The association between preoperative cardiopulmonary exercise test variables and short-term morbidity following oesophagectomy: a hospital-based cohort study.

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Abstract

Background: Postoperative complications after oesophagectomy are thought to be associated with reduced fitness. This observational study explored the associations between aerobic fitness, as determined objectively by preoperative cardiopulmonary exercise testing (CPEX), and 30-day morbidity after oesophagectomy. **Methods:** We retrospectively identified 254 consecutive patients who underwent oesophagectomy at a single academic teaching hospital between September 2011 and March 2017. Postoperative complication data were measured using the Esophageal Complications Consensus Group definitions and graded using the Clavien-Dindo classification system of severity (blinded to CPEX values). Associations between preoperative CPEX variables and postoperative outcomes were estimated using logistic regression. **Results:** Two hundred and six patients (77% male) were included in the analyses, with a mean age of 67 years (SD 9). The mean values for VO_{2peak} and AT were 21.1ml/kg/min (SD 4.5) and 12.4ml/kg/min (SD 2.8), respectively. The vast majority of patients (98.5%) had malignant disease; predominantly adenocarcinoma (84.5%), for which most received neoadjuvant chemotherapy (79%) and underwent minimally invasive Ivor Lewis oesophagectomy (53%). Complications at postoperative day 30 occurred in 111 patients (54%), the majority of which were cardiopulmonary (72%). No associations were found between preoperative CPEX variables and morbidity for either VO_{2peak} (OR 1.00, 95% CI 0.94-1.07) or AT (OR 0.98, 95% CI 0.89-1.09).

Conclusions: Preoperative CPEX variables were not associated with 30-day complications following oesophagectomy. The findings do not support the use of CPEX as an isolated preoperative screening tool to predict short-term morbidity after oesophagectomy. This modestly sized observational work highlights the need for larger studies examining associations between preoperative CPEX and outcomes after oesophagectomy to look for consistency in our findings.

Introduction

Oesophageal resection and reconstruction (oesophagectomy) is the only consistent treatment modality that offers a potential cure for oesophageal cancer,[1] but carries a high risk of postoperative complications. UK national audit figures report that 33% of patients suffer a complication after oesophagectomy, most of which (74%) affect the cardiopulmonary system (52% respiratory and 22% cardiac).[2] Increased preoperative physical fitness may reduce the number of postoperative complications. Exercise results in a greater cardiac output, improved respiratory muscle strength and skeletal muscle adaptations (improved transport and metabolism of oxygen to produce adenosine triphosphate (ATP)).[3] These adaptations may attenuate the physiological insults of oesophagectomy which include; disruption of normal lung mechanics through incisional pain and diaphragmatic dysfunction;[4] blood loss and sympathetic activation, resulting in splanchnic vasoconstriction - which jeopardises any newly formed gastroesophageal anastomosis; and a surgical stress response, resulting in catabolism of skeletal muscle protein [5] and increased oxygen demand and consumption.[6] Accurate measurement of preoperative cardiopulmonary fitness may identify patients at higher risk of complications due to low cardiopulmonary reserves. This could allow better perioperative management to improve outcomes, including modification of fitness with an exercise programme.

CPEX is an objective, quantitative and composite measure of a person's overall aerobic fitness. Two specific CPEX variables; VO_{2peak} (the maximal oxygen consumed at the peak of exercise) and VO_2 at estimated anaerobic threshold (AT) have shown promise in observational studies to predict both morbidity and mortality.[7-13] In a study of 187 elderly patients undergoing major abdominal surgery, a preoperative AT cut-off of <11ml/kg/min had a sensitivity of 91% and specificity of 74% for predicting mortality.[7] In a multi-centre study of 346 lung cancer patients undergoing resection via thoracotomy, a VO_{2max} cut-off of <16ml/kg/min predicted patients more likely to suffer a complication (p=0.0001).[14] To the best of our knowledge, there have only been three relatively small observational studies of CPEX testing prior to oesophagectomy (n=78,[12] n=91,[10] n=103 [11]). And whilst two of these studies reported an inverse association between VO_{2peak} and cardiopulmonary complications [10 12], one did not.[11] Similar conflicting findings were found for AT, with only one study reporting a significant association.[11] Differences in the measurement of outcomes by non-blinded assessors is likely to have introduced methodological error, which may explain the variation in findings. As such, the utility of CPEX prior to oesophagectomy is uncertain. Our study aimed to clarify the associations between CPEX variables, specifically VO_{2peak} and AT, and 30-day morbidity after oesophagectomy through the use of a larger sample size and measurement of outcomes using a standardised assessment tool, blinded to CPEX data.

Methods

Study setting and patient population

This hospital-based cohort study was conducted in the Department of Upper Gastrointestinal (UGI) Surgery at the Norfolk and Norwich University Hospitals (NNUH) Foundation Trust, Norwich, United Kingdom. The NNUH is a 1,000 bed teaching hospital, which provides care to a population of approximately 825,000 residents in Norfolk and adjacent counties. Approximately 45 oesophagectomies are performed at this unit each year. We retrospectively identified all patients who underwent an oesophagectomy at our institution between 1st September 2011 (the date of the first CPEX test prior to oesophagectomy) and 9th March 2017 (the latest date that would allow 30-day outcome assessment). At our centre, CPEX testing is used in all patients undergoing oesophagectomy after the decision to operate has been made. None of the authors had any input in the initiation of CPEX testing at our centre. Patients were excluded if they had emergency or palliative surgery, a pharyngolaryngo-oesophagectomy, oesophagectomy and gastrectomy or did not undergo CPEX testing. The study protocol was registered on ClinicalTrials.Gov (NCT03216694) and formal ethical approval was granted by the North West - Liverpool Central Research Ethics Committee after proportionate review (17/NW/0435, IRAS Project ID: 222793).

Cardiopulmonary exercise testing

CPEX testing was undertaken in a respiratory laboratory at the NNUH on an electromagnetically braked cycle ergometer (Ergoselect 200, Ergoline GmbH, Lindenstrasse 5, D-72475, Bitz, Germany). Testing consisted of a 3 minute rest period, 3 minutes of free pedalling and an incremental ramped phase, usually lasting 8-12 minutes, until volitional termination. Gas exchange was measured using a metabolic cart (Jaeger Oxycon Pro, CareFusion, Germany 234 GmbH, Leibnizstrasse 7, 97204, Hoechberg). AT was estimated using the V-slope method (change in the linear relationships between VCO_2 and VO_2) and VO_{2peak} was averaged over 30 seconds during peak exercise. The median time between CPEX testing and surgery was 11 days (interquartile range (IQR) = 7-19 days). None of the patients were deemed unfit for CPEX testing. At surgery, patients underwent either: McKeown, partially laparoscopic assisted (hybrid), or fully laparoscopic (minimally invasive) Ivor Lewis oesophagectomy. All patients were admitted to a high dependency unit (HDU) for the first night following surgery. Step down to ward care was decided by the HDU consultant.

Variable measurement

The following patient data were obtained by review of medical notes: age, gender, smoking status (never, former, current), body mass index (BMI), comorbidities (classified according to the Charlson comorbidity index), TNM staging, chemotherapy regimen, type of surgery received and histology. To reduce the risk of selective reporting bias, CPEX variables of interest (VO_{2peak} and AT) were decided *a priori* under a registered protocol. CPEX data was obtained by an investigator (G.H) who was not involved in the collection of outcome data. Similarly, the outcome assessor (S.L) was blinded to preoperative CPEX values and not involved in the collection of CPEX data. In order to reduce measurement error, short-term morbidity was measured by hand review of the medical notes, in strict accordance with Esophageal Complications Consensus Group (ECCG) definitions.[15] Each complication was then graded in accordance with the Clavien-Dindo classification.[16] In brief; grade 1 complications do not require pharmacological intervention above usual postoperative care, while grade 2 complications do. Grade 3a complications require a surgical intervention without general anaesthesia; grade 3b require a return to theatre; and grade 4 require organ support on ITU. The primary aim was to establish the association between the preoperative CPEX variables VO_{2peak} and AT and 30-day morbidity (all cause, cardiopulmonary and non-cardiopulmonary) as defined by ECCG of Clavien-Dindo grade 2 or above (complications of significant clinical importance). Secondary aims were to measure associations between CPEX variables and specific common complications and 30 and 90 day mortality.

Statistical methods

Continuous variables were reported as mean and standard deviation or median and IQR depending on the distributions. Categorical variables were presented as frequency (%). P-values were obtained using Student-t tests, X^2 or Fisher's exact tests. For the comparative analyses in table 2, statistical significance was taken at p=0.0008 after Bonferroni correction for multiple statistical testing. A Multivariable logistic regression model was constructed based on variables with both a plausible and univariable association with outcome, with CPEX values treated as a continuous variable. All statistical analyses were done using Stata (version 12.1, StataCorp, 4905 Lakeway Drive, College Station, Texas 77845, USA).

Results

Between 1st September 2011 and 9th March 2017 (5 ½ years) 254 patients underwent an oesophagectomy at the NNUH. Of these patients, 48 were excluded: 40 did not undergo CPEX testing, 4 had emergency surgery and 4 had extended and palliative oesophagectomies. Therefore, 206 patients (77% male) were included in the analyses, with a mean age of 67 years (SD 9) at the time of surgery (table 1). In the whole cohort, the mean values for VO_{2peak} and AT were 21.1ml/kg/min (SD 4.5) and 12.4 ml/kg/min (SD 2.8), respectively. The vast majority of patients (98.5%) had malignant disease; predominantly adenocarcinoma (84.5%), for which most received neoadjuvant chemotherapy (79%) and underwent minimally invasive Ivor Lewis oesophagectomy (53%). Thirty day complications occurred in 111 patients (54%), the majority of which were cardiopulmonary (72%). The 40 patients who underwent oesophagectomy without preoperative CPEX were similar in their demographics and outcomes compared to those with CPEX data (supplementary table 1). The reasons for absence of CPEX testing was not documented in the notes, and were most were likely due to logistical issues associated with arranging these tests. The assumption was that these data were missing completely at random (MCAR). There was no documented evidence that any of these patients were selected not to undergo CPEX testing. The median length of hospital stay was 9 days (IQR 7-14 days). No deaths occurred at postoperative day 30, but 7 patients died at day 90 (3.4%); 2 due to malignant progression, 2 due to cardiopulmonary complications (VO_{2peak} 16.2 and 21.1ml/kg/min and AT 10.1 and 9.5ml/kg/min), and 3 due to non-cardiopulmonary complications (VO_{2peak} 14.5, 15.6 and 20.8ml/kg/min and AT 8.7, 8.8 and 10.6ml/kg/min).

Table 2 shows patients grouped by whether or not they suffered; any complication, a cardiopulmonary, or a non-cardiopulmonary complication. These groups differed in ASA grade I, type of operation, duration of surgery and length of stay. However, only length of stay met statistical significance after adjustment for multiple statistical testing (Bonferroni correction, p=0.0008). Neither VO_{2peak} or AT were associated with complications of any type or severity (table 3). We further grouped patients by whether or not they suffered one of the commonest complications, namely pneumonia, atrial fibrillation or anastomotic leak (supplementary table 2). Length of hospital stay in patients who suffered an anastomotic leak was significantly increased compared to those without this event (8 days vs. 22 days, p=<0.00001), but no other variable was significantly different between groups after correction for multiple testing.

Finally, we undertook univariable logistic regression using variables with a plausible association with outcome (age, gender, Charlson comorbidity index, smoking status, BMI, and type of operation) and estimated ORs for; any complication, cardiopulmonary and non-cardiopulmonary complications in turn. Only age and operation type showed associations (<p=0.10) and were included in a multivariable regression model as shown in table 4 (values are from the model excluding CPEX variables). The CPEX variables VO_{2peak} and AT were then added individually (due to collinearity) to the model to derive their ORs. No associations were found between preoperative CPEX variables and morbidity for either VO_{2peak} (OR 1.00, 95% CI 0.94-1.07) or AT (OR 0.98, 95% CI 0.89-1.09) and any type of complication. Similar null associations were found for cardiopulmonary and non-cardiopulmonary complications.

Discussion

This study investigated the association between preoperative CPEX values and 30-day morbidity in 206 patients undergoing oesophagectomy. No associations were found between preoperative cardiopulmonary fitness, as measured by CPEX testing, and short-term postoperative morbidity.

This finding is surprising in that it contradicts a seemingly intuitive inverse association. CPEX testing is a measure of how efficiently patients are able to deliver oxygen from the environment to cellular mitochondria and we would therefore expect patients with large volumes of VO_{2peak} to have a lower risk of complications in the early postoperative period, when the demand for oxygen is increased up to 1.5 times the normal resting state. [6] However, oesophagectomy is a complex operation which delivers a large physiological insult, with complications related to the operative field (anastomotic leak, pneumonia and atrial fibrillation). Therefore, the effect of improved aerobic fitness, if present, is likely to have a small effect on complications directly related to the surgery. However, cardiorespiratory and musculoskeletal reserves may be critical in the ability of a patient to respond once a complication has occurred.[17] Unfortunately, our study was unable to measure this association as mortality was a rare event (n=7).

Three similar, but smaller, studies to ours have been published to date. [10-12] The largest was a Japanese retrospective analysis of 91 patients from a single institution who underwent McKeown oesophagectomy for squamous cell carcinoma.[10] Only cardiopulmonary complications were measured and occurred in 19% of patients. Mean VO_{2peak} (measured in ml/min/m^2) was found to be lower in those with vs. those without cardiopulmonary complications (789ml/min/m^2 vs. 966ml/min/m^2, *t-test* p=<0.001). These values approximate to 20.9ml/kg/min vs. 25.6ml/kg/min [our conversion using the average height and weight of a Japanese male].[18] No association was found between AT and complications (*t-test,* p=0.12). The second largest study was a UK retrospective investigation of 78 patients, predominantly with adenocarcinoma (74%), undergoing oesophagectomy (64% with neoadjuvant chemotherapy).[12] Cardiopulmonary outcomes occurred in 42% of patients (n=33) and non-cardiopulmonary in 24% (n=19). Similar to the Japanese study, mean VO_{2peak} was associated with cardiopulmonary complications although the mean difference was small (19.2ml/kg/min in those with complications vs. 21.4ml/kg/min in those without, *t-test* p=0.04). AT was also similarly not associated with complications (13.2ml/kg/min in those with complications vs. 14.4ml/kg/min in those without, *t-test* p=0.07). ROC curve analysis estimated the predictive value of both VO_{2peak} and AT to be poor (i.e., <70), AUC 0.63 (95% CI 0.50-0.76, p=0.02) and 0.62 (95% CI 0.49-0.75, p=0.03, respectively. Finally, there is a retrospective observational study of 103 patients with both oesophageal and gastric cancers who underwent CPEX testing prior to oesophagectomy (62%) and gastrectomy.[11] This study reported that AT was associated with cardiopulmonary complications (9.9ml/kg/min in those with complications vs. 11.2ml/kg/min in those without, p=0.05), while VO_{2peak} was not (16.6ml/kg/min in those with complications vs. 14.6ml/kg/min in those without, p=0.07). ROC analysis again found both AT and VO_{2peak} to be poorly predictive of complications (AUC 0.62 (95% CI 0.50-0.74, p=0.06) and 0.60 (95% CI 0.48-0.72, p=0.08, respectively). The most significant limitations of all three studies, apart from their small sample sizes and single institution design is the potential for detection bias due to unblinded outcome assessment, particularly for complications which can be subjectively diagnosed. This would lead to an inflation of the association between CPEX variables and outcomes.

The strengths of our study include a pre-registered *a priori* statistical plan, limiting the risk of selective reporting bias and type I and II error through sub-analyses. Measurement error was limited through the use of a defined diagnostic criteria for complications. We also included blinded outcome assessment, which would limit detection bias. Furthermore, our work is the largest study of its kind, with a sufficiently high event rate to detect associations. We undertook a *post hoc* power calculation and estimated that our sample size (n=206) could identify a mean difference in $VO_{2peak,}$ (between groups with and without a complication of any cause) of 1.75ml/kg/min and 1.1ml/kg/min for AT, with 80% power and alpha level at 0.05. We are therefore satisfied that our study had adequate power to detect a small difference in CPEX variables between groups if it were present.

However, there are limitations associated with our methodology. As with all observational studies, confounding cannot be excluded. For example, a low VO_{2peak} and AT may not differentiate between cardiac disease and poor aerobic fitness.[19] However, as the aim was to determine associations and not causality between CPEX values and complications (with comorbidity evident by poor CPEX scores) it is unlikely that such confounding is relevant here. Performance bias may also have occurred due to the clinical team being aware of poor CPEX scores and altering clinical management accordingly. This would result in reducing associations between low CPEX scores and morbidity towards the null. However, there was no obvious deviation from clinical practice according to CPEX results (such as extended HDU stay) in the medical notes, and we consider that such effects on binary outcomes are likely to be small. CPEX data was also missing in 16% of the patient population who otherwise met the inclusion criteria. However, data was likely to be MCAR and this group was comparable to the included group in demography and outcome (supplementary table 1), which reduced the risk of selection bias. Finally, our total sample represents a select population of patients whom are deemed fit for both neoadjuvant chemotherapy and major surgery. However, this selected population had a large distribution of CPEX values (figure 1). We are therefore satisfied that patients with ‘low’ scores were included in the analyses, with 35% of patients (n=72) having an AT of ≤11ml/kg/min. Finally, as death was a rare event, we were unable to examine the associations between fitness and mortality.

Conclusions

CPEX testing provides an objective measure of fitness in patients undergoing oesophagectomy. However, we have shown, that in this specific patient population, aerobic fitness was not associated with 30-day morbidity. We postulate that aerobic fitness is likely to have an effect on complication rates, as there is a plausible biological mechanism, but the effect size – in the context of the magnitude of the surgery - is likely to be small (explaining why we were unable to measure it in our present modestly sized study). The findings from this study, as well as previous work, challenges the utility of CPEX testing as a preoperative screening tool prior to oesophagectomy, which is poorly discriminatory at best.[11 12] This observational work highlights the need for further studies examining associations between preoperative CPEX and outcomes after oesophagectomy to look for consistency in our findings.

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Figure Legend

Figure 1. Dot plots showing the distribution of VO_{2peak} (A) and AT (B) for patients with and without any complications

Figure 1 footnote: n=206, 0=absence of a complication, 1=presence of a complication. For VO_{2peak} the median value for the whole cohort was 20.8ml/kg/min (range 11.6 to 34.9). For AT the median value for the whole cohort was 12.1ml/kg/min (range 7.1 to 22.8)

Table 1. Patient characteristics

Variable	Study cohort (n=206) Number and percentage (unless otherwise stated)
Gender (male)	158 (76.7)
Age at operation (mean + SD)	66.9 years (9.2)
Charlson co-morbidity index	
0	128 (62.1)
1	48 (23.3)
2	19 (9.2)
3 or above	11 (5.4)
WHO BMI category (kg/m^2)	
Underweight (<18.5)	5 (2.4)
Normal weight (18.5-24.9)	56 (27.2)
Overweight (25-29.9)	89 (43.2)
Class I obesity (30-34.9)	42 (20.4)
Class II obesity (35-39.9)	10 (4.9)
Class III obesity (≥40)	4 (1.9)
Smoking status	
Never	65 (31.6)
Former	120 (58.3)
Current	12 (5.8)
Missing	9 (4.4)
T staging (TNM)	
T1	14 (6.8)
T2	25 (12.1)
T3	156 (75.7)
T4	6 (2.9)
Unable to be staged	5 (2.4)
N staging (TNM)	
N0	93 (45.1)
N1	66 (32.1)
N2	45 (21.8)
Unable to be staged	2 (1.0)
Histology	
Adenocarcinoma	174 (84.5)
Squamous cell	29 (14.1)
Other (leiomyoma, high-grade dysplasia)	3 (1.5)
Received neoadjuvant chemotherapy	162 (78.6)
Type of oesophagectomy	
Open McKeown	14 (6.8)
Open or partially laparoscopic assisted Ivor Lewis	83 (40.3)
Fully laparoscopic (minimally invasive) Ivor Lewis	109 (52.9)

Table 2. Comparisons between variables of interest according to postoperative complications (any complication, cardiopulmonary and non-cardiopulmonary complications).

Variable	Any complication		Cardiopulmonary complications		Non-cardiopulmonary complications	
	Yes (n=111)	No (n=95)	Yes (n=80)	No (n=126)	Yes (n=59)	No (n=147)
Gender (male)	82 (74%)	76 (80%)	62 (78%)	96 (76%)	42 (71%)	116 (79%)
Mean age at operation (years + SD)	66.0 (9.4)	67.9 (9.0)	66.2 (10.0)	67.3 (8.7)	65.0 (8.5)	67.6 (9.4)
Charlson co-morbidity index						
0	73 (65.8)	55 (57.9)	48 (60.0)	80 (63.5)	37 (62.7)	91 (61.9)
1	22 (19.8)	26 (27.4)	17 (21.3)	31 (24.6)	12 (20.3)	36 (24.5)
2	10 (9.0)	9 (9.5)	10 (12.5)	9 (7.1)	6 (10.2)	13 (8.8)
3 or above	6 (5.4)	5 (5.3)	5 (6.3)	6 (4.8)	4 (6.8)	7 (4.8)
BMI (mean in kg/m^2 + SD)	27.5 (5.7)	27.0 (4.7)	27.5 (5.2)	27.1 (5.3)	27.3 (6.0)	27.3 (4.9)
Smoking status						
Never	35 (31.5)	30 (31.6)	25 (31.3)	40 (31.7)	17 (28.8)	48 (32.7)
Former	65 (58.6)	55 (57.9)	45 (56.3)	75 (59.5)	36 (61.0)	84 (57.1)
Current	7 (6.3)	5 (5.3)	7 (8.8)	5 (4.0)	5 (8.5)	7 (4.8)
Missing	4 (3.6)	5 (5.3)	3 (3.8)	6 (4.8)	1 (1.7)	8 (5.4)
T staging						
T1	9 (8.1)	5 (5.3)	7 (8.8)	7 (5.6)	6 (10.2)	8 (5.4)
T2	15 (13.5)	10 (10.5)	14 (17.5)	11 (8.7)	7 (11.9)	18 (12.2)
T3	80 (72.1)	76 (80.0)	52 (65.0)	104 (82.5)	43 (72.9)	113 (76.9)
T4	4 (3.6)	2 (2.1)	4 (5.0)	2 (1.6)	1 (1.7)	5 (3.4)
Unable to be staged	3 (2.7)	2 (2.1)	3 (3.8)	2 (1.6)	2 (3.4)	3 (2.0)
N staging						
N0	53 (47.7)	40 (42.1)	40 (50)	53 (42.1)	31(52.5)	62 (42.2)
N1	35 (31.5)	31 (32.6)	23 (28.8)	43 (34.1)	18 (30.5)	48 (32.7)
N2	22 (19.8)	23 (24.2)	16 (20.0)	29 (23.0)	10 (16.9)	35 (23.8)
Unable to be staged	1 (0.9)	1 (1.1)	1 (1.3)	1 (0.8)	0	2 (1.4)
Histology						
Adenocarcinoma	91 (82.0)	83 (87.4)	64 (80.0)	110 (87.3)	51 (86.4)	123 (83.7)
Squamous cell	18 (16.2)	11 (11.6)	14 (17.5)	15 (11.9)	8 (13.6)	21 (14.3)
Other (leiomyoma, HGD)	2 (1.8)	1 (1.1)	2 (2.5)	1 (0.8)	0	3 (2.0)
Received neoadjuvant chemotherapy	85 (76.6)	77 (81.1)	59 (73.8)	103 (81.7)	46 (78.0)	116 (78.9)
Type of oesophagectomy						
Open McKeown	10 (9.0)	4 (4.2)	5 (6.3)	9 (7.1)	8 (13.6)	6 (4.1)[d]
Open or partially laparoscopic assisted Ivor Lewis	48 (43.2)	35 (36.8)	32 (40.0)	51 (40.5)	32 (54.2)	51 (34.7)[c]
Fully laparoscopic (minimally invasive) Ivor Lewis	53 (47.7)	56 (58.9)	43 (53.8)	66 (52.4)	19 (32.2)	90 (61.2)[b]
Duration of surgery in mins (median, 25th- 75th percentile)	464 (365-542)	455 (381-525)	478 (391-556)	443 (369-519)[f]	424 (334-509)	465 (385-541)[e]
Length of stay in days (median, 25th-75th percentile)	12 (8 – 20)	7 (6-9)**[a]**	11.5 (8-18.5)	8 (6-11)**[a]**	17 (12-29)	8 (7-10)**[a]**

For categorical variable, X^2 tests were used, but only when total cell counts were >50, otherwise Fisher's exact tests were applied. For continuous variables with a normal distribution, Students-t tests were used, where distribution was non-normal, Mann-Whitney U tests were used. All percentages represent the proportion of patients with or without a complications (yes/no). P-values reaching conventional statistical significance (p=0.05) are shown in superscript. Bonferroni adjusted significance is p=0.0008, in which case the superscript is shown in bold. **[a]***P=<0.00001,* [b]*P=0.001,* [c]*P=0.01,* [d]*P=0.02,* [e]*P=0.04,* [f]*P=0.05.*

Table 3. Comparisons between mean cardiopulmonary exercise testing variables according to post-operative complication outcomes (type and severity).

CPEX variable	Type of complication		*P-value*
	Any complications (n=111)	**No complications (n=95)**	
VO_{2peak} (ml/kg/min)	21.3 (4.7)	20.9 (4.2)	0.54
AT (ml/kg/min)	12.4 (2.9)	12.4 (2.8)	0.95
	Any complications of C-D grade 3 (n=39)	**No complications (n=95)**	
VO_{2peak} (ml/kg/min)	20.4 (4.4)	20.9 (4.2)	0.52
AT (ml/kg/min)	12.2 (3.1)	12.4 (2.8)	0.73
	Any complications of C-D grade 4 (n=16)	**No complications (n=95)**	
VO_{2peak} (ml/kg/min)	21.0 (3.3)	20.9 (4.2)	0.94
AT (ml/kg/min)	13.0 (3.1)	12.4 (2.8)	0.42
	Cardiopulmonary complications (n=80)	**No cardiopulmonary complications (n=126)**	
VO_{2peak} (ml/kg/min)	21.7 (5.0)	20.8 (4.1)	0.14
AT (ml/kg/min)	12.5 (2.9)	12.3 (2.8)	0.59
	Non-cardiopulmonary complications (n=59)	**No non-cardiopulmonary complications (n=143)**	
VO_{2peak} (ml/kg/min)	20.8 (4.1)	21.2 (4.6)	0.56
AT (ml/kg/min)	12.4 (2.9)	12.3 (2.8)	0.91

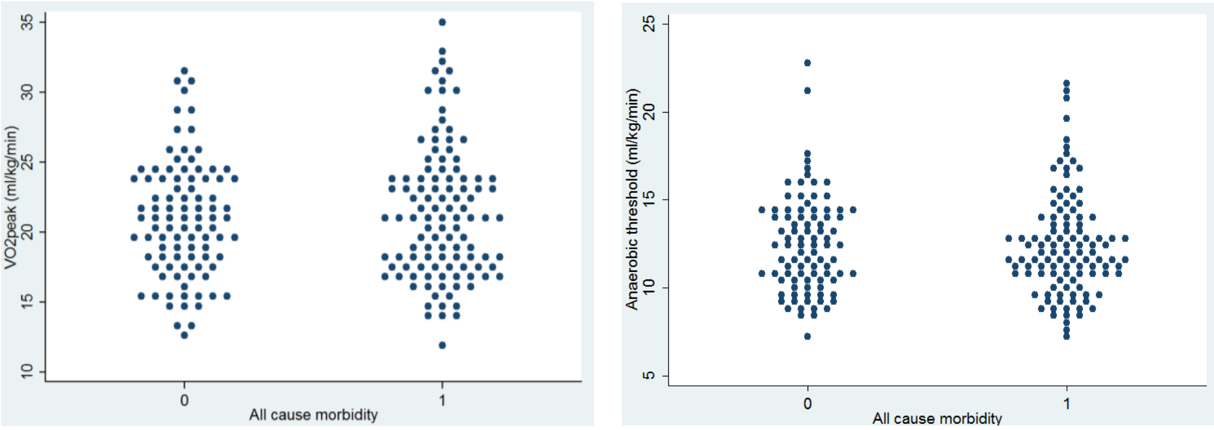
C-D= Clavien-Dindo severity classification. All *P*-values obtained using Student-t tests.

Table 4. Multivariable logistic regression modelling

CPEX variable	Any complication Odds ratio , 95% CI and P-value	Cardiopulmonary complications Odds ratio , 95% CI and P-value	Non-cardiopulmonary complications Odds ratio , 95% CI and P-value
VO_{2peak} (ml/kg/min)	1.00 (0.94-1.07), p=0.862	1.04 (0.98-1.12), p=0.204	0.98 (0.88-1.03), p=0.191
AT (ml/kg/min)	0.98 (0.89-1.09), p=0.769	1.02 (0.92-1.13), p=0.675	0.98 (0.88-1.11), p=0.792

The ORs are for the individual CPEX variables and risk of complications after adjustment for age and type of operation by category (minimally invasive, open or hybrid Ivor Lewis, McKeown oesophagectomy).

Figure 2. Dot plots showing the distribution of VO_{2peak} (A) and AT (B) for patients with and without any complications



A **B**

n=206, 0=absence of a complication, 1=presence of a complication. For VO_{2peak} the median value for the whole cohort was 20.8ml/kg/min (range 11.6 to 34.9). For AT the median value for the whole cohort was 12.1ml/kg/min (range 7.1 to 22.8)

Supplementary Table 1. Comparison of cohorts with and without CPEX data (by any complication)

Variable	Any complication of included cohort (n=206)		Any complication of excluded cohort (n=40)	
	Yes (n=111)	No (n=95)	Yes (n=19)	No (n=21)
Gender (male)	82 (74%)	76 (80%)	13 (68.4)	17 (81.0)
Mean age at operation (years + SD)	66.0 (9.4)	67.9 (9.0)	66.7 (9.8)	63.8 (9.1)
Charlson co-morbidity index				
0	73 (65.8)	55 (57.9)	15 (78.9)	16 (76.2)
1	22 (19.8)	26 (27.4)	4 (21.1)	4 (19.0)
2	10 (9.0)	9 (9.5)	0	1 (4.8)
3 or above	6 (5.4)	5 (5.3)	0	0
Smoking status				
Never	35 (31.5)	30 (31.6)	4 (21.1)	9 (42.9)
Former	65 (58.6)	55 (57.9)	10 (52.6)	11 (52.4)
Current	7 (6.3)	5 (5.3)	4 (21.1)	0
Missing	4 (3.6)	5 (5.3)	1 (5.3)	1 (4.8)
T staging				
T1	9 (8.1)	5 (5.3)	3 (15.8)	2 (9.5)
T2	15 (13.5)	10 (10.5)	3 (15.8)	3 (14.3)
T3	80 (72.1)	76 (80.0)	13 (68.4)	16 (76.2)
T4	4 (3.6)	2 (2.1)	0	0
Unable to be staged	3 (2.7)	2 (2.1)	0	0
N staging				
N0	53 (47.7)	40 (42.1)	8 (42.1)	13 (61.9)
N1	35 (31.5)	31 (32.6)	5 (26.3	6 (28.6)
N2	22 (19.8)	23 (24.2)	5 (26.3)	2 (9.5)
Unable to be staged	1 (0.9)	1 (1.1)	1 (5.3)	0
Histology				
Adenocarcinoma	91 (82.0)	83 (87.4)	14 (73.7)	18 (85.7)
Squamous cell	18 (16.2)	11 (11.6)	5 (26.3)	3 (14.3)
Other (leiomyoma, HGD)	2 (1.8)	1 (1.1)	0	0
Received neoadjuvant chemotherapy	85 (76.6)	77 (81.1)	15 (78.9)	18 (85.7)
Type of oesophagectomy				
Open McKeown	10 (9.0)	4 (4.2)	3 (15.8)	1 (4.8)
Open or partially laparoscopic assisted Ivor Lewis	48 (43.2)	35 (36.8)	8 (42.1)	12 (57.1)
Fully laparoscopic (minimally invasive) Ivor Lewis	53 (47.7)	56 (58.9)	8 (42.1)	8 (38.1)
Length of stay in days (median, 25^{th}-75^{th} percentile)	12 (8 – 20)	7 (6-9)	11 (10-22)	7 (6-7)
Duration of surgery in mins (median, 25^{th}- 75^{th} percentile)	464 (365-542)	455 (381-525)	421 (337-519)	416 (345-480)

Supplementary table 2. Comparisons between variables of interest according to common post-operative complications.

Variable	Pneumonia		Atrial fibrillation		Anastomotic leak	
	Yes (n=42)	No (n=164)	Yes (n=36)	No (n=170)	Yes (n=39)	No (n=167)
Gender (male)	35 (83.3)	123 (75.0)	26 (72.2)	132 (77.6)	31 (79.5)	127 (76.0)
Mean age at operation (years + SD)	68.1 (9.1)	66.6 (9.3)	68.3 (8.9)	66.6 (9.3)	64.1 (8.5)	67.5 (9.3)[f]
COPD diagnosis	8 (19.0)	18 (11.0)	9 (25.0) [d]	17 (10.0)	8 (20.5)	18 (10.8)
Previous MI	6 (14.3)	12 (7.3)	3 (8.3)	15 (8.8)	5 (12.8)	13 (7.8)
BMI (mean in kg/m^2 + SD)	27.7 (5.2)	27.2 (5.2)	27.6 (5.2)	27.2 (5.3)	28.0 (6.6)	27.1 (4.9)
Smoking status						
Never	14 (33.3)	51 (31.1)	11 (30.6)	54 (31.8)	9 (23.1)	56 (33.5)
Former	23 (54.8)	97 (59.1)	24 (66.7)	96 (56.5)	24 (61.5)	96 (57.5)
Current	3 (7.1)	9 (5.5)	1 (2.8)	11 (6.5)	4 (10.3)	8 (4.8)
Missing	2 (4.8)	7 (4.3)	0	9 (5.3)	2 (5.1)	7 (4.2)
Had neoadjuvant chemotherapy	27 (64.3)	135 (82.3) [d]	29 (80.6)	133 (78.2)	32 (82.1)	130 (77.8)
Type of oesophagectomy						
Open McKeown	2 (4.8)	12 (7.3)	2 (5.6)	12 (7.1)	6 (15.4)	8 (4.8)[e]
Open or partially laparoscopic assisted Ivor Lewis	19 (45.2)	64 (39.0)	11 (30.6)	72 (42.4)	20 (51.3)	63 (37.7)
Fully laparoscopic (minimally invasive) Ivor Lewis	21 (50)	88 (53.7)	23 (63.9)	86 (50.6)	13 (33.3)	96 (57.5)[c]
Duration of surgery (mins)	475 (344-545)	455 (370-526)	489 (427-556)	451 (365-526) [f]	406 (334-490)	462 (381-536) [f]
Length of stay in days (median, 25th to 75th percentile)	10 (8-15)	8.5 (7-13)	13 (8-19.5)	8 (7-12) **[b]**	22 (15-35)	8 (7-10) **[a]**
CPEX (mean + SD)						
VO2peak (ml/kg/min)	20.8 (5.0)	21.2 (4.3)	21.2 (5.2)	21.1 (4.3)	20.7 (3.7)	21.2 (4.6)
AT (ml/kg/min)	12.0 (2.6)	12.5 (2.9)	12.5 (3.2)	12.3 (2.8)	12.7 (2.9)	12.3 (2.8)

For categorical variable, X^2 tests were used, but only when total cell counts were >50, otherwise Fisher's exact tests were applied. For continuous variables with a normal distribution, Students-t tests were used, where distribution was non-normal, Mann-Whitney U tests were used. All percentages represent the proportion of patients with or without a complications (yes/no). P-values reaching conventional statistical significance (p=0.05) are shown in superscript. Bonferroni adjusted significance is p=0.0008, in which case the superscript is shown in bold. ***[a]****P=<0.00001, [b]P=0.0008, [c]P=0.007, [d]P=0.01, [e]P=0.02, [f]P=0.04.*