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Clinical Investigation

CLINICAL INVESTIGATION

Exercise-induced myocardial dysfunction detected by cardiopulmonary exercise testing is associated with increased risk of mortality in major oncological colorectal surgery

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Abstract

Background: Cardiopulmonary exercise testing (CPET) identifies high-risk patients before major surgery. In addition to using oxygen uptake and ventilatory efficiency to assess functional capacity, CPET can be used to identify underlying myocardial dysfunction through the assessment of the oxygen uptake to heart rate response (oxygen pulse response). We examined the relationship of oxygen pulse response, in combination with other CPET variables and known cardiac risk factors, with mortality after colorectal cancer surgery.

Methods: This work focused on a retrospective cohort study of patients who had CPET and underwent colorectal cancer surgery. The primary outcome was a composite of in-hospital and 30-day mortality. Ventilatory inefficiency (V_E/V_{CO_2}>34) and exercise-induced myocardial dysfunction (abnormal oxygen pulse response) were investigated for an association with mortality using bivariable analysis and multivariable Cox regression.

Results: A total of 1214 patients who underwent colorectal cancer surgery were included, and the primary outcome occurred in 26 patients (2.1%). Multivariable Cox regression showed abnormal oxygen pulse response was independently associated with the primary outcome (odds ratio [OR]=2.75; 95% confidence interval [CI], 1.17–6.47). Bivariable analysis showed that V_E/V_{CO_2} >34 was associated with the primary outcome (OR=3.43; 95% CI, 1.47–8.01). Combining V_E/V_{CO_2} >34 and abnormal oxygen pulse response conferred an increased risk for the primary outcome (OR=4.47; 95% CI, 1.62–12.34), compared with V_E/V_{CO_2} >34 and normal oxygen pulse response.

Conclusion: Ventilatory inefficiency and an abnormal oxygen pulse response were independently associated with short- (30-day) and long-term (2-yr) mortality. Oxygen pulse response may provide additional information when considering perioperative risk stratification.

Keywords: cardiopulmonary exercise testing; colorectal surgery; exercise test; mortality; myocardial ischaemia; post-operative period

Editor's key points

- Cardiopulmonary exercise testing can be used to generate indices of cardiac dysfunction.
- Peak oxygen pulse and oxygen pulse response have been associated with increased mortality in heart failure.
- This study found that an abnormal oxygen pulse response was associated with mortality after colorectal surgery.
- Future studies are warranted to define thresholds in colorectal and other types of surgery.

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Major surgery is associated with a high incidence of postoperative complications and places a significant burden on healthcare resources.[1] Approximately 30 000 patients were diagnosed with bowel cancer in the UK in 2015–16, with almost 20 000 of these undergoing major colorectal resections. Of those proceeding to major resection, 1.9% of patients died within 90 days after planned surgery.[2] In order to reduce mortality rates in elective surgery, it is necessary to identify patients at increased risk so interventions which may improve outcome can be focused on this group.

Standard preoperative assessment alone has limitations when trying to identify the higher risk patient. Reduced aerobic fitness, or impaired functional capacity, is predictive of worse outcomes after major elective surgery.[3–5] We know that physician assessment of functional capacity is unreliable, and although self-reporting by patients may have some utility,[6] objective measurement of aerobic fitness using cardiopulmonary exercise testing (CPET) provides the most accurate information. Reduced functional capacity as measured by CPET has repeatedly been shown to be associated with a poorer outcome after operation.[3–5]

Using CPET, reduced functional capacity can be determined by measurement of peak oxygen consumption, oxygen consumption at anaerobic threshold (AT) or ventilation–perfusion (V/Q) mismatching through CPET.[7] Patients with V/Q mismatch require a higher minute volume to excrete the same amount of carbon dioxide (CO_2) produced compared to those that do not. It is measured as the ratio of minute ventilation to CO_2 production (V_E/V_{CO_2}) and termed the ventilatory equivalent for CO_2. Increased V_E/V_{CO_2} has multiple aetiologies, including heart failure, obstructive airway disease, pulmonary hypertension, pulmonary embolism, and deconditioning. All aetiologies can cause increasing values, which indicate higher degrees of V/Q mismatch and relate to a reduction in functional capacity. A range of values of V_E/V_{CO_2} measured at AT from >34 to >39 has shown to be predictive of mortality in surgical[3,8] and heart failure populations.[3,9–11]

In addition to measures of functional capacity, CPET can generate additional variables associated with underlying myocardial dysfunction or ischaemic heart disease.[12] Oxygen uptake divided by heart rate is known as oxygen pulse, and is a surrogate for stroke volume by the application of the Fick principle.[13] Plotting oxygen pulse by time allows the interpretation of oxygen pulse throughout the duration of the test, and at our trust, is termed oxygen pulse response. Myocardial dysfunction is characterised by a patient's reduced ability to increase stroke volume during incremental exercise and precedes the development of ST segment changes and angina.[12] Oxygen pulse response has been shown to be more specific for the diagnosis of ischaemic heart disease when compared with standard treadmill ECG testing.[12] This may confer an advantage over static measurements of cardiac function which may not detect early or subtle exercise-induced myocardial dysfunction (EIMD), such as ECG and echocardiography.[12]

The aim of this study was to evaluate the oxygen pulse response as an adjunct to other CPET parameters for risk prediction of mortality after major elective colorectal surgery.

Methods

We conducted a retrospective analysis of prospectively acquired data that aimed to investigate CPET parameters and adverse postoperative outcomes. York Teaching Hospital Foundation Trust sponsored the study, which was approved by the UK Health Research Authority (IRAS 228489).

Data extracts were anonymised and analysed for the period June 1, 2004 to December 31, 2016 for patients older than 55 yr, or younger if any known cardiorespiratory risk factors were present, who were referred for a preoperative evaluation, including CPET, and subsequently underwent surgery for colorectal cancer. A description of the York CPET protocol has been described elsewhere.[3] Patients who did not undergo colorectal cancer surgery or did not have an oxygen pulse response recorded were excluded.

All preoperative data were recorded prospectively on a secure trust database and included patient demographics (age, sex, height, weight, and BMI), presence of metastatic disease, co-morbidities (ischaemic heart disease, cerebrovascular disease, heart failure, dysrhythmias, hypertension, diabetes mellitus, lung disease, and renal insufficiency), medications (beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, calcium channel blockers, diuretics, nitrates, other antihypertensives, antiplatelet medication, anticoagulants, statins, insulin therapy, and systemic steroids). Lee's revised cardiac risk index (RCRI) was calculated using the aforementioned data. CPET parameters recorded for this study were: V_{O_2} at AT, V_E/V_{CO_2} at AT, and the quality of the V_{O_2}/work rate (V_{O_2}/WR) and oxygen pulse response. At York Hospital, a consultant anaesthetist trained in CPET interprets the oxygen pulse graph as normal or abnormal depending on the shape of the plotted line, corresponding heart rate, and achievement of predicted values calculated for weight, sex, age, and ethnicity. An abnormal response is characterised by the onset of a plateau instead of a continuing increasing response, or a decreasing inflection accompanied by a corresponding compensatory increase in heart rate. Similarly for V_{O_2}/WR, a consultant anaesthetist interprets the graph of work rate and V_{O_2} by time as normal or abnormal depending on whether the plotted line of oxygen consumption has a low trajectory compared with work rate, includes a decreasing inflection point, or both.

Outcome data were gathered after hospital discharge from the Trust's core patient database. Status at discharge (alive or dead), prolonged hospital length of stay (PHLOS), unplanned critical care use, long-term status, and survival time were recorded. PHLOS was defined as a length of stay greater than that of the 75th centile of the whole study cohort. Unplanned critical care use was defined as any unexpected admission or re-admission to high dependency unit (HDU) or ICU from the general surgical ward.

For increased risk of postoperative morbidity and mortality, AT was defined as a value of less than 11 ml^{-1} kg^{-1} min^{-1},[3,4] and V_E/V_{CO_2} risk (ventilatory inefficiency) was defined as a value greater than 34 at the point of AT[3,11] in accordance with the clinical practice at the time. Oxygen pulse response is a subjective assessment of the graph; oxygen pulse by time (minutes). Peak V_{O_2} could not be used in this study as the CPET protocol used sub-maximal testing for a large majority of patients, resulting in 625 missing values.

Clinicians were informed of the CPET results, and patients were stratified as either high or standard risk based on a combination of CPET data (AT and V_E/V_{CO_2}) and clinical risk factors. Intraoperatively, patients received goal-directed fluid therapy, and whether surgery was open or laparoscopically assisted was recorded. After surgery, patients were allocated to either HDU (level 2), or to a nursing enhanced unit (NEU, level 1) on the general surgical wards. NEU is an area of eight

beds in a general surgical ward with a nurse/patient ratio of 1:4 enabling closer observation and monitoring than routine ward care. Postoperative care was under the control of the surgical team, or intensivists if the patient was on HDU or ICU.

The primary outcome was a composite of in-hospital mortality and mortality within 30 days of surgery. Secondary outcomes were 90-day and 2-yr mortality, prolonged hospital stay, and unplanned critical care admission.

Bivariable analysis was used to test differences in patient baseline demographics, risk factors, and outcomes. Analysis included unpaired Student's *t*-test for normally distributed continuous variables or Mann–Whitney *U*-test for non-parametric data, and χ^2 or Fisher's exact test for categorical variables as appropriate. Differences between groups were estimated using odds ratios (ORs) with 95% confidence intervals (CIs) and Cox regression with backward selection to control for confounders. Kaplan–Meier curves were constructed to compare survival between oxygen pulse response groups. SPSS Statistics was used for statistical analysis (SPSS Statistics version 25; IBM Corporation, Armonk, NY, USA). A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 1782 patients were assessed in the anaesthetic preoperative assessment clinic before colorectal surgery. Overall, 213 patients were excluded because oxygen pulse response was unreported (described in Supplementary Table S1) and 355 were excluded as they did not have malignancy, leaving 1214 patients who underwent colorectal cancer surgery.

Twenty-six (2.1%) patients died within 30 days or during their postoperative hospital stay. Age, sex (male), V_E/V_{CO_2} >34, and oxygen pulse response were associated with all-cause mortality using bivariable analysis (Table 1).

Oxygen pulse response

In the whole cohort, patients with a normal and abnormal oxygen pulse response differed statistically in demographics, co-morbidities, and CPET results (Supplementary Table S2). A total of 246 (20.3%) patients exhibited an abnormal oxygen pulse response, of whom 11 died, producing a mortality rate of 4.5%. The mortality rate for patients with normal oxygen pulse response was 1.5%.

In total, 1150 were eligible for multivariable Cox regression analysis (see Supplementary Fig. S1). Table 2 displays the adjusted ORs produced for the primary and secondary outcomes. An abnormal oxygen pulse response remained independently associated with 30-day, 90-day, and 2-yr mortality. When controlled for patient sex, chronic obstructive pulmonary disease (COPD), and V_E/V_{CO_2} >34, an abnormal oxygen pulse had an increased risk for the primary outcome (OR=2.75;

Table 1 Descriptive statistics of all cause mortality within 30 days. Categorical variables analysed by χ^2 or Fisher's exact test (*), continuous variables compared with independent t-test and displayed as mean (standard deviation, SD). Percentages calculated including missing values. BMI, revised cardiac risk index (RCRI), V_{O_2} at anaerobic threshold (AT), oxygen pulse response (O_2PR), V_{O_2}/work rate (V_{O_2}/WR).

	All patients (*n*=1214)	30-day mortality		*P*-value
		No (*n*=1188)	Yes (*n*=26)	
Age (yr), *n*=1208	71.7 (8.8)	71.7 (8.8)	75.4 (9.0)	0.031
BMI (kg m^{-2}), *n*=1179	27.3 (4.9)	27.3 (4.9)	26.8 (4.2)	0.56
Sex, *n* (%)				
Male	713 (58.7)	692 (58.2)	21 (80.8)	0.021
Female	501 (41.3)	496 (41.8)	5 (19.2)	
BMI category, *n* (%)				
Underweight (<18.5)	15 (1.2)	14 (1.2)	1 (3.8)	0.33*
Healthy (18.5–24.9)	375 (30.9)	365 (30.7)	10 (38.4)	
Overweight (25–29.9)	479 (39.5)	471 (39.6)	8 (30.8)	
Obese (≥30)	310 (25.5)	303 (25.5)	7 (26.9)	
Metastases, *n* (%)	*n*=1214			
None	756 (62.3)	735 (61.9)	21 (80.8)	0.049
Metastases	458 (37.7)	453 (38.1)	5 (19.2)	
Laparoscopic, *n* (%)	*n*=1214			
Open	1014 (83.5)	991 (83.4)	23 (88.5)	0.79*
Laparoscopic	200 (16.5)	197 (16.6)	3 (11.5)	
Lee's RCRI, *n* (%)	*n*=1214			
Low (<1%)	943 (77.7)	926 (77.9)	17 (65.4)	0.13
Elevated (>1%)	271 (22.3)	262 (22.1)	9 (34.6)	
AT risk, *n* (%)	*n*=1205			
≥11 ml kg^{-1} min^{-1}	665 (54.8)	653 (53.5)	12 (46.2)	0.35
<11 ml kg^{-1} min^{-1}	540 (44.5)	526 (44.3)	14 (53.8)	
V_E/V_{CO_2} risk, *n* (%)	*n*=1193			
≤34	729 (60)	721 (60.7)	8 (30.8)	0.003
>34	464 (38.2)	447 (37.6)	17 (65.4)	
O_2PR, *n* (%)	*n*=1214			
Normal	969 (79.7)	953 (80.2)	15 (57.7)	0.005
Abnormal	246 (20.3)	235 (19.8)	11 (42.3)	
V_{O_2}/WR response, *n* (%)	*n*=1213			
Normal	1073 (88.4)	1053 (88.6)	20 (76.9)	0.11*
Abnormal	140 (1213)	134 (11.3)	6 (23.1)	

Table 2 Coefficients for oxygen pulse response calculated by multivariable Cox regression when analysing primary and secondary outcomes. 30 day mortality controlled for sex, chronic obstructive pulmonary disease (COPD), and V_E/V_{CO_2} ≤34; 90 day mortality controlled for age, sex, and COPD; 2 yr mortality controlled for age, sex, metastases, BMI (continuous), COPD, and V_E/V_{CO_2} ≤34. All eligible cases included in analysis, cases with missing data were excluded (n=1150). Full regression model included in supplementary material. CI, confidence interval.

Outcome	Oxygen pulse response Cox regression coefficient			
	B	*P*-value	Exp(*B*)	95% CI Exp(*B*)
30-day mortality	1.01	0.02	2.75	1.17–6.47
90-day mortality	1.02	0.005	2.76	1.36–5.60
2-yr mortality	0.45	0.014	1.56	1.10–2.23

95% CI, 1.17–6.47; P=0.02). Figures 1 and 2 display Kaplan–Meier plots for 30 day and 2 yr mortality, showing short- and long-term survival for patients with normal and abnormal oxygen pulse responses.

Ventilatory inefficiency

The characteristics of patients with and without ventilatory efficiency (V_E/V_{CO_2} ≤34 and >34) were significantly different in most variables analysed, including demographics, co-morbidities, and CPET results (Supplementary Table S3).

A total of 21 patients were excluded from bivariable analysis because of missing V_E/V_{CO_2} data. The primary outcome occurred in 17 patients with V_E/V_{CO_2} >34 (3.7%) (OR=3.43; 95% CI, 1.47–8.01). Table 3 shows ventilatory inefficiency was also associated with 90-day and 2-yr mortality, and prolonged LOS using bivariable analysis (n=1193). There was no evidence that V_E/V_{CO_2} was associated with unplanned critical care admission (Table 3).

Ventilatory inefficiency and oxygen pulse response combined

Comparing patients with a normal and abnormal oxygen pulse response who had a V_E/V_{CO_2} ≤34, showed no association with the primary or secondary outcomes (Supplementary Table S4). For patients with ventilatory inefficiency (V_E/V_{CO_2} >34), the addition of having an abnormal pulse response increased the risk of the primary outcome, 90 day and 2 yr mortality using bivariable analysis. The rate of the primary outcome for this group was 7.8%, compared with a rate of 1.9% of patients with a V_E/V_{CO_2} >34 and a normal oxygen pulse response (OR=4.47; 95% CI, 1.62–12.34) (Table 4). There was no evidence that an abnormal oxygen pulse response was associated with increased length of hospital stay or unplanned critical care admission in patients with an increased V_E/V_{CO_2}.

Discussion

We have demonstrated that an abnormal oxygen pulse response is independently associated with mortality after colorectal surgery, both in the short- and long-term. The risk is especially increased for those patients exhibiting ventilatory inefficiency and an abnormal oxygen pulse. The results do not infer causation, and confounders are difficult to identify and control; however, to our knowledge, this is the largest cohort of patients in which the association between abnormal oxygen pulse response and mortality was studied.

There are few studies exploring the use of oxygen pulse response in predicting postoperative outcomes. A small retrospective study assessed postoperative complications and found oxygen pulse to be a significant predictor; however, it is not clear how oxygen pulse abnormality was defined.[14] A retrospective study modelled preoperative variables to predict 5-yr survival, and oxygen pulse at AT was a significant predictor of mortality. However, this study's population was heterogeneous for surgical type, which included a wide variety of mortality rates, and did not include co-morbidities as predictive variables meaning their effects as confounders are unknown.[15]

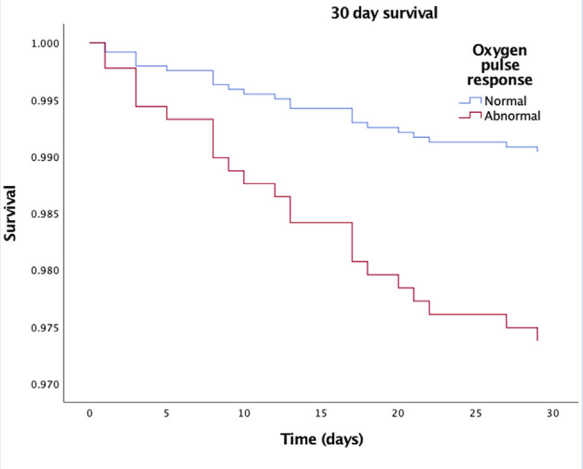

Fig 1. Kaplan–Meier plot for 30 day mortality comparing normal and abnormal oxygen pulse response.

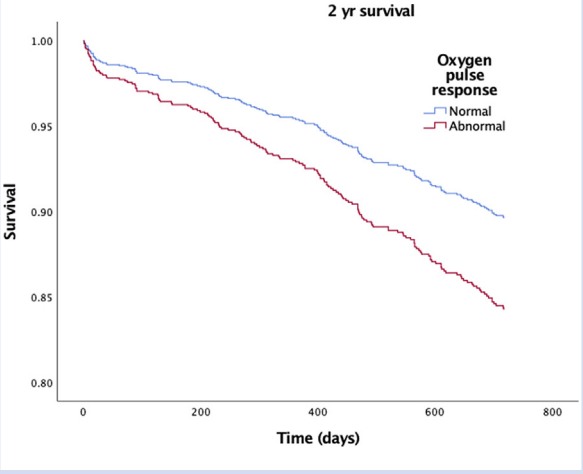

Fig 2. Kaplan–Meier plot for 2-yr mortality comparing normal and abnormal oxygen pulse response.

In non-surgical populations, peak oxygen pulse and oxygen pulse response have been associated with increased mortality in healthy individuals and those with heart failure.[16,17] In a study investigating patients presenting with exertional dyspnoea, 26.5% of patients had an abnormal oxygen pulse response, correlating with myocardial dysfunction as demonstrated by echocardiography.[18] There is conflicting evidence for ischaemic heart disease; oxygen pulse response has been shown to be superior at identifying EIMD than standard testing such as exercise ECG,[12] but in a recent study did not correlate with coronary artery disease with >50% stenosis.[19] Other studies have shown severity of ischaemic heart disease and left ventricular function to correlate with abnormal oxygen pulse response.[20,21] Guidelines also state the use of oxygen pulse in the reporting standards of CPET, but it has been excluded from preoperative risk assessment recommendations.[7] The uncertainty around oxygen pulse with ischaemic heart disease may stem from the varying severity of disease and the emergence of non-obstructive coronary microvascular endothelial dysfunction as a recognised risk factor for cardiovascular events.[22,23]

Exercise-induced myocardial dysfunction

Using oxygen pulse response adds incremental value for predicting short- and long-term survival. In multivariable Cox regression, an abnormal oxygen pulse response was associated with nearly three times the risk of 30-day and 90-day mortality. The subgroup analyses offer possible insight to where EIMD may be most significant; if a patient has normal functional capacity ($V_E/V_{CO_2} \leq 34$), then the presence of EIMD had no effect on 30-day mortality. It appears that patients with normal functional capacity are capable of meeting the physiological demands of colorectal surgery regardless of any possible underlying cardiorespiratory disease. However, if patients have reduced functional capacity ($V_E/V_{CO_2} > 34$), then the presence of EIMD significantly increases mortality with approximately four and a half times the odds of 30-day mortality. Although plausible, and strengthened by the association seen in the multivariable analysis, it is important to note that these patient cohorts differed significantly in baseline demographics and patient characteristics and caution is advised when interpreting these unadjusted subgroup analyses.

The current American Heart Association (AHA) guidelines for perioperative cardiovascular management of noncardiac surgery[24] use the RCRI to direct patients to low risk (<1%) or elevated risk pathways. The elevated risk group have a functional capacity assessment and if this is reduced, they proceed to further investigation. In this study, 943 out of 1214 patients (77.7%) would be deemed low risk using the AHA guidelines and would proceed to surgery. However, using $V_E/V_{CO_2} > 34$ as a surrogate for reduced functional capacity, 342 out of 943 (36.3%) patients, defined as higher risk by CPET, would have undergone surgery without further investigation. Furthermore, out of these 342 patients, 102 (29.8%) had an abnormal oxygen pulse response which this study has shown to be significantly associated with mortality (Supplementary Fig. S2).

CPET may be revealing previously undiagnosed functional limitation from subclinical pathology, which is being missed by medical history, scoring systems, or static testing. It appears that in order to identify a greater proportion of those at high risk, all patients undergoing major surgery require such an assessment. These findings are in keeping with current literature, which has shown a raised V_E/V_{CO_2} to be prognostic in surgical patients[3,25–27] and also echoes what was originally shown by Older and colleagues,[4] where a significant proportion of patients without known ischaemia had a reduced AT and increased mortality. Furthermore, the same study showed that patients with known ischaemic heart disease and a decreased AT had a significantly increased risk of mortality,[4] which highlights the need for CPET in high-risk patients.

Limitations

This is a retrospective analysis, with the limitations of this type of research. A subjective assessment of oxygen pulse was used despite the inherent nature of inter-observer variation

Table 3 Bivariable analysis comparing $V_E/V_{CO_2} \leq 34$ and >34 for primary and secondary outcomes. OR, odds ratio; CI, confidence interval; PHLOS, prolonged hospital length of stay.

	$V_E/V_{CO_2} \leq 34$ (n=729)	$V_E/V_{CO_2} > 34$ (n=464)	OR	95% CI	P-value
30-day mortality					
No	721 (98.9)	447 (96.3)	3.43	1.47–8.01	0.003
Yes	8 (1.1)	17 (3.7)			
90-day mortality					
No	715 (98.1)	444 (95.7)	2.30	1.15–4.60	0.016
Yes	14 (1.9)	20 (4.3)			
2-yr mortality					
No	657 (90.1)	368 (79.3)	2.38	1.71–3.32	<0.001
Yes	72 (9.9)	96 (20.7)			
PHLOS					
No	576 (79.0)	322 (69.4)	1.66	1.27–2.17	<0.001
Yes	153 (21.0)	142 (30.6)			
Unplanned critical care					
No	680 (93.3)	427 (92.0)	1.20	0.77–1.87	0.415
Yes	49 (6.7)	37 (8.0)			

Table 4 Bivariable analysis of patients with a reduced functional capacity ($V_E/V_{CO_2} > 34$), comparing normal and abnormal oxygen pulse responses. Odds ratio (OR), confidence intervals (CI), and prolonged hospital length of stay (PHLOS).

	Oxygen pulse response		OR	95% CI	P-value
	Normal (n=323)	Abnormal (n=141)			
30-day mortality					
No	317 (98.1)	130 (92.2)	4.47	1.62–12.34	0.002
Yes	6 (1.9)	11 (7.8)			
90-day mortality					
No	315 (97.5)	129 (91.5)	3.66	1.46–9.17	0.003
Yes	8 (2.5)	12 (8.5)			
2-yr mortality					
No	265 (82.0)	103 (73.0)	1.69	1.06–2.69	0.028
Yes	58 (18.0)	38 (27.0)			
PHLOS					
No	224 (69.3)	98 (69.5)	0.99	0.64–1.53	0.974
Yes	99 (30.7)	43 (30.5)			
Unplanned critical care					
No	301 (93.2)	126 (89.4)	1.63	0.82–3.24	0.162
Yes	22 (6.8)	15 (10.6)			

and stems from no documented consensus on its interpretation. The low incidence of the primary outcome and finding EIMD in patients without known cardiac disease is reflected in the wide 95% CIs and inability to show difference between some groups. During the collection of the data and patient management, clinicians were not blinded to the CPET results, incorporating an unknown bias to the study. This perhaps reduced the magnitude of association seen in this study, as these patients were identified as higher risk and treated as such, although this was usually defined by the presence of impaired functional capacity, rather than EIMD. The results are derived from a large and unfiltered group of patients in one surgical specialty, treated without the constraints of a study protocol, but conversely this may make the data more representative of real day-to-day practice.

Owing to the use of sub-maximal testing, V_{O_2} peak was not available for analysis because of a large proportion of missing data and hinders the study's comparability. There were also a large number of patients excluded from the analysis because of a missing oxygen pulse response, which are described in the Supplementary material. Importantly, there was no difference in mortality between the included and missing patients, and there was no obvious pattern to the statistically different variables, which would infer a reason for the missing oxygen pulse response.

The study lacks comparison of oxygen pulse response with other investigations of heart disease. Comparing ECG changes during CPET with oxygen pulse response was unreliable—firstly, because gas exchange evidence of EIMD occurs several minutes before ST segment changes are seen,[12] and secondly, with a submaximal testing protocol, in many cases it is likely the test would be completed before the onset of ST changes.[12]

The primary outcome of 30-day mortality diverts from recent practice to use 90-day mortality as an improved measure of survival and was a result of an earlier study protocol design. However, the secondary outcomes included 90-day mortality, which also demonstrated the same associations with a similar magnitude.

Conclusions

The results from this study provide evidence that EIMD defined by an abnormal oxygen pulse response, is independently associated with mortality after colorectal cancer surgery. Patients with a reduced functional capacity as defined by a V_E/V_{CO_2} >34, appear to be of particular risk of mortality in the presence of EIMD. It appears advantageous to objectively assess functional capacity at the first instance of a risk stratification algorithm, preferably with CPET and including the measurement oxygen pulse response. Further research is warranted to define more precisely a normal and an abnormal oxygen pulse response, and to further examine the relationship with morbidity and mortality after major surgery.

Declaration of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

Study design: JM, SD, AH, PD.
Data collection: JM, SD, AH, PD.
Data analysis and interpretation: JM, SD, AH, PD.
Writing the first draft of the manuscript: JW, DY, MW.
Manuscript revision: JW, DY, MW, AH, PD.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.12.043.

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