Cardiopulmonary Exercise Testing and Cardiopulmonary Morbidity in Patients Undergoing Major Head and Neck Surgery

Abstract

Cardiopulmonary exercise testing (CPET) is used as a risk stratification tool for patients undergoing major surgery. In this study, we investigated the role of CPET in predicting day five cardiopulmonary morbidity in patients undergoing head and neck surgery.

This observational cohort study included 230 adults undergoing major head and neck surgery. We recorded preoperative CPET variables and day five postoperative cardiopulmonary morbidity.

Full data from 187 patients were analysed; 43 patients either had incomplete data sets or declined surgery/CPET. One hundred and nineteen patients (63.6%) developed cardiopulmonary morbidity at day five. Increased preoperative heart rate and duration of surgery were independently associated with day five cardiopulmonary morbidity. Those with such morbidity also had lower peak $\dot{V}O_2$ 11.4(IQR 8.4-18.0) vs 16.0(IQR 14.0-19.7)ml.kg^{-1}.min^{-1}, P<0.0001 and $\dot{V}O_2$ at AT 10.6(IQR 9.1-13.1) vs 11.5(IQR 10.5-13.0)ml.kg^{-1}.min^{-1}, P=0.03. Logistic regression model containing peak $\dot{V}O_2$ and duration of surgery demonstrated that increased peak $\dot{V}O2$ was associated with a reduction in the likelihood of cardiopulmonary complications OR 0.92(95%CI 0.87-0.96), P=0.001. The area under the receiver operating characteristic curve for this model was 0.75(95%CI 0.68-0.82), P<0.0001, 64% sensitivity, 81% specificity.

CPET can help to predict day five cardiopulmonary morbidity in the patients undergoing head and neck surgery. A model containing peak $\dot{V}O_2$ allowed identification of those with such complications

Keywords: Cardiopulmonary exercise testing; postoperative morbidity; maxillofacial surgery; risk stratification

Introduction

Postoperative complications are common after major head and neck surgery, with published rates varying between 55% and 72%.[1-3] In particular, patients undergoing such surgery are at high risk of developing cardio-vascular and respiratory complications in the early postoperative period.[4] Current perioperative pathways seem to be unable to consistently predict or reduce postoperative morbidity in patients undergoing major head and neck surgery.[2] In this study, we evaluated the incidence of cardiopulmonary morbidity and high-grade morbidity[5] defined by the Postoperative Morbidity Survey (POMS)[6] and investigated the role of CPET to predict such morbidity. CPET is an established part of preoperative assessment and has been used for risk stratification in thoracic, abdominal and vascular surgery.[7-10] Despite requiring a moderate to high level of exertion, CPET is well-tolerated by patients[11,12] and is safe to conduct on most patient cohorts according to international guidelines.[13,14] While CPET has proven to be a useful perioperative risk stratification tool for major surgery, there are no studies evaluating the role of CPET in perioperative assessment of patients undergoing head neck surgery. The aim of this observational study was to investigate the ability of CPET variables to predict early cardiopulmonary morbidity in patients undergoing major head and neck surgery.

Materials and Methods

Patients

The study was undertaken at University College London Hospitals NHS Foundation Trust, where participants underwent CPET as part of their routine preoperative assessment. There was full compliance with Caldicott Guidelines relating to data collection and confidentiality. Ethical approval for collection and analysis of postoperative morbidity data were not required as this study was deemed a service evaluation by the local research department and by using the NHS Health Research Authority decision tool. Adult patients scheduled for major head and neck surgery, with or without immediate reconstruction, between September 2011 and December 2017 were included. Patients with missing morbidity data, inability to perform CPET or who did not proceed with surgery were excluded. The patients with intraoperative or early postoperative death (prior to the postoperative day five) were included into the analysis.

Perioperative Variables

Patient characteristics including age, gender, body mass index, resting heart rate (HR) and the American Society of Anesthesiologists (ASA) physical status score were recorded preoperatively. Surgical variables such as length of operation and type of surgery also were recorded. Surgical interventions were categorised based on modality of reconstruction, i.e. resection followed by immediate reconstruction with free or pedicled tissues transfer; resection followed by reconstruction with local tissues and/or skin grafts and delayed reconstruction of a pre-existing defect.

Cardiopulmonary Exercise Testing

CPET was conducted in accordance with the American Thoracic Society and American College of Chest Physicians (ATS/ACCP) Guidelines.[13] Patients performed a symptom-limited ramp test to volitional exhaustion. Incremental cycle ergometry was performed using an electro-magnetically braked cycle-ergometer (Lode, Groningen, Netherlands) with continuous ECG monitoring (Customed GmbH, Ottobrunn, Germany). Patients wore a Cortex face-mask (Hans Rudolph Inc, Kansas City, USA) to which a flow/volume turbine was attached. Breath-by-breath gas analysis was performed (Cortex Metalyzer 3B, Biophysik, Leipzig, Germany). During exercise, arterial blood pressure measurements were taken every two minutes (Orbit-K, SunTech Medical, Morrisville, USA) attached to a Cortex Multilyzer (Cortex, Biophysik, Leipzig, Germany).

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CPET Protocol

Before testing the equipment was calibrated in accordance to the ATS/ACCP Guidelines.[13] A suitable ramp was chosen, using a predicted work-rate increment equation.[15] Exercise testing consisted of a 3-minute rest period after which unloaded cycling was performed at a constant cadence of 60rpm for 3 minutes. Thereafter, patients performed a symptom-limited incremental ramp test until either volitional exhaustion or until the test was terminated by the physiologist. Criteria for test termination were: inability to maintain a constant cadence above 40rpm for 30 seconds, experience of adverse symptoms (e.g. chest pain) or if the physiological data indicated a potential adverse event (e.g. ECG abnormalities).[13]

CPET Variables

Throughout CPET oxygen uptake ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were recorded, together with respiratory rate and tidal volume and end-tidal gas tensions ($P_{ET}O_2$ and $P_{ET}CO_2$). Ventilation and gas exchange variables derived from CPET included the ventilatory equivalents for oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$), as well as the oxygen pulse ($\dot{V}O_2$/HR). The anaerobic threshold (AT) was determined through a combination of the modified V-slope method (breakpoint in the relationship between $\dot{V}CO_2$ and $\dot{V}O_2$)[16], changes in ventilatory equivalents and end-tidal gas tensions.[17] Combination of the above methods has been shown to improve the precision of AT detection.[18] The $\dot{V}_E/\dot{V}CO_2$ was recorded as the value measured at the AT.[17] Peak $\dot{V}O_2$ was defined as the highest average $\dot{V}O_2$ over the last 30 seconds of ramped exercise.[19] Values for peak $\dot{V}O_2$ and AT were adjusted for body mass.

Morbidity

The primary outcome was POMS-defined cardiopulmonary morbidity at day five using cardiac and respiratory domains.[6]. As a secondary outcome, we recorded high-grade POMS morbidity as described by Wong et al.[5] for this cohort of patients. Length of stay in the intensive care unit (ICU) or high dependency unit (HDU) was recorded prospectively for all patients.

Statistical Analysis

Statistical analysis was performed using SPSS 25 (IBM Corp, NY, USA) and Prism 8 (GraphPad Software, CA, USA). $P<0.05$ was taken to be statistically significant. The Shapiro-Wilk test was used assess normality of the data with subsequent comparisons were made between those who did and did not have cardiopulmonary morbidity on day five using parametric (independent sample t-test or Fisher's exact test) or non-parametric analyses (Mann-Whitney) where appropriate. Grouped data are reported as either Median (interquartile range, IQR) or mean±standard deviation (SD). Receiver

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operated characteristic (ROC) curves were constructed for peak $\dot{V}O_2$, and $\dot{V}O_2$ at AT to evaluate their ability to predict day five cardiopulmonary morbidity. The optimal cut-off point for these CPET variables to distinguish patients with and without cardiopulmonary morbidity were calculated using Youden's J-index[20]. Multivariable logistic regression analysis included variables which were found to differ significantly in patients with and without cardiopulmonary morbidity. The final model was obtained using forward stepwise multivariable logistic regression. A ROC curve was constructed for this model to assess its ability to predict postoperative cardiopulmonary morbidity. Kaplan-Meir survival curves were constructed, using optimal cut-off values for peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT to assess differences in length of stay in the ICU/HDU.

Results

Two hundred and thirty patients undergoing major head and neck surgery with immediate or delayed reconstruction were included in this study, of whom four had no surgery (due to high risk of intraoperative death and/or personal choice) and 13 were not able to perform CPET. Out of the remaining 213 patients, complete perioperative morbidity data were available for 187(26 patients had incomplete data sets). Two patients died within the first five days after surgery.

Complete demographic and surgical data, including incidence of cardiopulmonary morbidity at day five, is presented in Table 1. Patients were grouped by the absence or presence of day five cardiopulmonary morbidity and differed significantly in resting HR [72.0(IQR 64.2-84.0) vs 78(70.0-88.0)bpm, P=0.0079] and duration of operation [607.5(IQR 473.3-706.0) vs 726(IQR 595.0-837.0)minutes, P <0.0001].

Ninety-four patients (50.3%) required respiratory support at postoperative day 5. Three patients (1.6%) developed new myocardial infarction or ischaemia; one of two patients with myocardial infarction died on the 4th postoperative day, despite maximal support on ICU. One patient suffered from an extensive haemorrhagic stroke at postoperative day one which lead to death. Other high-grade POMS-defined morbidity findings are presented in Supplementary Table 1.

Patients with day 5 postoperative cardiopulmonary morbidity had significantly lower peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT (Table 2). Optimal cut-off points for prediction of day five

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cardiopulmonary morbidity for peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT were calculated at 12.3ml.kg^{-1}.min^{-1} and 10.1ml.kg^{-1}.min^{-1}, respectively (Supplementary Table 2). The area under the receiver operating characteristic (AUROC) for peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT were 0.68(95%CI 0.6-0.7), P<0.001 and 0.59(95%CI 0.51-0.67), P=0.03 respectively.

All cases with day five POMS-defined cardiopulmonary morbidity were dichotomised around the optimal cut-off point for $\dot{V}O_2$ at AT, as described previously.[21] Significantly higher rates of day five POMS-defined pulmonary complications were observed in patients with $\dot{V}O_2$ at AT<10.1ml.kg^{-1}.min^{-1}. Forty-five patients (62.5%) required respiratory support (P=0.01), while 52(72.2%) patients had increased oxygen requirements (P=0.0008) (Supplementary Table 3). Independently, resting HR, ASA, duration of operation and peak $\dot{V}O_2$ were associated with day 5 cardiopulmonary morbidity (P<0.05). These variables were used for the multivariable regression analysis (Table 3). The odds of cardiopulmonary complications were higher in patients who underwent longer surgical procedures odds ratio (OR) 1.003(95%CI 1.001-1.005), P=0.002. In addition, an increase in peak $\dot{V}O_2$ was associated with a reduction in odds of such morbidity (OR 0.92(95%CI 0.876-0.972), P=0.003. This model had reasonable power in discriminating between patients with and without day five cardiopulmonary morbidity (AUROC 0.75(95%CI 0.68-0.82), P<0.0001, 64% sensitivity, 81% specificity) (Figure 1). Survival analysis demonstrated that, independently of all other variables, patients with peak $\dot{V}O_2$ and $\dot{V}O_2$ at AT below the cut-off points had significantly longer stays in the ICU/HDU (P=0.004 and P=0.002), as shown in Figure 2-3 and Supplementary Table 4.

Discussion

This observational, cohort study is the first to provide evidence supporting the use of CPET for objective preoperative risk assessment in patients undergoing major head and neck surgery. Interestingly, there were no significant age differences in those with or without cardiopulmonary complications, while elevated preoperative HR in this group of patients was associated with the incidence of cardiopulmonary morbidity at day five after surgery. These findings are in line with the recently published data on the association of preoperative HR with postoperative cardiac morbidity.[22]

Peak $\dot{V}O_2$ < 12.3ml.kg^{-1}.min^{-1} and $\dot{V}O_2$ at AT < 10.1ml.kg^{-1}.min^{-1} were both independent predictors of day five cardiopulmonary morbidity in patients undergoing

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major head and neck surgery. However, these CPET variables had poor predictive value on their own. This finding is consistent with the data from other similar studies.[21] The poor predictive value can be explained by complex interactions between patients' premorbid states and the extent of surgical insult. We hereby demonstrated that peak $\dot{V}O_2$ can significantly affect the risk of developing postoperative cardiopulmonary morbidity. Both single variable and multivariable logistic regression analyses demonstrated that patients undergoing longer surgical procedures had a significantly higher rate of postoperative cardiopulmonary morbidity. Our findings are consistent with data from studies demonstrating that increased operative time is associated with higher rates of postoperative complications.[1,23,24] The multivariable logistic regression analysis demonstrated that peak $\dot{V}O_2$ and duration of surgery were predictors of cardiopulmonary morbidity in patients undergoing major head and neck surgery.

Our study provides new data on objective preoperative fitness assessment in patients undergoing major head and neck surgery. While there is no data available for CPET variables in patients undergoing surgery involving the upper aero-digestive tract, three recent systematic reviews investigated the correlation between CPET variables, morbidity and mortality in patients undergoing non-cardiopulmonary surgery.[7,8,10] The review by Moran et al.[7] concluded that $\dot{V}O_2$ at AT can be used to predict postoperative morbidity and level of postoperative care in patients undergoing intra-abdominal surgery (morbidity with $\dot{V}O_2$ at AT of <10.1 $ml.kg^{-1}.min^{-1}$ and caution in cases where $\dot{V}O_2$ at AT <10.1–12$ml.kg^{-1}.min^{-1}$). Interestingly, Moran et al.[7] also recommended peak $\dot{V}O_2$ of 15$ml.kg^{-1}.min^{-1}$ as a predictor of 90-day survival in patients undergoing pancreatic surgery. Findings by Forshaw at el.[25] in patients undergoing oesophagectomy demonstrated a higher rate of cardiopulmonary complications in those with low peak $\dot{V}O_2$(19.2±5.1$ml.kg^{-1}.min^{-1}$), although mean difference in peak $\dot{V}O_2$ in those patients with and without cardiopulmonary morbidity was considered to be equivocal (2.3$ml.kg^{-1}$.min-1, 95%CI 0.06-4.5$ml.kg^{-1}.min^{-1}$;P=0.04).[10]

Our study is in line with other published data on the relationship between the duration of surgery and postoperative cardiopulmonary morbidity for both head and neck surgery[1,3] and surgery in general.[23,24,26] Cannandy et al.[1] demonstrated that patients who were exposed to extended surgical interventions in the head and neck area had a significantly higher rate of postoperative complications, independent of the extent of

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the surgical intervention.

Potential weaknesses of this study are its un-blinded nature and single-centre design. The un-blinded nature of this study may have contributed to confounding by indication and reduced recorded rates of postoperative morbidity as both anaesthetic and surgical teams were aware and may have acted upon the CPET results.

Conclusion

In this study, which is the first to investigate the role of CPET in predicting cardiopulmonary morbidity in patients undergoing major head and neck surgery, we demonstrated that peak $\dot{V}O_2$ of $12.3ml.kg^{-1}.min^{-1}$ could be used as a risk stratification threshold to predict cardiopulmonary complications in the postoperative period. As postoperative morbidity in head and neck surgery remains high, further studies assessing the role of perioperative factors (both CPET and non-CPET derived) are crucial in the effort to reduce complication rates in patients undergoing major head and neck surgery.

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Figure 1 Receiver operating curve for the multivariable logistic regression

Figure 2 Kaplan-Meir survival curves for the length of stay in the ICU or HDU dichotomised at the optimal cut-off points for $\dot{V}O_2$ at anaerobic threshold (Cum Survival – cumulative survival)

Figure 3 Kaplan-Meir survival curves for the length of stay in the ICU or HDU dichotomised at the optimal cut-off points for peak $\dot{V}O_2$. (Cum Survival – cumulative survival)

	Overall	No cardiopulmonary morbidity at day 5	Cardiopulmonary morbidity at day 5	P Value
Number (%)	187	68 (36.4)	119 (63.6)	
Age, years	58.2 (13.7)	58.5 (14.0)	58.1 (13.6)	0.81
Body mass index (BMI), kg/m2	25.2(22.8-28.9)	25.1 (22.0-28.7)	25.7 (23.0-29.2)	0.77
Resting heart rate, bpm	76.0 (67.0-86.0)	72.0 (64.2-84.0)	78.0 (70.0-88.0)	0.0079
Gender				
Male (%)	117 (63.1)	47 (70.1)	70 (58.3)	
Female (%)	70 (36.9)	20 (29.9)	50 (41.7)	0.12
ASA				
ASA II (%)	115 (61.5)	49 (75.4)	66 (58.9)	
ASA III (%)	62 (33.1)	16 (24.6)	46 (41.2)	0.03
Operation time, minutes	675.0 (553.0-795.0)	607.5(473.3-706.0)	726.0 (595.0-837.0)	<0.0001
Operation type				
Resection followed by reconstruction with a free flap (%)	114 (61.0)	36 (52.9)	78 (65.5)	
Resection followed by reconstruction with a pedicled flap (%)	21 (11.2)	6(8.8)	15 (12.6)	
Resection and reconstruction with local tissue only (%)	39 (20.9)	18 (26.5)	21 (17.6)	
Reconstruction only (%)	13 (7.0)	8 (11.8)	5 (4.2)	

Table 1 Demographic and surgical data presented as median (25th -75th percentile), mean (SD) or frequency (%). P values were obtained using Mann-Whitney, independent samples t-test or Fisher's exact tests.

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	Overall	No cardiopulmonary morbidity at day 5	Cardiopulmonary morbidity at day 5	P Value
Peak VO_2 ($ml.kg^{-1}.min^{-1}$)	14.7 (9.2-18.9)	16.0 (14.0-19.7)	11.4 (8.4-18.0)	<0.0001
VO_2 at anaerobic threshold ($ml.kg^{-1}.min^{-1}$)	11 (9.7-13)	11.5 (10.5-13.0)	10.6 (9.1-13.1)	0.03
VE/VCO_2 at anaerobic threshold	31.1 (27.9-34.8)	31.7(28.8- 35.2)	31.1 (27.6-34.7)	0.34

Table 2 CPET variables presented as median (25th -75th percentile). P values were obtained using Mann-Whitney test.

	Beta coefficient	SE coefficient	P value	OR	95% CI for OR
Peak VO_2	-0.080	0.027	0.003	0.923	(0.876-0.927)
Operation time	0.003	0.001	0.002	1.003	(1.001-1.005)
ASA grade	0.726	0.366	0.047	2.067	(1.009-4.233)

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Formatted Table

Table 3 Probability of developing day five postoperative cardiopulmonary complications using multivariable logistic regression (Nagelkerke R square 0.172); Beta coefficient, unstandardised beta coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

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