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Original Article

An evaluation of the validity of the pre-operative oxygen uptake efficiency slope as an indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery

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Summary

This study aimed to investigate the validity of the oxygen uptake efficiency slope as an objective and submaximal indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery. Patients ≥ 60 years of age, with a metabolic equivalent score using the Veterans Activity Questionnaire ≤ 7 and scheduled for major colorectal surgery participated in a pre-operative cardiopulmonary exercise test. The oxygen uptake efficiency slope was calculated up to different exercise intensities, using 100%, 90% and 80% of the exercise data. Data from 71 patients (47 men, mean (SD) age 75.2 (6.7) years) were analysed. The efficiency slope obtained from all the data was statistically significantly different from the values when 90% ($p = 0.027$) and 80% ($p = 0.023$) of the data were used. The 90% and 80% values did not differ significantly from each other ($p = 0.152$). Correlations between the oxygen uptake efficiency slope and the peak oxygen uptake ranged from 0.816 to 0.825 (all $p < 0.001$), and correlations between oxygen uptake efficiency slope and the ventilatory anaerobic threshold ranged from 0.793 to 0.805 (all $p < 0.001$). Receiver operating characteristic curves showed that the oxygen uptake efficiency slope is a sensitive and specific predictor of a peak oxygen uptake ≤ 18.2 $ml.kg^{-1}.min^{-1}$, with an area under the curve (95%CI) of 0.876 (0.780–0.972, $p < 0.001$) and a ventilatory anaerobic threshold ≤ 11.1 $ml.kg^{-1}.min^{-1}$, with an area under the curve (95%CI) of 0.828 (0.726–0.929, $p < 0.001$). These correlations suggest that the oxygen uptake efficiency slope provides a valid (sub)maximal measure of cardiorespiratory fitness in these patients, and the predictive ability described indicates that it might help discriminate patients at higher risk of postoperative morbidity. However, future research should investigate the prognostic value of the oxygen uptake efficiency slope for postoperative outcomes.

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Introduction

Cardiorespiratory fitness, as indicated by the highest measured oxygen uptake (peak oxygen uptake) and/or the oxygen uptake at the ventilatory anaerobic threshold, is widely recognised as an important measure in the evaluation of the risk of peri-operative complications in major abdominal surgery. Similar to immunological and neuroendocrine reserve, cardiorespiratory fitness indicates the physiological reserve capacity of the patient to maintain homeostasis with adequate responses to allostatic load (allostasis). These are required to cope with the psychophysiological consequences of diagnosis, the pre-admission period and the stress of surgery. Those patients with higher cardiorespiratory fitness might be more resilient to the increased metabolic demands from these perioperative challenges. Pre-operative cardiorespiratory fitness has been found to have a consistent relation with postoperative outcome indicators in major elective abdominal surgery (e.g. morbidity, mortality, length of stay) [1–12].

An incremental cardiopulmonary exercise test up to maximal exertion is considered the best test for assessing cardiorespiratory fitness. A recent systematic review [13] demonstrated that peak oxygen uptake, and the oxygen uptake at the ventilatory anaerobic threshold, are the most commonly used pre-operative cardiopulmonary exercise test measures recorded before major elective abdominal surgery. There are, however, several clinical limitations when determining cardiorespiratory fitness using peak oxygen uptake and/or the ventilatory anaerobic threshold; moreover, assessing only these two measures leads to substantial loss of physiological data. It would, therefore, be worthwhile evaluating how useful alternative objective (sub)maximal exercise parameters might be in assessing and predicting prognosis in patients undergoing major surgery. One such parameter, the oxygen uptake efficiency slope (OUES), has been reported to have prognostic value in predicting major cardiac events and mortality in patients with heart failure and coronary artery disease [14–17]. The oxygen uptake efficiency slope concept is based on the curvilinear relationship between the minute ventilation and oxygen uptake throughout an incremental cardiopulmonary exercise test. Baba et al. [18] introduced and validated a logarithmic transformation of the minute ventilation over the entire exercise period, resulting in a linear relationship between the minute ventilation and oxygen uptake during the entire, and especially the last part, of the cardiopulmonary exercise test. The regression coefficient of the regression line describing this linear relationship is the oxygen uptake efficiency slope. The theoretical linearity of the oxygen uptake efficiency slope implies that it does not require a maximal effort and can thus be derived rather accurately from submaximal exercise data as well. The oxygen uptake efficiency slope has been reported to correlate strongly with well-established measures of cardiorespiratory fitness such as peak oxygen uptake and the ventilatory anaerobic threshold in different groups of adults and children [18–30]. The oxygen uptake efficiency slope has also been found to have excellent test–retest reliability in general surgical patients, with a reliability coefficient (95%CI) of 0.89 (0.81–0.97) [31]. However, the validity of it as an effort-independent alternative measure of pre-operative cardiorespiratory fitness, and its ability to predict postoperative outcomes, are unknown. To the best of our knowledge, only one study investigated the predictive value of the oxygen uptake efficiency slope for a 5-year survival period after a major surgery, and concluded that it did not appear to be a strong predictor of mortality [32]. Therefore, we aimed to investigate the validity of the oxygen uptake efficiency slope as an effort-independent indicator of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery, by correlating it with peak oxygen uptake and the ventilatory anaerobic threshold, and assessing its stability throughout the last part of the cardiopulmonary exercise test.

Methods

All patients ≥ 60 years of age requiring colorectal resection for colorectal cancer of dysplasia grade 1–3 at the Medisch Spectrum Twente (a non-academic teaching hospital in the Netherlands) were identified at the multi-disciplinary oncology meeting. They were seen in the outpatient clinic by the surgeon or surgical resident and asked to fill in the veterans-specific activity questionnaire (VSAQ) [33]. Patients with a metabolic equivalent score using this questionnaire of ≤ 7 (low subjective metabolic equivalent score [4]) were invited to participate in the study. Patients not able to perform a cardiopulmonary exercise test, or patients who were undergoing emergency colorectal surgery, were not studied. The study was approved by the Medical Research Ethics Committee of the Medisch Spectrum Twente, Enschede, the Netherlands, and written informed consent was obtained from each participant.

After providing consent, the patient underwent a cardiopulmonary exercise test between February 2013 and July 2016. These formed the study data and were retrospectively analysed after this period.

All participants performed an incremental cardiopulmonary exercise test up to maximal exertion in an upright position on an electronically braked cycle ergometer (Ergoline, Ergoselect 100, Bitz, Germany). The seat height was adjusted to the participant's leg length. After assessment of baseline cardiopulmonary values during a 2-min rest period while seated at the cycle ergometer, patients performed a 3-min warm-up phase that consisted of unloaded cycling. After the warm-up, the work rate was increased by constant increments of 5, 10 or 15 W.min^{-1}, depending on the patient's subjective physical fitness level, aiming to reach maximal effort within 8–12 min. Throughout the test, patients had to maintain a pedalling frequency of between 60 and 80 revolutions.min^{-1}. The protocol continued until the patient's pedalling frequency fell definitely below 60 revolutions.min^{-1}, despite strong verbal encouragement, or when the patient met the criteria for exercise termination before being limited by symptoms [34].

During the cardiopulmonary exercise test, patients breathed through a facemask (Hans Rudolph, Kansas City, MO, USA) connected to an ergospirometry system (Oxycon Pro, Jaeger, Hoechberg, Germany) that was calibrated for respiratory gas analysis measurements (ambient air and a gas mixture of 16% oxygen and 5% carbon dioxide) and volume measurements (3 litre syringe). Expired gas was passed through a flow meter (Triple V volume sensor, Jaeger, Hoechberg, Germany), an oxygen analyser and a carbon dioxide analyser. The flow meter and gas analysers were connected to a computer, which calculated breath-by-breath minute ventilation, oxygen uptake, carbon dioxide production and the respiratory exchange ratio averaged at 10-s intervals. Heart rate was measured by continuous 12-lead electrocardiography. A test was considered to be at or near the maximal level when participants: showed clinical signs of intense effort (e.g. unsteady cycling, sweating and clear unwillingness to continue exercising despite strong encouragement); were unable to maintain the required pedalling speed; and when at least one of the following criteria was met – a heart rate at peak exercise of > 95% of predicted (predicted peak heart rate [beats.min^{-1}] = 208−(0.7 × age [years]) or a respiratory exchange ratio at peak exercise of > 1.10.

Cardiopulmonary parameters were averaged into 10-s intervals; after outliers (> 3 SD from the local mean) were removed [35]. Data interpretation was performed independently from the clinicians involved, and without knowledge about the clinical status of the included patients, by a trained and experienced clinical exercise physiologist (BB). Absolute values at peak exercise were calculated as the average value over the last 30 s before termination of the test. Peak heart rate was defined as the highest heart rate achieved during the test. The ventilatory anaerobic threshold was defined as the point at which the ventilatory equivalent for oxygen and the partial end-tidal oxygen tension reached a minimum and thereafter began to rise in a consistent manner, coinciding with an unchanged ventilatory equivalent for carbon dioxide and partial end-tidal carbon dioxide tension [34]. When this ventilatory equivalents method appeared to provide uncertain results for a patient's ventilatory anaerobic threshold, the point at which the linear slope of the relation between the carbon dioxide production and oxygen uptake changed was taken as the ventilatory anaerobic threshold, according to the V-slope method [36]. The ventilatory anaerobic threshold was expressed as an absolute and relative value (normalised for body mass). The graphical presentation of the minute ventilation as a function of carbon dioxide production during the incremental cardiopulmonary exercise test was used to determine the point at which the minute ventilation increased out of proportion to carbon dioxide production, that is, the respiratory compensation point. The slope of the relationship between the minute ventilation and carbon dioxide production was calculated by linear least squares regression of the relation between the minute ventilation and carbon dioxide production up to the respiratory compensation point. The oxygen uptake efficiency slope was calculated using the following equation: oxygen uptake = a × log (minute ventilation) + b, in which the constant 'a' represents the rate of increase in oxygen uptake in response to an increase in minute ventilation, called the oxygen uptake efficiency slope (regression coefficient) and 'b' corresponds to the intercept [18]. As depicted in Fig. 1, a steeper slope, reflected by a higher oxygen uptake efficiency slope, represents a more efficient oxygen uptake: a smaller ventilation quantity is required for a given oxygen uptake. Data from the first minute of exercise were excluded because of the often very irregular breathing pattern at the onset of exercise [37]. In order to evaluate the robustness of the oxygen uptake efficiency slope during the last part of the cardiopulmonary exercise test, it was calculated up to three different exercise intensities. Based on the findings in a previous study [38], it was calculated up to the point of the levelling-off of oxygen uptake in case of a clear oxygen uptake plateau (a decrease in oxygen uptake during the last 30 s with an increase in work rate). For the determination of the OUES100, all data gained during the cardiopulmonary exercise test were used (data as of the first minute after the start of the work rate increments, up to peak exercise or up to the oxygen uptake plateau), whereas for the determination of the OUES90 and the OUES80, only data up to 90% and 80% of the total exercise duration were used, respectively. Oxygen uptake efficiency slope values were also normalised for body mass (OUES.kg^{-1}). Sex-, age- and body surface area-related predictive equations [20] were used to express each patient's oxygen uptake efficiency slope value as a percentage of predicted.

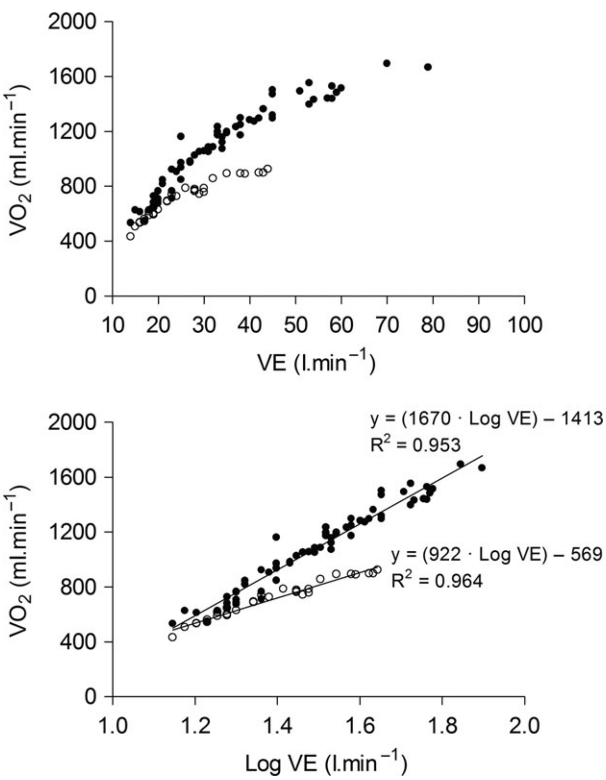

Figure 1 Relation between oxygen uptake and minute ventilation during a cardiopulmonary exercise test in a 71-year-old woman with a ventilatory anaerobic threshold (VAT) of 12.3 ml.kg^{-1}.min^{-1} (●) and in an 82-year-old woman with a VAT of 9.1 ml.kg^{-1}.min^{-1} (○). The values of the oxygen uptake efficiency slope (calculated using all exercise data) are 1698.8 and 931.3, respectively, and the data are presented as linear (top graph) and semi-log plots of the x-axis (bottom graph). Log VE, common logarithm of the minute ventilation; VO_2, oxygen uptake.

All data were analysed using SPSS for Windows (version 22; IBM, SPSS Inc., Chicago, IL, USA). Tests for normality were performed with the Shapiro–Wilk test. Variability in peak oxygen uptake, the ventilatory anaerobic threshold, and oxygen uptake efficiency slope were evaluated by calculating the coefficient of variation, defined as 100 × (SD/mean). To assess the construct validity of the oxygen uptake efficiency slope, repeated-measures analysis of variance (ANOVA) was used to evaluate differences in values calculated at the three different exercise intensities to indicate the effect of exercise duration on the oxygen uptake efficiency slope, thereby showing its linear characteristics. Additional post-hoc analyses, with Bonferroni adjustment for multiple testing, were performed on the outcomes of the repeated-measures ANOVA tests to locate the exact significant differences. Receiver operating characteristic curves were used to establish threshold values of oxygen uptake efficiency slope to predict a peak oxygen uptake ≤ 18.2 ml.kg^{-1}.min^{-1} or a ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1}. These peak oxygen uptake and ventilatory anaerobic threshold values are based on the cut-off points described by West et al. [12]. In addition, Pearson or Spearman correlation coefficients, as appropriate, were calculated to examine associations between the oxygen uptake efficiency slope and peak oxygen uptake and the ventilatory anaerobic threshold. To evaluate the group validity of the oxygen uptake efficiency slope, the total group was divided into a sub-group with a ventilatory anaerobic threshold > 11.1 ml.kg^{-1}.min^{-1} and a sub-group with a ventilatory anaerobic threshold

Table 1 Baseline characteristics. Values are mean (SD) or number (proportion).

Variable	
Age; years	75.1 (6.7)
Sex; male	47 (66.2%)
Height; cm	171.6 (9.4)
Weight; kg	84.3 (14.1)
BMI; $kg.m^{-2}$	28.6 (4.0)
Body surface area; m^2	2.0 (0.2)
Charlson comorbidity index	
0	18 (25.4%)
1	29 (40.8%)
2+	24 (33.8%)
Comorbidity	
Cardiac disease	37 (52.1%)
Diabetes	15 (21.1%)
Chronic obstructive pulmonary disease	12 (16.9%)
Orthopaedic disease	19 (26.8%)
None of the above	16 (22.5%)
Beta blockers	
Yes	30 (42.3%)
American Joint Committee on Cancer stage[a,b]	
1	19 (31.7%)
2	9 (15.0%)
3	27 (45.0%)
4	5 (8.3%)
ASA physical status	
1	2 (2.8%)
2	55 (77.5%)
3	13 (18.3%)
4	1 (1.4%)
Surgical procedure	
Right hemicolectomy	23 (32.4%)
Transverse hemicolectomy	3 (4.2%)
Left hemicolectomy	3 (4.2%)
Sigmoid colectomy	19 (26.8%)
Abdominoperineal resection	3 (4.2%)
Low anterior resection	5 (7.0%)
Hartmann's	1 (1.4%)
Extended right hemicolectomy	2 (2.8%)
Extended left hemicolectomy	1 (1.4%)
Other	6 (8.5%)
No surgery	5 (7.0%)
Method of surgery	
Open	13 (18.3%)
Laparoscopic	46 (64.8%)
Conversion to open	7 (9.9%)
No surgery	5 (7.0%)

[a]Dysplasia grade 1, 2 or 3 requiring colorectal resection (n = 9), colorectal liver metastasis (n = 1) and colorectal lung metastasis (n = 1), so in this case n = 60.
[b]American Joint Committee on Cancer colon and rectum cancer staging (7th edition).

$\leq$ 11.1 $ml.kg^{-1}.min^{-1}$. Differences in oxygen uptake efficiency slope values and other exercise parameters between these sub-groups were assessed using independent-samples t-tests or Mann–Whitney U-tests, as appropriate. Significance was set at the 0.05 level.

Results

Between February 2013 and July 2016, a sample of 72 eligible patients took part in this study and undertook a cardiopulmonary exercise test a mean (SD) of 26.8 (29.8) days before colorectal resection (Table 1). Cardiopulmonary exercise test data of a 73-year-old female patient were excluded because she stopped the test before she reached the ventilatory anaerobic threshold.

All 71 patients performed the cardiopulmonary exercise test without any complications or adverse events during or after the test. They all showed subjective signs of a maximal effort. Most patients (n = 54, 76.1%) also showed objective signs of maximal effort, as indicated by a peak heart rate > 95% of predicted and/or a peak respiratory exchange ratio > 1.10. A total of 19 patients (26.8%) showed a clear oxygen uptake plateau during the last part of the cardiopulmonary exercise test. The oxygen uptake efficiency slope could be determined in all 71 patients, whereas the ventilatory anaerobic threshold was undeterminable in two (2.8%) patients. Coefficients of variation were 27.2% for peak oxygen uptake, 19.0% for the ventilatory anaerobic threshold and 28.2% for the OUES100. Normalised for body mass, coefficients of variation were 24.2% for peak oxygen uptake, 18.5% for the ventilatory anaerobic threshold and 26.3% for the OUES100. All cardiopulmonary exercise test results are shown in Table 2.

The mean (SD) predicted oxygen uptake efficiency slope was 2001 (433); hence, the current patient group scored 79% (20%) of predicted, with values ranging from 28 to 123% of predicted. A statistically significant difference was found between the OUES100 and the OUES90 (p = 0.027), as well as between the OUES100 and the OUES80 (p = 0.023), with lower OUES100 values. OUES90 and OUES80 showed no statistically significant difference from each other (p = 0.152).

Compared with patients with a ventilatory anaerobic threshold > 11.1 $ml.kg^{-1}.min^{-1}$, patients with a ventilatory anaerobic threshold $\leq$ 11.1 $ml.kg^{-1}.min^{-1}$ had lower oxygen uptake efficiency slope values (Table 2), which corresponds to the lower values for

Table 2 Cardiopulmonary exercise test results. Values are mean (SD).

	Whole group n = 71	Ventilatory anaerobic threshold > 11.1 ml.kg^{-1}.min^{-1} n = 20	Ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1} n = 49	p value
Peak heart rate; beats.min^{-1a}	128 (22)	139 (20)	124 (21)	0.015
Peak respiratory exchange ratio	1.16 (0.11)	1.18 (0.12)	1.15 (0.11)	0.354
Peak work rate; W	99.1 (33.9)	119.3 (33.2)	93.0 (30.3)	0.002*
Peak work rate; W.kg^{-1}	1.2 (0.4)	1.5 (0.4)	1.1 (0.3)	< 0.001*
Peak oxygen uptake; ml.min^{-1}	1292 (351)	1518 (313)	1220 (319)	0.001*
Peak oxygen uptake; ml.kg^{-1}.min^{-1}	15.4 (3.7)	18.9 (2.8)	14.2 (3.0)	< 0.001*
Ventilatory anaerobic threshold; ml.min^{-1b}	876 (166)	1010 (127)	821 (149)	< 0.001*
Ventilatory anaerobic threshold; ml.kg^{-1}.min^{-1b}	10.5 (1.9)	12.7 (1.6)	9.6 (1.2)	< 0.001*
Peak oxygen pulse; ml.beat^{-1a}	10.2 (2.6)	11.3 (2.9)	9.8 (2.3)	0.052
Peak oxygen pulse; ml.kg^{-1}.beat^{-1} × 100^{a,c}	12.3 (2.5)	14.1 (2.4)	11.7 (2.1)	< 0.001*
VE/VCO$_2$-slope	33.5 (6.7)	32.2 (4.9)	33.8 (7.3)	0.408
Peak minute ventilation; l.min^{-1}	56.9 (17.4)	67.8 (18.0)	53.2 (15.1)	0.007
Peak minute ventilation; l.kg^{-1}.min^{-1}	0.7 (0.2)	0.8 (0.2)	0.6 (0.2)	< 0.001*
OUES100	1557 (439)	1821 (396)	1463 (417)	0.002*
OUES90	1573 (442)	1859 (405)	1471 (411)	0.001*
OUES80	1583 (418)	1862 (374)	1484 (390)	< 0.001*
OUES100; % of predicted	79 (20)	93 (17)	74 (18)	< 0.001*
OUES100.kg^{-1}	18.4 (4.9)	22.5 (4.0)	16.9 (4.3)	< 0.001*
OUES90.kg^{-1}	18.7 (5.0)	23.1 (4.2)	17.1 (4.3)	< 0.001*
OUES80.kg^{-1}	18.9 (4.8)	23.1 (3.9)	17.3 (4.1)	< 0.001*

[a]Heart rate was invalid in two patients (3%) with a ventilatory anaerobic threshold > 11.1 ml.kg^{-1}.min^{-1} and in six patients (8%) with a ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1}, so in this case n = 18 and n = 43, respectively.
[b]The ventilatory anaerobic threshold was not determinable in two patients (3%), so in this case n = 69.
[c]Relative oxygen pulse values are multiplied by 100 to increase readability.
*Statistically significant after Bonferroni correction to counteract the problem of multiple comparisons.
OUES100, OUES90 and OUES80, oxygen uptake efficiency slope calculated using all exercise data, 90% of the data and 80% of the data, respectively; OUES100.kg^{-1}, OUES90.kg^{-1} and OUES80.kg^{-1}, oxygen uptake efficiency slope normalised for body mass calculated using all exercise data, 90% of the data and 80% of the data, respectively; VE/VCO$_2$-slope, minute ventilation to carbon dioxide production relationship.

peak oxygen uptake and the ventilatory anaerobic threshold in this sub-group.

Correlation coefficients between the oxygen uptake efficiency slope, determined at different relative exercise intensities, and peak oxygen uptake and the ventilatory anaerobic threshold are summarised in Table S1 in the online Supporting information. Figure 2 shows the relation between the oxygen uptake efficiency slope and peak oxygen uptake, between the oxygen uptake efficiency slope and the ventilatory anaerobic threshold, and between the ventilatory anaerobic threshold and peak oxygen uptake. When normalised for body mass, a correlation coefficient of 0.792 ($p < 0.001$) was observed between peak oxygen uptake and the ventilatory anaerobic threshold.

The receiver operating characteristic analysis depicted in Fig. 3 shows the value of the oxygen uptake efficiency slope in predicting a peak oxygen uptake ≤ 18.2 ml.kg^{-1}.min^{-1}. The OUES100.kg^{-1} had an area under the curve (95%CI) of 0.876 (0.780–0.972, $p < 0.001$), the OUES90.kg^{-1} 0.880 (0.779–0.981, $p < 0.001$) and the OUES80.kg^{-1} 0.890 (0.797–0.983, $p < 0.001$). Figure 3 also shows the value of the oxygen uptake efficiency slope to predict a ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1}. The OUES100.kg^{-1} had an area under the curve (95%CI) of 0.828 (0.726–0.929, $p < 0.001$), the OUES90.kg^{-1} 0.840 (0.743–0.938, $p < 0.001$) and the OUES80.kg^{-1} 0.859 (0.769–0.948, $p < 0.001$). Optimal cut-off values for oxygen uptake efficiency slope including sensitivity and specificity can be found in Table 3.

Discussion

This study aimed to investigate the validity of the oxygen uptake efficiency slope as an alternative measure of cardiorespiratory fitness in elderly patients

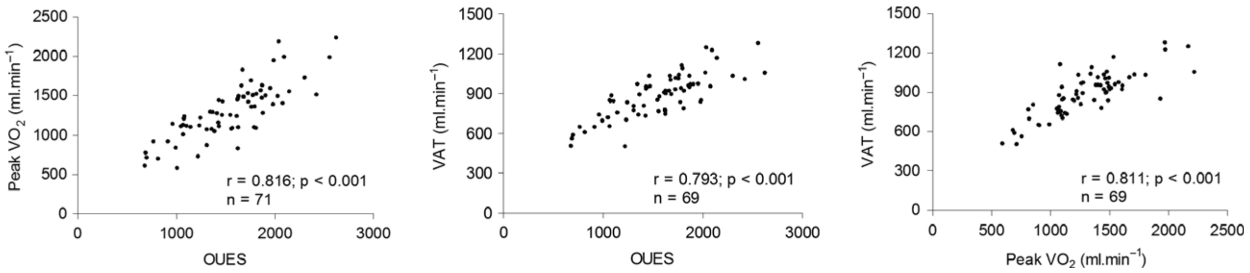

Figure 2 Relation between the oxygen uptake efficiency slope (OUES) and peak oxygen uptake (peak VO_2) (left graph), between the OUES and the ventilatory anaerobic threshold (VAT; middle graph) and between the peak oxygen uptake and the VAT (right graph). Black dots represent patients.

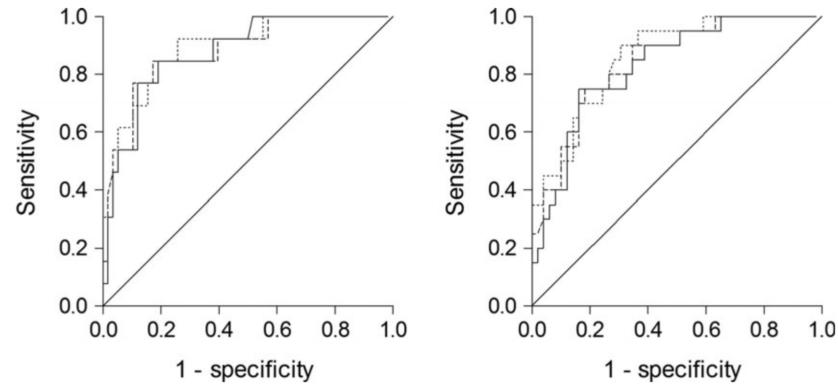

Figure 3 Receiver operator curves for predicting a peak oxygen uptake $\leq$ 18.2 $ml.kg^{-1}.min^{-1}$ (left graph) and a ventilatory anaerobic threshold $\leq$ 11.1 $ml.kg^{-1}.min^{-1}$ (right graph) from the oxygen uptake efficiency slope normalised for body mass calculated using all exercise data (—), 90% of the data (---) and 80% of the data (···).

undergoing major elective colorectal surgery. The main results show that the oxygen uptake efficiency slope provides an objective and valid measure of cardiorespiratory fitness in these patients, as indicated by the strong correlations with peak oxygen uptake and the ventilatory anaerobic threshold. Furthermore, its ability to predict cut-off points for peak oxygen uptake and the ventilatory anaerobic threshold might help discriminate patients at higher risk of postoperative morbidity at the stage of diagnosis and contemplation of elective surgery.

Theoretically, the oxygen uptake efficiency slope should be relatively insensitive to the duration of the cardiopulmonary exercise test, which is an essential characteristic when a patient is either unwilling or unable to deliver a maximal effort. Most studies found no significant differences between maximal and submaximal oxygen uptake efficiency slope values [19, 21, 22, 24, 25, 28], whereas other studies reported small differences [14, 18, 20, 26]. The current study found that within patients, OUES100 values were slightly but statistically significant lower than OUES90 and OUES80 values, whereas OUES90 and OUES80 values did not differ within the study group. These small differences might be explained by the fact that the oxygen uptake efficiency slope profile throughout the cardiopulmonary exercise test demonstrates an 'S'-shaped or sigmoid curve, with (1) an initial slow rising phase; (2) a subsequent accelerated rising phase followed by a decelerating rising phase; and (3) a final slow rising phase at maximal exercise [38]. As a consequence, Niemijer et al. [38] recommended that oxygen uptake efficiency slope values should be interpreted with caution when patients do not reach the ventilatory anaerobic threshold or when an oxygen uptake plateau is present. We performed a post-hoc analysis in patients with a difference of $>$ 200 between OUES100 and OUES80 values in order to elucidate the statistically

Table 3 Optimal cut-off values for oxygen uptake efficiency slope including sensitivity and specificity.

	Optimal cut-off	Sensitivity	Specificity
Peak oxygen uptake ≤ 18.2 ml.kg^{-1}.min^{-1}			
OUES100.kg^{-1}	20.6	0.846	0.810
OUES90.kg^{-1}	20.9	0.846	0.828
OUES80.kg^{-1}	19.8	0.923	0.741
Ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1} [a]			
OUES100.kg^{-1}	20.5	0.750	0.837
OUES90.kg^{-1}	20.1	0.750	0.816
OUES80.kg^{-1}	19.3	0.900	0.694

[a]The ventilatory anaerobic threshold was not determinable in two patients (3%), so in this case n = 69.
OUES100.kg^{-1}, OUES90.kg^{-1} and OUES80.kg^{-1}, oxygen uptake efficiency slope normalised for body mass calculated using all exercise data, 90% of the data and 80% of the data, respectively.

significant differences between the OUES100 and the OUES90, and between the OUES100 and the OUES80. The two patients (both men, 72.3 and 75.9 years of age) who had a difference of > 200 between OUES100 and OUES80 values, demonstrated a consistent levelling-off of oxygen uptake during the last part of the cardiopulmonary exercise test, without showing a clear oxygen uptake plateau (see Fig. S1 in the online Supporting information for an example). After excluding these two patients, the differences between the OUES100, OUES90 and OUES80 were not longer statistically significant. Additionally, the small differences between the OUES100 and the OUES90, and between the OUES100 and the OUES80 do not seem clinically relevant, as OUES100, OUES90 and OUES80 values all correlated strongly with each other, as well as with peak oxygen uptake and the ventilatory anaerobic threshold. This strong correlation between the oxygen uptake efficiency slope and peak oxygen uptake is in agreement with other studies [e.g. 14, 18–30] and indicates that the oxygen uptake efficiency slope is an objective measure of cardiorespiratory fitness.

We defined patients being ‘fit’ or ‘unfit’ based on the recently-published thresholds of peak oxygen uptake ≤ 18.2 ml.kg^{-1}.min^{-1} and ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1} [12]. Receiver operating characteristic analysis showed that the oxygen uptake efficiency slope normalised for body mass (OUES.kg^{-1}) is a sensitive and specific predictor of peak oxygen uptake ≤ 18.2 ml.kg^{-1}.min^{-1} and a ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1}. Although these thresholds for risk are derived from a different patient population and study, the current study indicates that the oxygen uptake efficiency slope might possess sufficient discriminative power to distinguish between patients with a higher likelihood (ventilatory anaerobic threshold ≤ 11.1 ml.kg^{-1}.min^{-1}) and patients with a lower likelihood (ventilatory anaerobic threshold > 11.1 ml.kg^{-1}.min^{-1}) of in-hospital morbidity after major colorectal surgery (Table 2).

Evaluating physiological markers of cardiorespiratory fitness, obtained at specific time-points during the cardiopulmonary exercise test (e.g. peak oxygen uptake or the ventilatory anaerobic threshold) remains the most common clinical test for pre-operative risk stratification in major elective abdominal surgery. The measurement of peak oxygen uptake, however, can be strongly influenced by the patient’s motivation to deliver a maximal effort, and might be invalid in patients whose performance may be limited due to pain or fatigue rather than cardiorespiratory deficiency. In case of a submaximal effort due to premature cessation of the cardiopulmonary exercise test, the oxygen uptake occurring at the ventilatory anaerobic threshold may represent a submaximal indicator of cardiorespiratory fitness. Although the inter-observer variability in a pre-operatively measured ventilatory anaerobic threshold has been reported to be acceptable for experienced clinicians [39], it cannot always be determined, and its values have been reported to depend on the choice of ergometer, exercise protocol and method of detection [40–43]. Additionally, only focusing on physiological parameters at specific time-points (e.g. peak oxygen uptake, ventilatory anaerobic threshold and the ventilatory equivalent for carbon dioxide at the ventilatory anaerobic threshold) leads to the loss of a significant amount of data generated during a cardiopulmonary exercise test that might better reflect continuous, dynamic cardiopulmonary responses throughout the test. Due to the aforementioned limitations of peak oxygen uptake and the ventilatory anaerobic threshold, it would be of interest to investigate the clinical usefulness of alternative objective (sub)maximal exercise parameters that incorporate cardiopulmonary response profiles for the assessment of cardiorespiratory fitness and prognosis in patients undergoing major surgery. The oxygen uptake efficiency slope gives an estimation of the efficiency of minute ventilation with respect to oxygen uptake throughout the cardiopulmonary exercise test by providing a log-transformed response profile indicative of cardiorespiratory function during exercise. Without significant lung disease, the oxygen uptake efficiency slope is indicative of cardiovascular function throughout exercise, in which higher oxygen uptake efficiency slope values indicate a more efficient oxygen uptake. As such, the oxygen uptake efficiency slope might reflect the resilience of a patient to meet the increased metabolic demands from surgical stress.

This is the first study to investigate the validity of the oxygen uptake efficiency slope in patients undergoing major elective colorectal surgery. Although oxygen uptake efficiency slope values were found to be strongly correlated with peak oxygen uptake and the ventilatory anaerobic threshold, the small intra-individual differences in maximal and submaximal values might limit the clinical utility of this measure; this requires further research. Future research should also address the prognostic value of the oxygen uptake efficiency slope for different postoperative outcomes in major abdominal surgery, as only one study [32] evaluated the predictive value of the oxygen uptake efficiency slope; this focused on mortality. From the latter study, it is unclear whether the authors normalised absolute oxygen uptake efficiency slope values for body mass, which we believe is necessary, just as with peak oxygen uptake and the ventilatory anaerobic threshold. As already pointed out by Niemijer et al. [38], it remains debatable whether oxygen uptake efficiency slope values should be calculated after careful visual inspection of oxygen uptake data, in order to use oxygen uptake and minute ventilation data up to the oxygen uptake plateau, or up to the point where a consistent levelling-off of oxygen uptake is observed, even without showing a clear oxygen uptake plateau.

The current study has several limitations. Firstly, due to the retrospective evaluation of the tests, there is a possibility of bias. Secondly, our data are derived from a single centre and therefore may not apply to patients from other centres. Thirdly, the number of patients (n = 71) is relatively small and we did not perform a prospective sample size calculation. These issues affect statistical analysis and generalisability, as does the fact that the thresholds for risk of the peak oxygen uptake and ventilatory anaerobic threshold were based on the cut-off points described in another study and patient population [12]. Finally, no direct clinical outcomes were presented, which might hinder clinicians from estimating more exactly the seriousness of illness of the population at hand. However, as our aim was to investigate the validity of the oxygen uptake efficiency slope as an effort-independent indicator of cardiorespiratory fitness, we do not consider the latter issue to be crucial.

In conclusion, the strong correlations with peak oxygen uptake and the ventilatory anaerobic threshold indicate that the oxygen uptake efficiency slope provides an objective and valid measure of cardiorespiratory fitness in elderly patients scheduled for major colorectal surgery, and its ability to predict cut-off points for peak oxygen uptake and the ventilatory anaerobic threshold indicates that it might help discriminate patients at higher risk of postoperative morbidity. Future research should investigate the prognostic value of the oxygen uptake efficiency slope for postoperative outcomes in this group.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Oxygen uptake and work rate throughout the cardiopulmonary exercise test in a 72-year-old man.

Table S1 Correlation between oxygen uptake efficiency slope values at different exercise intensities, peak oxygen uptake and the ventilatory anaerobic threshold.

