**Cardiopulmonary exercise variables are associated with postoperative morbidity after major colonic surgery – a prospective blinded observational study**

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Short title - CPET and morbidity after colonic surgery

**Summary**

**Background**: Post-operative complications are associated with reduced fitness. Cardiopulmonary exercise testing (CPET) has been used in risk stratification. We investigated the relationship between pre-operative CPET and in-hospital morbidity in major colonic surgery.

**Methods**: We prospectively studied 198 patients scheduled for major colonic surgery (excluding neoadjuvant cancer therapy), performing pre-operative CPET (reported blind to clinical state) and recording morbidity (assessed blind to CPET), postoperative outcome and length of stay.

**Results**: Of 198 patients, 62 were excluded: 11 had emergency surgery, 25 had no surgery, 23 had incomplete data and 3 were unable to perform CPET. One hundred and thirty six (89 males, 47 females) were available for analysis. Median age was 71 (interquartile range (IQR) 62-77) years. 65 patients (48%) had a complication at day 5 post-operatively. Measurements significantly lower in patients with complications than those without were O2 uptake (o2) at estimated lactate threshold (L) (median 9·9 (IQR 8.3-12.7) vs. 11.2 (9.5-14.2) ml.kg-1.min-1, p<0.01), o2 at peak (15.2 (12.6-18.1) vs. 17.2 (13.7-22.5) ml.kg-.min-1, p=0·01) and ventilatory equivalent for CO2 (E/co2) at L (31.3 (28.0-34.8) vs. 33.9 (30.0-39.1), p<0.01). A final multivariable logistic regression model contained o2 at L (one-point change odds ratio (OR) 0.77 (95% confidence interval (CI) 0.66-0.89), p<0.0005; two-point change OR 0.61 (0.46-0.81) and gender (OR 4.42 (1.78-9.88), p=0.001), and was reasonably able to discriminate those with and without complications (AUC 0.71, CI 0.62-0.80, 68% sensitivity, 65% specificity).

**Conclusions**: CPET variables are associated with postoperative morbidity. A multivariable model with o2 at L and gender discriminates those with complications following colonic surgery.

**Keywords**

Cardiopulmonary exercise test, colorectal surgery, morbidity, anaerobic threshold, postoperative complications

Major colorectal surgery carries substantial morbidity (15-20%) (1,2) and mortality, particularly in elderly patients and those with co-morbidities (3). Recent UK cancer audits show 30-day mortality of 2.3% for elective and 11.4% for emergency surgery (4). Outcome after major surgery depends both on modifiable factors such as peri-operative medical care, and physiological tolerance of surgical trauma. Accurate risk stratification permits modification of preoperative status as well as optimisation of intra- and postoperative management, and thus facilitates efficient use of resources (e.g. intensive care beds), and enhances shared decision-making (5). Approaches to risk evaluation include clinical acumen, clinical prediction scores (e.g. American Society of Anesthesiologists physical score (ASA-PS), Duke’s Activity Scores, POSSUM, CR-POSSUM) (6–8), plasma biomarkers (9), measures of cardiac function (10,11) and shuttle walk tests (12–14), but their effectiveness in predicting complications is not well established (15–17).

Cardiopulmonary exercise testing (CPET), which has been used for risk stratification before thoracic and abdominal surgery (17–21), tests cardiorespiratory reserve (physical fitness) at rest and under the stress of maximal exercise (mimicking that of major surgery), and is the most objective and precise means of evaluating pre-surgical fitness (22–24).

This prospective, blinded, observational study tests the hypothesis that CPET variables are related to short-term in-hospital morbidity in patients undergoing major colonic surgery.**Methods**

## Patients

We included all patients aged >18 years considered for major colonic surgery (benign or malignant), except those with inflammatory bowel disease, patients scheduled for neoadjuvant cancer therapy, or patients who were unable to perform CPET as part of their preoperative evaluation between February 2009 and December 2010. Patients were excluded on the basis of having no surgery performed or interim emergency surgery, lacking complete in-hospital morbidity data, or their inability to attain a definable lactate or anaerobic threshold (o2 at L). Discussions with Aintree University Hospitals NHS Foundation Trust and the North West Research Ethics Committee established that formal ethical approval was unnecessary, since CPET had been recently introduced as routine assessment in the hospital for major colorectal surgical patients, and results were not used by the multidisciplinary team (MDT) to alter clinical management as yet. We however adhered fully to Caldicott guidelines. 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 electrocardiograph (ECG) abnormalities were raised at the colorectal MDT meeting and referred appropriately.

## Cardiopulmonary Exercise Testing

CPET followed American Thoracic Society/ American College of Chest Physicians recommendations (25). After resting spirometry (flow-volume loops), CPET on an electromagnetically-braked cycle ergometer (Ergoline 2000) comprised 2 min rest, 2 min freewheel pedalling, ramped incremental pedalling until volitional termination, and 5 min recovery. Ventilation and gas exchange was measured using a metabolic cart (Geratherm Respiratory GmbH (Love Medical Ltd.). Pulse, 12-lead ECG, blood pressure and pulse oximetry were monitored throughout. Ramp gradient was set to 10-25 W/min based on a calculation (26) using predicted freewheel oxygen uptake (o2), predicted o2 at peak exercise, height and age. No major adverse clinical events occurred during CPET.

## Measurements

Patient characteristics recorded at CPET included age, gender, height, weight, diagnosis, staging (if malignancy), surgical procedure planned, WHO classification and American Society of Anesthesiologists - Physical Status Scores (ASA-PS), as well as diagnosis of diabetes, ischaemic heart disease, cerebrovascular disease, or heart failure. Resting flow-volume loops were used to derive Forced Expiratory Volume over 1 second (FEV1) and Forced Vital Capacity (FVC). 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 L and at peak exercise (26). L was estimated conventionally (breakpoint in the co2-o2 relationship (27), with increases in E/ o2 and end tidal (PET) o2 but no increase in E/co2 or decrease in PET co2 (28)). Peak o2 was averaged over the last 30 seconds of exercise. CPETs were reported by two experienced assessors both blind to patient demographics and outcome data.

Short-term surgical outcome was assessed as morbidity (by medical and nursing staff blind to any CPET data) using the 9 domains listed in the Post-Operative Morbidity Survey (29) on day 5, Clavien-Dindo Classification (30) (highest grade for the most serious sustained in-hospital complication) and in-hospital mortality. Length of hospital stay (days) was recorded prospectively, and patients were followed for 30 days post-discharge for re-admission and mortality. The patients and the colorectal MDT (including anaesthetists) were blind to all CPET data. No perioperative management or decisions were influenced by CPET data.

The primary aim was to establish the relationship between post-operative complications (POMS present or absent on day 5) and o2 at L; a secondary aim was to explore the multivariable relationship between CPET variables and other important prognostic variables with complications at Day 5 post-operatively.

## Statistical methods

Non-parametric receiver operator characteristic (ROC) curves were constructed for o2 at L, o2 at Peak, o2 Pulse at L and E/co2 at L in order to assess their independent ability to discriminate between patients with and without day 5 morbidity. Optimal cut-points were obtained by minimising the distance between points on the ROC curve and the upper left corner. Six variables (to satisfy the 10 events per variable rule (31)) were identified as candidates for a multivariable logistic regression model: o2 at L and at Peak, gender, operation type (laparoscopic/open), and o2 Pulse at L and E/co2 at L. A final multivariable model was obtained using forward stepwise selection (minimising Akaike Information Criteria (AIC)). Its sensitivity to variable exclusion and re-inclusion was also assessed using AIC. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test. In order to explore the univariate relationship between CPET variables and length of stay, continuous CPET variables were dichotomised at the optimal cut-point for the ROC curve and Kaplan-Meier curves were constructed. The log rank test was used to compare survival curves; patients who died before discharge (n=2) were treated as right-censored. Patients who left the study before day 5 (n=14) were excluded from the analysis of length of stay. All analyses were conducted using Stata (StataCorp. 2011 *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP.). Continuous variables are reported as mean and standard deviation (SD) or median and inter-quartile range (IQR) depending on the distribution. Categorical variables are presented as frequency (percentage). P-values in Tables 1 and 2 were obtained using univariate logistic regression (continuous) and Chi-squared or Fisher’s Exact tests (categorical). Statistical significance was taken at 5%.

**Results**

One hundred and ninety-eight patients consented, of whom 25 had no surgery (15 due to patient choice, 10 due to irresectable metastasis), 11 needed an emergency procedure and 3 were unable to perform a CPET. Of the 159 who had adequate CPET and underwent major elective surgery, 23 lacked complete data. Of the remaining 136 (89 male, 46 female), 41 had right and 9 left hemicolectomy, 46 anterior resection, 1 subtotal colectomy, 13 abdominoperineal resections, 8 Hartman’s procedure and 19 other major colonic resections. One patient developed a supraventricular tachycardia at peak exercise. The patients’ ECG was discussed at MDT and was subsequently referred to a cardiologist. Surgery on this patient proceeded as normal. Table 1 shows patients grouped by occurrence or not of in-hospital post-operative complications: these groups differed significantly in gender, age and pre-operative heart failure, but not in operation type, surgery or presence of anastomosis/stoma. Table 2 shows grouped CPET data: patients with a complication had significantly lower o2 at L, o2 at Peak and higher E/co2 at L. 3 patients unable to attain L sustained a complication and their discharge was delayed; these were excluded from analysis.

Sixty-five patients (48%) sustained a complication at day 5, of whom 2 died in hospital (1.5% mortality) from myocardial infarction (at days 3 and 5) and 8 (6.5%) suffered anastomotic leak at a median of 6 days (4 anterior resection, 3 right and 1 left hemicolectomy): of these 5 were re-operated, 3 treated conservatively with radiological-inserted drains and intravenous antibiotics. A further 2 patients were re-operated at median 5 days (1 patient suffered intestinal obstruction and another a necrotic stoma). All these suffered further complications and delayed hospital discharge. Table 3 shows POMS-defined complication at day 5 post-operatively and Clavien-Dindo classification. POMS episodes were dichotomised around the ROC curve cut-point for o2 at L. Pulmonary and infective complications (patients requiring antibiotics for a febrile episode) differed between groups (p<0.001 and p=0.02 respectively).

Independently o2 at L, o2 at Peak and E/co2 were associated with day 5 morbidity (p<0.05), whereas o2 Pulse at L and ASA were not (p=0.22 and 0.11 respectively). For o2 at L (area under curve (AUC) 0.63, CI 0.54-0.73) the optimal cut-point was 10.1 ml.kg-1.min-1, giving 68% sensitivity and 58% specificity (Figure 1), while for o2 at Peak (AUC 0.63, CI 0.53-0.73) cut-point was 16.7 ml.kg-1.min-1, giving 55% sensitivity and 69% specificity. For E/co2 at L (AUC 0.64, CI 0.55-0.74) cut-point was 32.9, giving 60% sensitivity and 66% specificity.

Onlyo2 at L and gender were retained in the final multivariable logistic regression model. In this model the odds of complications are higher for a male than a female with the same o2 at L (OR 4.19, CI 1.78-9.88, p<0.001); a 1.0 ml.kg-1.min-1 increase in o2 at L is associated with ~20% reduction in the odds of complications (OR 0.77, CI 0.66-0.89, p<0.0005) and a 2.0 ml.kg-1.min-1 increase with ~40% reduction (OR 0.60, CI 0.45-0.80, p<0.001), after adjustment for sex. The ability of this model to discriminate between patients with and without a complication was reasonable (AUC 0.71, CI 0.62-0.80, 68% sensitivity and 65% specificity at the optimal cut-point; Positive Predictive Value = 62%, Negative Predicative Value = 69%) (Figure 2).

There is evidence to suggest that, independent of other predictive variables, patients with o2 at L (p=0.003) (Figure 3) or o2 at Peak (p=0.004) above the cut-point and E/co2 at L (p<0.0001) below the cut-point have a significantly reduced length of hospital stay.

**Discussion**

## Main findings and comparison with other studies

This prospective blinded observational study provides novel evidence supporting CPET as an objective risk assessment tool before major colonic surgery. In this cohort o2 at L and Peak were significantly lower and E/co2 at L significantly higher, in patients encountering POMS-defined complication at day 5 post-operatively, and single variable analysis confirms these associations, albeit with only moderate sensitivity and specificity. The poor predictive performance of CPET variables in our study when assessed independently; is consistent with the literature (23,24) and reflects the complex interactions between baseline physiology and elective surgical trauma on post-operative outcomes. However, multivariable analysis showed thato2 at L and gender were independent predictors of complications following surgery with moderate discrimination between patients with, and without, complications. ASA was not independently related to outcome and inclusion of this variable in the multivariable model had a negligible effect.

This study adds to the literature supporting objective measures of physical fitness for risk assessment in major abdominal surgery. The findings by Older and colleagues (32) in 187 elderly patients undergoing major intra-abdominal surgery that preoperative L <11.0 ml.kg-1.min-1 was associated with increased cardiovascular mortality established CPET as a tool for pre-operative risk assessment and stratification. In a later study and a review (20,33) Older investigated triaging: if a patient had L <11 ml.kg-1.min-1 they were assigned to ICU pre-operatively. Assessing 843 patients >55 years undergoing major colorectal surgery, radical nephrectomies and cystectomies, Wilson and colleagues (18) concluded that L ≤10.9 ml.kg-1.min-1 andE/CO2 at L ≥ 34 had 88% sensitivity and 47% specificity for hospital mortality. Snowden and colleagues (17) evaluated CPET in preoperative risk assessment in elderly (mean age 70 years) patients undergoing major intra-abdominal surgery, finding that the L optimal cut-point of 10.1 ml.kg-1.min-1 gave 88% sensitivity and 79% specificity for discriminating postoperative complications (AUC 0.85; CI, 0.78–0.91; p<0.001). In 32 patients undergoing major intra-abdominal surgery, Hightower and colleagues (6) found that L <75% of predicted value predicted complications (AUC 0.72 (CI 0.57-0.87); sensitivity 88%; specificity 56%, p= 0.016). A particular strength of our study, and those of Snowden and Hightower, is that clinicians were blinded to CPET results, which eliminates ‘confounding by indication’ (34).

Junejo and colleagues (35) evaluated preoperative CPET in predicting outcome following major hepatic resection in 108 patients: L < 9·9 ml.kg-1.min-1 was 100% sensitive and 76% specific for in-hospital mortality, age and E/CO2 at L (84% specificity and 47% sensitivity) were related to postoperative complications and long-term survival with L <9·9 ml.kg-1.min-1 was significantly worse (Hazard Ratio 1·81, CI 1·04-3·17); however only 8 deaths out of 94 patients were recorded. Otto and colleagues (36) retrospectively studied aerobic exercise capacity in inflammatory bowel disease patients, finding that adjusted L in Crohn’s disease was lower than in colorectal cancer (mean ± SD: 11.4±3.4 vs. 13.2±3.5 ml.kg-1.min-1). This justifies our exclusion of inflammatory bowel disease patients as pathophysiologically distinct.

Our data further support CPET in peri-operative risk assessment (22–24). Our best prognostic markers of postoperative complications were E/CO2 at L with a cut-off at 32.9, o2 at L with a cut-off at 10.1 ml.kg-1.min-1and o2 at Peak with a cut-off at 16.7 ml.kg-1.min-1. These are similar to cut-off points found by Older (20), Snowden (17) and Junejo (35) and colleagues, although the sensitivity and specificity of individual variables was moderate when compared to other studies. However, our multivariable logistic regression model identifies gender and L as important predictors of day 5 complications, albeit with moderate AUC, specificity and sensitivity. Interestingly in upper gastrointestinal cancer surgery (37), bariatric surgery (38) and liver transplantation (39) surgery the association with outcome and the cut-off point for o2 at L is different. However, a recently published series by Colson and colleagues (40) concludes that single variable primary endpoints commonly derived from CPET (such as L) were not associated with 5 yr survival, although in a multivariable analysis, many CPET variables were important predictors.

## Strengths and Weaknesses

Strengths of this study include the homogeneous nature of the study population (only colonic surgical patients were included, rectal cancer patients who were scheduled to have cancer therapies were excluded), the blinded reporting of objectively-measured CPET variables, the prospective nature of the study, the blinding to CPET results of caring clinicians and outcome data collectors, and the use of POMS (29) (which has been validated in the UK) as a primary outcome measure and is currently used in National Institute for Health Research and Medical Research Council funded studies.

Potential weaknesses include the single centre design which limits generalizability to other centres, as the ROC curve cut-off points are optimised for this local cohort and future validation work in similar cohorts should be performed.

## Conclusion and further research

Our results indicate that when using CPET in patients awaiting colonic surgery, clinicians should consider using o2 at L (ROC cut-off 10.1ml.kg-1.min-1) and gender as a simple risk prediction tool. Of course, decisions regarding patient care or fitness for surgery should be made using the overall clinical and CPET picture. The identification of L and gender as a predictor for short term outcome in colonic surgery is novel; however, confirmation of these results in a larger colonic surgical cohort is encouraged to establish whether several preoperative risk assessment tools can be combined to predict risk more effectively. Furthermore, we suggest that improving physical fitness e.g. o2 at L and peak might improve surgical outcome in this population; to test this we are currently investigating the role of a structured preoperative exercise training programme (prehabilitation) in this patient group (NCT01325909)

**Author contribution**

M.A.W: Conception, study design, data acquisition, analysis, drafting article, revision and final approval

D.L: Analysis and interpretation of data, drafting article, revising for intellectual content and final approval

C.P.B: Study design, data acquisition, analysis, drafting article, revision and final approval

L.N: Study design, data acquisition, analysis, drafting article, revision and final approval

S.J: Conception, study design, revision and final approval

G.J.K: analysis and interpretation of data; critical revision of manuscript and final approval

M.P.W.G: Conception, study design, revision and final approval

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# Declaration of interest

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