Esophagus

The association between preoperative cardiopulmonary exercise–test variables and short-term morbidity after esophagectomy: A hospital-based cohort study

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A B S T R A C T

Background: Postoperative complications after esophagectomy 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 esophagectomy.

Methods: We retrospectively identified 254 consecutive patients who underwent esophagectomy 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 cardiopulmonary exercise testing values). Associations between preoperative cardiopulmonary exercise testing variables and postoperative outcomes were estimated using logistic regression.

Results: A total of 206 patients (77% male) were included in the analyses, with a mean age of 67 years (SD 9). The mean values for the maximal oxygen consumed at the peak of exercise (VO_{2peak}) and the anaerobic threshold were 21.1 mL/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 esophagectomy (53%). Complications at postoperative day 30 occurred in 111 patients (54%), the majority of which were cardiopulmonary (72%). No associations were found between preoperative cardiopulmonary exercise testing variables and morbidity for either VO_{2peak} (OR 1.00, 95% CI 0.94–1.07) or anaerobic threshold (OR 0.98, 95% CI 0.89–1.09).

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

Introduction

Oesophageal resection and reconstruction (esophagectomy) are the only consistent treatment modalities that offer a potential cure for oesophageal cancer[1] but carry a high risk of postoperative complications. UK national audit figures report that 33% of patients suffer a complication after esophagectomy, 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 physiologic insults of

esophagectomy, which include the following: disruption of normal lung mechanics through incisional pain and diaphragmatic dysfunction[4]; blood loss and sympathetic activation, resulting in splanchnic vasoconstriction, which jeopardizes 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 attributable to low cardiopulmonary reserves. This could allow better perioperative management to improve outcomes, including modification of fitness with an exercise program.

Cardiopulmonary exercise testing (CPEX) is an objective, quantitative, and composite measure of a person's overall aerobic fitness. Two specific CPEX variables, the maximal oxygen consumed at the peak of exercise (VO_{2peak}) and VO_2 at the 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 cutoff of <11 mL/kg/min had a sensitivity of 91% and specificity of 74% for predicting mortality.[7] In a multicenter study of 346 lung cancer patients undergoing resection via thoracotomy, a VO_{2max} cutoff of <16 mL/kg/min predicted that these patients are more likely to suffer a complication ($P = .0001$).[14] To the best of our knowledge, there have only been 3 relatively small observational studies of CPEX testing before esophagectomy ($n = 78$,[12] $n = 91$,[10] $n = 103$[11]). And although 2 of these studies reported an inverse association between VO_{2peak} and cardiopulmonary complications,[10,12] 1 did not.[11] Similar conflicting findings were found for AT, with only 1 study reporting a significant association.[11] Differences in the measurement of outcomes by nonblinded assessors is likely to have introduced methodologic error, which may explain the variation in findings. As such, the utility of CPEX before esophagectomy is uncertain. Our study aimed to clarify the associations between CPEX variables, specifically VO_{2peak} and AT, and the 30-day morbidity after esophagectomy through the use of a larger sample size and the measurement of outcomes using a standardized 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 Surgery at the Norfolk and Norwich University Hospitals (NNUH) Foundation Trust, Norwich, United Kingdom. The NNUH is a 1,000-bed teaching hospital that provides care to a population of approximately 825,000 residents in Norfolk, UK, and adjacent counties. Approximately 45 oesophagectomies are performed at this unit each year. We retrospectively identified all patients who underwent an esophagectomy at our institution between September 1, 2011, (the date of the first CPEX test before esophagectomy) and March 9, 2017, (the latest date that would allow a 30-day outcome assessment). At our center, CPEX testing is used in all patients undergoing esophagectomy after the decision to operate has been made. None of the authors had any input in the initiation of CPEX testing at our center. Patients were excluded if they had emergency or palliative surgery; a pharyngolaryngo-esophagectomy; or did not undergo CPEX testing. The study protocol was registered on ClinicalTrials.Gov (NCT03216694), available at https://clinicaltrials.gov/ct2/show/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, Bitz, Germany). Testing consisted of a 3-minute rest period, 3 minutes of free pedaling, and an incremental ramped phase, usually lasting 8 to 12 minutes, until volitional termination. Gas exchange was measured using a metabolic cart (Jaeger Oxycon Pro, CareFusion, Germany 234 GmbH, Hoechberg, Germany). AT was estimated using the V-slope method (change in the linear relationships between VCO_2 and VO_2), and VO_{2peak} was averaged throughout 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 esophagectomy. All patients were admitted to a high-dependency unit (HDU) for the first night after surgery. The 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; sex; smoking status (never, former, current); body mass index; comorbidities (classified according to the Charlson comorbidity index); tumor, node, metastasis 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 were 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. To reduce measurement error, short-term morbidity was measured by hand review of the medical notes, in strict accordance with Esophageal Complications Consensus Group definitions.[15] Each complication was then graded in accordance with the Clavien-Dindo classification.[16] In brief, grade 1 complications do not require pharmacologic intervention higher than the usual postoperative care, and 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 in an intensive treatment unit. 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 noncardiopulmonary) as defined by Esophageal Complications Consensus Group of the Clavien-Dindo grade 2 or higher (complications of significant clinical importance). Secondary aims were to measure associations between CPEX variables and specific common complications and 30-day 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, χ^2, or Fisher exact tests. For the comparative analyses, statistical significance was taken at $P = .0008$ 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

Table I
Patient characteristics

Variable	Study cohort ($n = 206$) number and percentage (unless otherwise stated)
Sex (male)	158 (76.7)
Age (years) at operation (mean + SD)	66.9 (9.2)
Charlson comorbidity 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 esophagectomy	
Open McKeown	14 (6.8)
Open or partially laparoscopic assisted Ivor Lewis	83 (40.3)
Fully laparoscopic (minimally invasive) Ivor Lewis	109 (52.9)

BMI, body mass index; *TNM*, tumor, node, metastasis.

statistical analyses were done using Stata (v 12.1, StataCorp, College Station, TX, USA).

Results

Between September 1, 2011 and March 9, 2017 (5.5 years), 254 patients underwent an esophagectomy 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 I). In the whole cohort, the mean values for VO$_{2peak}$ and AT were 21.1 mL/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 esophagectomy (53%). Complications had occurred in 111 patients (54%) within 30 days, the majority of which were cardiopulmonary (72%). The 40 patients who underwent esophagectomy without preoperative CPEX were similar in their demographics and outcomes compared with those with CPEX data (Supplementary Table I). The reasons for the absence of CPEX

testing was not documented in the notes and were most likely because of logistic issues associated with arranging these tests. The assumption was that these data were missing completely at random. We found 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 because of malignant progression, 2 because of cardiopulmonary complications (VO$_{2peak}$ 16.2 and 21.1 mL/kg/min and AT 10.1 and 9.5 mL/kg/min), and 3 because of noncardiopulmonary complications (VO$_{2peak}$ 14.5, 15.6 and 20.8 mL/kg/min and AT 8.7, 8.8 and 10.6 mL/kg/min).

Table II presents patients grouped by whether they suffered any complication, a cardiopulmonary, or a noncardiopulmonary complication. These groups differed in American Society of Anesthesiologists 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, $P = .0008$). Neither VO$_{2peak}$ or AT were associated with complications of any type or severity (Table III). We further grouped patients by whether they suffered 1 of the commonest complications, namely pneumonia, atrial fibrillation, or anastomotic leak (Supplementary Table II). Length of hospital stay in patients who suffered an anastomotic leak was significantly increased compared with those without this event (8 days vs 22 days, $P \leq .00001$), 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, sex, Charlson comorbidity index, smoking status, body mass index, and type of operation) and estimated ORs for any complication, cardiopulmonary and noncardiopulmonary complications in turn. Only age and operation type showed associations ($P \leq .10$) and were included in a multivariable regression model as presented in Table IV (values are from the model excluding CPEX variables). The CPEX variables VO$_{2peak}$ and AT were then added individually (because of 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 noncardiopulmonary complications.

Discussion

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

This finding is surprising because 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 complication in the early postoperative period, when the demand for oxygen is increased up to 1.5 times the normal resting state.[6] However, esophagectomy is a complex operation that delivers a large physiologic 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

Table II
Comparisons between variables of interest according to postoperative complications (any complication, cardiopulmonary and noncardiopulmonary complications)

Variable	Any complication		Cardiopulmonary complications		Noncardiopulmonary complications	
	Yes ($n = 111$)	No ($n = 95$)	Yes ($n = 80$)	No ($n = 126$)	Yes ($n = 59$)	No ($n = 147$)
Sex (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 comorbidity 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 esophagectomy						
Open McKeown	10 (9.0)	4 (4.2)	5 (6.3)	9 (7.1)	8 (13.6)	6 (4.1)[*]
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)[†]
Fully laparoscopic (minimally invasive) Ivor Lewis	53 (47.7)	56 (58.9)	43 (53.8)	66 (52.4)	19 (32.2)	90 (61.2)[‡]
Duration of surgery (minutes; median, 25th–75th percentile)	464 (365–542)	455 (381–525)	478 (391–556)	443 (369–519)[§]	424 (334–509)	465 (385–541)[∥]
Length of stay (days; median, 25th–75th percentile)	12 (8–20)	7 (6–9)[¶]	11.5 (8–18.5)	8 (6–11)[¶]	17 (12–29)	8 (7–10)[¶]

HGD, high grade dysplasia.

For categorical variable, χ^2 tests were used, but only when total cell counts were > 50. Otherwise the Fisher exact tests were applied. For continuous variables with a normal distribution, Student 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 complication (yes/no). P values reaching conventional statistical significance ($P = .05$) are presented in footnotes. Bonferroni adjusted significance is $P = .0008$, in which case the footnote is presented in bold.

[*] $P = .02$.
[†] $P = .01$.
[‡] $P = .001$.
[§] $P = .05$.
[∥] $P = .04$.
[¶] $P = < .00001$.

respond once a complication has occurred.[17] Unfortunately, our study was unable to measure this association because mortality was a rare event ($n = 7$).

To date, 3 similar, but smaller, studies to ours have been published.[10–12] The largest was a Japanese retrospective analysis of 91 patients from a single institution who underwent McKeown

Table III
Comparisons of mean cardiopulmonary exercise testing variables according to postoperative 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)	.54
AT (mL/kg/min)	12.4 (2.9)	12.4 (2.8)	.95
	Any complications of CD grade 3 ($n = 39$)	No complications ($n = 95$)	
VO$_{2peak}$ (mL/kg/min)	20.4 (4.4)	20.9 (4.2)	.52
AT (mL/kg/min)	12.2 (3.1)	12.4 (2.8)	.73
	Any complications of CD grade 4 ($n = 16$)	No complications ($n = 95$)	
VO$_{2peak}$ (mL/kg/min)	21.0 (3.3)	20.9 (4.2)	.94
AT (mL/kg/min)	13.0 (3.1)	12.4 (2.8)	.42
	Cardiopulmonary complications ($n = 80$)	No cardiopulmonary complications ($n = 126$)	
VO$_{2peak}$ (mL/kg/min)	21.7 (5.0)	20.8 (4.1)	.14
AT (mL/kg/min)	12.5 (2.9)	12.3 (2.8)	.59
	Noncardiopulmonary complications ($n = 59$)	No noncardiopulmonary complications ($n = 143$)	
VO$_{2peak}$ (mL/kg/min)	20.8 (4.1)	21.2 (4.6)	.56
AT (mL/kg/min)	12.4 (2.9)	12.3 (2.8)	.91

Note: All P values obtained using Student t tests.

Table IV
Multivariable logistic regression modelling

| CPEX variable	Any complication Odds ratio, 95% CI, and P value	Cardiopulmonary complications Odds ratio, 95% CI, and P value	Noncardiopulmonary complications Odds ratio, 95% CI, and P value
VO_{2peak} (mL/kg/min)	1.00 (0.94–1.07), $P = .862$	1.04 (0.98–1.12), $P = .204$	0.98 (0.88–1.03), $P = .191$
AT (mL/kg/min)	0.98 (0.89–1.09), $P = .769$	1.02 (0.92–1.13), $P = .675$	0.98 (0.88–1.11), $P = .792$

The odds ratios 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 esophagectomy).

esophagectomy 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 versus those without cardiopulmonary complications (789 mL/min/m^2 vs 966 mL/min/m^2, t test $P \leq .001$). These values approximate to 20.9 mL/kg/min vs 25.6 mL/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 $P = .12$). The second largest study was a UK retrospective investigation of 78 patients, predominantly with adenocarcinoma (74%), undergoing esophagectomy (64% with neoadjuvant chemotherapy).[12] Cardiopulmonary outcomes occurred in 42% of patients ($n = 33$) and noncardiopulmonary in 24% ($n = 19$). Similar to the Japanese study, mean VO_{2peak} was associated with cardiopulmonary complications, although the mean difference was small (19.2 mL/kg/min in those with complications vs 21.4 mL/kg/min in those without, t test $P = .04$). AT was also similarly not associated with complications (13.2 mL/kg/min in those with complications vs 14.4 mL/kg/min in those without, t test $P = .07$). Receiver operating characteristic curve analysis estimated the predictive value of both VO_{2peak} and AT to be poor (ie, < 70), with area under the curve at 0.63 (95% CI 0.50–0.76, $P = .02$) and 0.62 (95% CI 0.49–0.75, $P = .03$), respectively. Finally, there is a retrospective observational study of 103 patients with both oesophageal and gastric cancers who underwent CPEX testing before esophagectomy (62%) and gastrectomy.[11] This study reported that AT was associated with cardiopulmonary complications (9.9 mL/kg/min in those with complications vs 11.2 mL/kg/min in those without, $P = .05$), and VO_{2peak} was not (16.6 mL/kg/min in those with complications vs 14.6 mL/kg/min in those without, $P = .07$). Receiver operating characteristic analysis again found both AT and VO_{2peak} to be poorly predictive of complications (area under the curve 0.62 [95% CI 0.50–0.74, $P = .06$] and 0.60 [95% CI 0.48–0.72,

$P = .08$], respectively). The most significant limitations of all 3 studies, apart from their small sample sizes and single-institution design, is the potential for detection bias because of unblinded outcome assessment, particularly for complications that 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 preregistered a priori statistical plan, limiting the risk of selective reporting bias and type I and II error through subanalyses. 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 1.75 mL/kg/min and 1.1 mL/kg/min for AT, with 80% power, and α 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, because our 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 owing 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 toward the null. However, there was no obvious deviation from clinical practice according to CPEX results (such as extended HDU stay) in
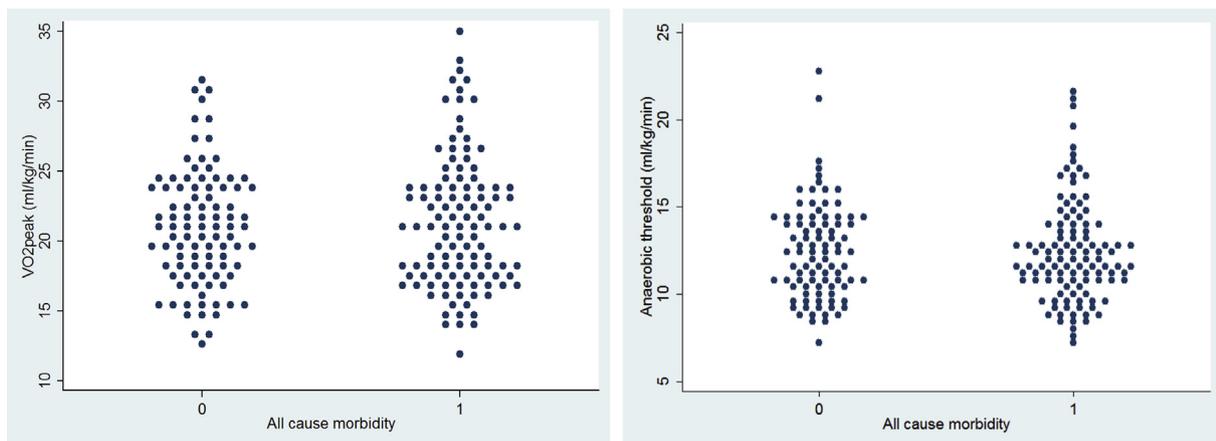
Figure. Dot plots presenting the distribution of (A) VO_{2peak} and (B) AT for patients with and without any complications. Note: $n = 206$, 0 = absence of a complication, 1 = presence of a complication. For VO_{2peak}, the median value for the whole cohort was 20.8 mL/kg/minutes (range 11.6–34.9). For AT the median value for the whole cohort was 12.1 mL/kg/minutes (range 7.1–22.8).

the medical notes, and we consider that such effects on binary outcomes are likely to be small. CPEX data were also missing in 16% of the patient population who otherwise met the inclusion criteria. However, data were likely to be missing completely at random, and this group was comparable to the included group in demography and outcome (Supplementary Table I), 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). We are therefore satisfied that patients with "low" scores were included in the analyses, with 35% of patients ($n = 72$) having an AT ≤ 11 mL/kg/min. Finally, because death was a rare event, we were unable to examine the associations between fitness and mortality.

In conclusion, CPEX testing provides an objective measure of fitness in patients undergoing esophagectomy. 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 because there is a plausible biologic 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, and earlier work, challenges the utility of CPEX testing as a preoperative screening tool before esophagectomy, 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 esophagectomy to look for consistency in our findings.

Acknowledgments

Conflicts of interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2019.02.001.

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