic regression.

**Table 3** Cardiopulmonary exercise testing variables

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total | No morbidity | Morbidity | *P*† |
| o2 at L (ml per kg per min) | 11.2 (9.4–13.4) | 12.7 (11.7–14.4) | 9.4 (8.6–10.5) | < 0.001 |
| Peak o2 (ml per kg per min)\* | 18.9(5.8) | 21.8(4.0) | 15.8(5.9) | < 0.001‡ |
| Oxygen pulse at L (ml/beat) | 9.1 (7.3–10.3) | 9.4 (8.3–10.7) | 8.0 (5.9–9.7) | 0.004 |
| E/co2 at L | 31.2 (27.6–33.8) | 30.5 (26.9–32.0) | 31.8 (28.5–35.3) | 0.071 |
| Work rate at L (W) | 54 (42–70) | 65 (52–76) | 45.5 (34.3–56) | < 0.001 |

Values aremedian (i.q.r.) unless indicated otherwise; \*values are mean (s.d.). o2 at L, oxygen uptake at estimated lactate threshold; peak o2, oxygen uptake at peak exercise; oxygen pulse at L, oxygen pulse at estimated lactate threshold; E/co2 at L, ventilatory equivalents for carbon dioxide at estimated lactate threshold; work rate at L, work rate at estimated lactate threshold. †??? test, except ‡univariable logistic regression or Fisher’s exact tests where cell counts were insufficient.**Table 4** Total in-hospital morbidity assessed for the nine domains of the Postoperative Morbidity Survey21 at day 5 after surgery

|  |  |  |  |
| --- | --- | --- | --- |
| POMS domain | o2 at L < 10.6(*n* = 39) | o2 at L ≥ 10.6(*n*= 56) | *P*\* |
| Infection | 21 (54) | 5 (9) | < 0.001 |
| Wound dehiscence | 5 (13) | 0 (0) | 0.010† |
| Pulmonary | 11 (28) | 2 (4) | 0.001 |
| Renal | 6 (15) | 2 (4) | 0.061† |
| Gastrointestinal | 12 (31) | 6 (11) | 0.014 |
| Cardiovascular | 7 (18) | 2 (4) | 0.019 |
| Neurological | 0 (0) | 0 (0) | 1.000† |
| Haematological | 3 (8) | 3 (5) | 0.687† |
| New postop. pain | 4 (10) | 1 (2) | 0.155† |

Values are numbers of patients (with percentages in parentheses) dichotomized at optimal cut-off for oxygen uptake at estimated lactate threshold (o2 at L of 10.6 ml per kg per min). POMS, Postoperative Morbidity Survey. \*χ2 test, except †Fisher’s exact test.

**Table 5** Total postoperative morbidity according to the Dindo–Demartines–Clavien classification22

|  |  |  |
| --- | --- | --- |
| Grade | o2 at L < 10.6(*n* = 39) | o2 at L ≥ 10.6(*n*= 56) |
| 1 | 7 (18) | 3 (5) |
| 2 | 14 (36) | 5 (10) |
| 3a | 1 (3) | 0 (0) |
| 3b | 8 (23) | 1 (2) |
| 4a | 5 (13) | 1 (2) |
| 4b | 0 (0) | 1 (2) |
| 5 | 0 (0) | 0 (0) |

Values are numbers of patients (with percentages in parentheses) dichotomized at optimal cut-off for oxygen uptake at estimated lactate threshold (o2 at L of 10.6 ml per kg per min). *P* < 0.001 (Fisher’s exact test).