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Safety and feasibility of cardiopulmonary exercise testing in head and neck cancer survivors

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Abstract

Purpose: Assess safety and feasibility of the cardiopulmonary exercise test (CPET) for evaluating head and neck cancer (HaNC) survivors. Also compare their cardiorespiratory fitness to age and sex-matched norms and establish current physical activity levels.

Methods: Fifty HaNC survivors [29 male; mean (*SD*) age, 62 (8) years], who had completed treatment up to 1 year previously, were recruited. Participants performed a CPET on a cycle ergometer to symptom-limited tolerance. Participants completed a questionnaire to report contributory factors they perceived as influencing test termination. Physical activity levels were determined using a self-reported physical activity questionnaire.

Results: Three participants did not complete the CPET because (1) poor fitting mouthpiece and naso-oral mask due to facial disfiguration from surgery; (2) knee pain elicited by cycling; and (3) early CPET termination due to electrocardiogram artefacts. Participants reached a mean peak oxygen uptake that was 34% lower than predicted and the mean (*SD*) CPET duration of 7:52 (2:29) min:s was significantly lower than the target test duration of 10 min ($p < 0.001$). Leg muscle aches and/or breathing discomfort were major contributory factors influencing test termination for 78% of participants, compared to 13% for dry mouth/throat and/or drainage in the mouth/throat. No major adverse events occurred. Participants were categorised as 26% active, 8% moderately active, and 66% insufficiently active.

Conclusion: These preliminary data suggest the CPET appears safe and feasible for most HaNC survivors when strict exclusion criteria are applied; however, low levels of cardiorespiratory fitness should be considered when calculating an appropriate ramp rate.

KEYWORDS

cardiorespiratory fitness, CPET, CPX, oncology, peak oxygen uptake, risk

1 | INTRODUCTION

Head and neck cancer (HaNC) and its treatment are often associated with a high symptom burden, including weight loss, fatigue, intolerance to physical activity, shoulder and neck dysfunction, head and neck oedema, dry mouth, mouth sores, trismus, dysphagia, pain, depression, and reduced health-related quality of life (Haisfield-Wolfe et al., 2012; Lokker et al., 2013). Exercise programmes undertaken during and/or post-treatment can have positive effects on HaNC survivors, such as improvements in lean body mass, levels of fatigue, physical functioning, and health-related quality of life (Bye et al., 2020; Lynch et al., 2021). The cardiopulmonary exercise test (CPET) provides important information for determining the appropriateness of referring someone to an exercise programme, informing the content and evaluating the efficacy of that programme (ATS/ACCP, 2003), giving cancer survivors insight into their physical limitations, and setting a baseline for motivating them to exercise (Knutsen et al., 2006). Other indications relevant to HaNC survivors include assessing fitness for surgery and evaluating exercise intolerance and unexplained dyspnoea (ATS/ACCP, 2003). Despite the considerable potential benefits of conducting CPET with HaNC survivors, currently this is typically not a routine procedure in this population.

A CPET involves progressive increments in work rate where the participant is encouraged to exercise until symptom-limited tolerance, during which minute ventilation, pulmonary gas exchange, blood pressure, electrocardiogram (ECG), and oxyhaemoglobin saturation are measured. The CPET is a non-invasive global assessment of the pulmonary, cardiovascular, hematopoietic, skeletal muscle, and neuropsychological systems while experiencing maximal physiological strain, which makes it a unique clinical procedure (ATS/ACCP, 2003). Moreover, it is considered the most reliable and objective assessment of functional capacity (Robson et al., 2016) and regarded as the gold standard measure of cardiorespiratory fitness (ATS/ACCP, 2003). Limited research suggests that conducting CPETs with survivors of various cancers, such as breast and lung (Jones et al., 2007), and prostate (Wall et al., 2014) is relatively safe and feasible. A recent study investigated the utility of the CPET for perioperative risk assessment in HaNC survivors and observed that lower cardiorespiratory fitness predicts day 5 cardiopulmonary morbidity (Lalabekyan et al., 2021). To our knowledge, however, no study has investigated the safety and feasibility of CPET in HaNC survivors beyond the perioperative period (which extends from the moment of contemplation of treatment through to recovery at home), or after treatment with (chemo)radiotherapy.

An important issue is that peak physiological values obtained from the CPET are supposed to represent the limits of oxygen transport and any factors that result in early test termination (i.e., not related to cardiorespiratory endurance) can potentially invalidate results (ATS/ACCP, 2003). Many unique post-treatment symptoms are the most cited barriers to exercise by HaNC survivors, such as dry mouth and throat, difficulty swallowing, drainage in the mouth and throat, and shoulder weakness and pain (Midgley et al., 2018). Some symptoms can last over 1-year post-treatment (Wulff-Burchfield et al., 2019) and might prove problematic in regards the feasibility of completing a CPET. The maximal nature of a CPET also means the risk of an adverse event is increased compared to rest or a submaximal exercise test. Therefore, the main aim of the present study was to establish the safety and feasibility of CPET for evaluating a heterogenous group of HaNC survivors tested up to 1-year post-treatment. This information should provide insight into the appropriateness of the CPET for consideration as an assessment tool for HaNC survivors and highlight potential issues that may arise that test administrators need to consider. Secondary aims were to compare the cardiorespiratory fitness of HaNC survivors to age and sex-matched norms and establish HaNC survivors' physical activity levels.

2 | METHODS

2.1 | Participants

Fifty HaNC survivors were recruited over a 13-month period to undertake a single CPET. Inclusion criteria were: (1) previous diagnosis of a head and neck squamous cell carcinoma treated with curative intent at Aintree University Hospital, located in Liverpool in the UK; and (2) aged ≥18 years old. Exclusion criteria were: (1) patients that had a laryngectomy; and (2) presence of absolute contraindications to CPET according to American Thoracic Society/American College of Chest Physicians guidelines (ATS/ACCP, 2003). The latter included patients with severe ischaemic heart disease or heart failure, stages IV–V chronic kidney disease, uncontrolled hypertension, those unable to consent such as patients with cognitive impairment, and those with severe musculoskeletal disease such as back, hip, and knee arthritis. Recruitment involved sending eligible patients a letter containing information about the study 2 weeks before their next routine clinical review at the hospital. A clinical trials nurse discussed the study with patients during the clinical review. The study received favourable opinion from the Cambridge South NHS Research Ethics Committee (Ref. 15/EE/0429) and all patients provided written informed consent before participating in any study procedures.

2.2 | Overview or procedures

All testing was conducted in the CPET laboratory at Aintree University Hospital, which is the largest centralised HaNC unit in the UK, and where CPET is not routinely conducted with HaNC survivors. Upon arrival to the laboratory, each participant's height and body mass were measured using a wall stadiometer (The Leicester Height Measure, Seca Birmingham, UK) and electronic scales (model 799; Seca gmbh & Co.), respectively. Participants then performed a forced vital capacity test using standardised procedures (Miller et al., 2005) to determine forced vital capacity and forced expiratory volume in 1 s. A CPET was then performed that conformed to the joint procedural guidelines of the American Thoracic Society

and the American College of Chest Physicians (ATS/ACCP, 2003). Participants then completed a questionnaire to establish what they perceived as the major and minor contributory factors that influenced the decision to terminate the CPET. This questionnaire has previously been used with apparently healthy individuals and designed primarily based on the responses from semi-structured interviews (Midgley et al., 2017), but was adapted for HaNC survivors using research that reported physical symptoms and barriers to exercise in this population (Haisfield-Wolfe et al., 2012; Lokker et al., 2013; Midgley et al., 2018). The level of weekly physical activity within the 7 days immediately before testing was established for each participant using a self-reported physical activity questionnaire (Godin & Shephard, 1985). The weekly Leisure-time Activity Score was calculated for each participant using the weekly frequencies of strenuous, moderate, and mild physical activity from the questionnaire responses, as follows: (9 × Strenuous) + (5 × Moderate) + (3 × Mild). A weekly Health Contribution Score also was calculated for each participant as follows: (9 × Strenuous) + (5 × Moderate). Health Contribution Scores were then classified according to expected health-related benefits: ≥24 units = active (substantial benefits); 14–23 units = moderately active (some benefits); and <14 units = insufficiently active (less substantial or low benefits) (Godin, 2011).

Participants were instructed to refrain from exercise on the day of the CPET, abstain from smoking for at least 8 h before the test, ingest a light meal no less than 2 h before the test, and to take any medications as prescribed (ATS/ACCP, 2003). Participants also were advised on appropriate clothing and footwear suitable for exercise participation and to arrive at the laboratory wearing this attire.

2.3 | Cardiopulmonary exercise test

All CPETs were performed on an electronically braked cycle ergometer (Ergoselect 200; Ergoline GmbH). Participants first sat stationary on the ergometer for 3 min for baseline physiological measurements, followed by a 3-min warm-up consisting of unloaded cycling, and then small work rate increments every 5 s. An appropriate work rate increment was calculated using the guidelines of Cooper and Storer (2001) and was that which predicted the achievement of peak work rate in 10 min during the ramp-incremented portion of the CPET. The CPET stopped when either the participant volitionally terminated the test, or the test administrator stopped the test due to safety concerns (ATS/ACCP, 2003). Twelve-lead ECG (ECGpro®, AMEDTEC Medizintechnik Aue GmbH) and oxyhaemoglobin saturation (Oxystik pulse oximeter, Geratharm Respiratory GmbH) were recorded continuously at baseline and throughout the CPET. Blood pressure by auscultation (Accoson sphygmomanometer, A.C. Cossor & Son Ltd.) was measured immediately before the participant started cycling, at the end of the 3 min of unloaded cycling, when the respiratory exchange ratio approximated 1.00 during the incremental portion of the CPET, and immediately upon CPET termination.

Minute ventilation and pulmonary gas exchange were determined breath-by-breath using an automated open-circuit gas analysis system (Ergostik, Geratherm Respiratory GmbH) connected to a silicone oro-nasal face mask (Hans Rudolph Inc.). The gas analysers were calibrated immediately before and after each CPET using ambient air and certified standard gases containing 15% oxygen and 5% carbon dioxide, balanced with nitrogen. A 3-L syringe (Series 5530; Hans Rudolph Inc.) was used to verify that the turbine was functioning within the manufacturer-defined acceptable limits immediately before each CPET. Due to the relatively high levels of inherent random variability in breath-by-breath ventilatory responses, peak values of the rate of pulmonary oxygen uptake ($\dot{V}O_{2peak}$), minute ventilation, respiratory exchange ratio, and oxygen pulse were regarded as the highest 30-s time-averaged values in accordance with American Thoracic Society/American College of Chest Physicians guidelines (ATS/ACCP, 2003). Peak work rate and heart rate were regarded as the last recorded values for a completed 5 s work rate stage. The lowest 30-s time-averaged oxyhemoglobin saturation also was recorded. Relative $\dot{V}O_{2peak}$ was compared to age and sex-matched reference values for apparently healthy non-smokers calculated using the equation of de Souza e Silva et al. (2018). The American College of Sport Medicine guidelines were used to categorise cardiorespiratory fitness level according to sex and age (Liguori et al., 2022). Ventilatory reserve was defined as the difference between the peak minute ventilation and maximal voluntary ventilation (predicted from the forced expiratory volume in 1 s × 35; ATS/ACCP, 2003), and was expressed as a percentage. Exertional dyspnoea and leg discomfort were evaluated at 1-min intervals during the ramp-incremented portion of the CPET using Borg's Category-Ratio (CR10) Scale (Borg, 1998). Participants were given detailed verbal instructions before the CPET on how to interpret this scale. Participants were observed for at least 15 min after CPET termination and ECG, blood pressure, and pulse oximetry were monitored for the first 5 min 30 s to 7 min 30 s of this observation period. The longer monitoring period in some participants reflects that the blood pressure had not decreased sufficiently at the time of the first measurement, and a further measurement was taken. The change in heart rate at peak work rate during the CPET to 1 min into the recovery period was calculated, since a reduction of ≤12 beats·min^{-1} has been shown to be a powerful predictor of overall mortality (Cole et al., 1999).

Traditional $\dot{V}O_{2max}$ criteria were not applied given their apparent limitations and lack of validity (Martin-Rincon & Calbet, 2020; Midgley et al., 2009; Poole et al., 2008). The term 'peak' has been used when reporting physiological values, as no assumption has been made that the data reflect maximal physiological values (Meyer et al., 2005). The CPET outcome variables are reported in accordance with published clinical oncology guidelines (Jones et al., 2008).

2.4 | Statistical analyses

All data were analysed using SPSS statistical analysis software (Released 2017. IBM SPSS Statistics for Windows, Version 25.0.

Armonk, NY: IBM Corp.). Descriptive statistics are reported as the mean and standard deviation for normally distributed data and as the median and interquartile range (or range) for non-normally distributed data. Differences between the observed $\dot{V}O_{2peak}$ values versus predicted $\dot{V}O_{2\,max}$ derived from age and sex-matched reference values for apparently healthy non-smokers (de Souza e Silva et al., 2018) were analysed using paired samples *t* tests. The effect of sex, smoking status, TNM staging, World Health Organisation performance status, and the Adult Comorbidity Evaluation (ACE-27) score on the percentage of predicted $\dot{V}O_{2\,max}$ attained were analysed using factorial between-subjects analysis of variance (ANOVA). The ANOVA effect sizes are reported as partial eta squared (η^2). Sidak-adjusted p values are reported for multiple post hoc comparisons. The relationship between the percentage of predicted $\dot{V}O_{2\,max}$ attained and the Leisure-time Activity Scores was investigated using the Spearman rank correlation coefficient given the non-linear relationship. Sex differences between the Leisure-time Activity Score and Health Contribution Score were analysed using Mann-Whitney U Tests due to non-normal distributions. All statistical assumptions were checked using standard methods (Grafen & Hails, 2002). Two-tailed statistical significance was accepted as $p < 0.05$.

3 | RESULTS

3.1 | Participant characteristics

Table 1 shows summary statistics for participant characteristics, clinical information, timing of the CPET, and physical activity levels for the 50 participants. Only two participants were medicated with beta-blockers, and none were medicated with other drugs known to lower heart rate, such as ivabradine and non-dihydropyridine calcium channel blockers. Notable differences were observed between males and females for TNM staging and treatment. For example, only 14% of females in the sample were TNM stage 4 compared to 38% of males. Also, only 5% of females underwent surgery with post-operative radiotherapy compared to 38% of males. The number of days between treatment and presenting for the CPET were not significantly different between males and females ($Z = 0.2$, $p = 0.82$). Twenty six percent of the participants were categorised as active, 8% as moderately active, and 66% as insufficiently active. No significant differences were observed between males and females for the Leisure-time Activity Score ($Z = 0.6$, $p = 0.52$) or Health Contribution Score ($Z = 0.4$, $p = 0.67$).

3.2 | Safety

No major adverse events occurred during or within 15 min after CPET termination. The CPET of one participant with a muscle tremor was terminated early by the test administrator for safety reasons, since the ECG response could not be properly monitored due to tremor-related movement artefacts.

3.3 | Feasibility

Data for three participants were not included in the analysis of CPET responses. One participant did not start the test because facial disfiguration meant he could not seal his lips around the mouthpiece, and a naso-oral mask would not fit properly. Surgery had left exposed metal from the cheek and a gap continually present between the lips. One participant could not complete the CPET as knee pain was elicited as soon as she started cycling. The CPET of the third participant was terminated early due to not being able to properly monitor the ECG, as detailed above in the 'Safety' section. The mean (*SD*) CPET duration of 7:52 (2:29) min:s for the 47 participants that exercised to their limit of tolerance was significantly lower than the target test duration of 10 min based on the prediction equation of Cooper and Storer (mean difference = −2.2 min, 95% confidence interval [CI] = −2.8, −1.4, $p < 0.001$).

Table 2 shows the factors that 47 participants perceived as contributing to them volitionally terminating the CPET. There were 21 different factors among the cohort that contributed to test termination. The most common major contributory factor was muscle aches in the legs, cited by 70% of the participants, followed by breathing discomfort/breathlessness (32%). In regards factors specific to HaNC, 13% of participants cited dry mouth and throat and/or drainage in the mouth and throat as major contributory factors. No participants terminated the test due to concerns about their safety, although one participant was concerned she would vomit, but this was only cited as a minor contributory factor.

3.4 | CPET response

Table 3 shows the mean (*SD*) resting, peak, and recovery CPET responses. The mean (*SD*) $\dot{V}O_{2peak}$ of 18.6 (5.7) $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ was significantly lower than the mean (*SD*) predicted $\dot{V}O_{2\,max}$ of 28.3 (7.6) $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ based on age and sex (mean difference = −9.7; 95% CI = −11.9 to −7.5; $p < 0.001$). Significant effects were observed for sex ($F = 5.7$, $p = 0.022$, partial $\eta^2 = 0.12$), smoking status ($F = 12.0$, $p = 0.001$, partial $\eta^2 = 0.23$), and TNM staging ($F = 3.7$, $p = 0.019$, partial $\eta^2 = 0.22$) for the percentage of predicted $\dot{V}O_{2\,max}$ that was attained. Males reached a lower percentage of predicted $\dot{V}O_{2\,max}$ than females (58.3% vs. 70.9%, mean difference = −12.6, 95% CI = −23.3 to −2.0, $p = 0.022$). According to American College of Sports Medicine guidelines, the average female was classified as having 'fair' cardiorespiratory fitness and the average male as 'very poor'. Regarding TNM staging, the mean percentages of predicted $\dot{V}O_{2\,max}$ attained were 67.5% for stage 1, 75.7% for stage 2, 64.6% for stage 3, and 50.4% for stage 4. Participants at TNM stage 4 scored significantly lower than for stage 2 (mean difference = −25.3, 95% CI = −48.4 to −2.2, $p = 0.026$), whereas paired comparisons between other stages were not statistically significant ($p \geq 0.057$). Current smokers attained significantly lower percentages of their predicted $\dot{V}O_{2\,max}$ than non-smokers (54.3% vs. 74.9%, mean difference = −20.6, 95% CI = −32.7 to −8.6, $p = 0.001$). The

TABLE 1 Participant characteristics, clinical information, timing of cardiopulmonary exercise test (CPET), and physical activity levels

	Male (*n* = 29)	Female (*n* = 21)	Total (*n* = 50)
Participant characteristics (mean, *SD*)			
Age (year)	60 (7)	64 (9)	62 (8)
Height (m)	1.73 (0.060)	1.59 (0.065)	1.67 (0.093)
Body mass (kg)	76.5 (12.4)	66.0 13.7)	72.1 (13.8)
Body mass index (kg·m^2)	25.5 (3.8)	26.1 (5.1)	25.7 (4.4)
Smoking status (frequency)			
Current smoker	9	4	13
Quit smoking	8	2	10
Never smoked	11	15	26
Unknown	1	0	1
WHO performance status (frequency)			
0	20	16	36
1	3	1	4
2	1	1	2
9—unknown	5	3	8
ACE-27 comorbidity score (frequency)			
0—none	18	9	27
1—mild	3	7	10
2—moderate	1	0	1
9—unknown	7	5	12
Medications (frequency)			
Beta-blocker	2	0	2
Vasodilators[a]	4	7	11
Diuretic	1	3	4
Statin	4	2	6
Bronchodilator	3	4	7
Cancer site (frequency)			
Oral	11	12	23
Oropharyngeal	12	6	18
Laryngeal	5	2	7
Other	1	1	2
TNM staging (frequency)			
Stage 1	11	11	22
Stage 2	3	5	8
Stage 3	4	2	6
Stage 4	11	3	14
Treatment (frequency)			
Surgery	11	15	26
Surgery and post-operative radiotherapy	11	1	12
Chemoradiotherapy	5	2	7

(Continues)

TABLE 1 (Continued)

	Male (n = 29)	Female (n = 21)	Total (n = 50)
Surgery and post-operative chemoradiotherapy	2	3	5
CPET timing (median, interquartile range)[b]			
Days between treatment and presenting for CPET	182 (82)	166 (158)	182 (112)
Physical activity levels (median, interquartile range)			
Weekly Leisure-time Activity Score[c]	21 (30)	23 (32)	21 (29)
Health Contribution Score[d]	0 (20)	8 (34)	5 (28)

Abbreviations: ACE, adult comorbidity evaluation; CPET, cardiopulmonary exercise test; WHO, world health organisation.

[a]Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers. calcium channel blockers, and potassium channel activators.

[b]Data are for the 47 participants that completed the CPET.

[c]Calculated from strenuous, moderate, and mild intensity physical activity.

[d]Calculated only from strenuous and moderate intensity physical activity.

TABLE 2 Number of participants who stated specific reasons for test termination during the cardiorespiratory exercise test that were either a major contributory factor, a minor contributory factor, or a not a contributory factor (n = 47)

Reason	Contributory factor?		
	Major	Minor	No
Muscle ache in legs	33	9	5
Breathing discomfort/breathlessness	15	11	21
Muscle weakness	6	9	32
Lack of energy	5	13	29
Dry mouth or throat	5	7	35
Overall (whole body) feeling of exhaustion	4	7	36
Pain	3	3	41
Overall (whole body) feeling of discomfort	2	8	37
Drainage in mouth or throat	2	2	43
Buttock discomfort	0	6	41
Reached personal exercise goal	0	3	44
Lack of motivation to continue	0	2	45
Dizzy/light-headed	0	2	45
Concerned might aggravate a previous injury	0	2	45
Did not understand purpose of the test	0	2	45
Concerned might faint/black out	0	1	46
Boredom	0	1	46
Concerned might sustain a new injury	0	0	47
Concerned might make condition worse	0	0	47
Concerned might have a heart attack	0	0	47
Nausea/sick feeling	0	0	47
Coughing causing difficulty with exercise	0	0	47
Sweat in eye	0	0	47
Other[a]	2	2	43

[a]Reasons given under the open-ended 'other' category were as follows: Issues with leg surgery (major, n = 1), mask was hot and felt needed fresh air (major, n = 1), concerned would vomit (minor, n = 1), and issues with existing hernia (minor, n = 1).

TABLE 3 Mean (*SD*) resting and cardiopulmonary exercise test results ($n = 47$)

	Male ($n = 27$)		Female ($n = 20$)		Total ($n = 47$)	
Resting data						
Heart rate (beats·min^{-1})	79	(16)	85	(12)	82	(14)
Systolic blood pressure (mmHg)	129	(9)	126	(9.8)	127	(9)
Diastolic blood pressure (mmHg)	83	(7)	83	(6)	83	(7)
Oxyhemoglobin saturation (%)	99	(96–99)	99	(94–99)	99	(94–99)
Forced vital capacity (FVC) (L)	4.4	(0.8)	2.9	(0.7)	3.8	(1.1)[a]
Forced expiratory volume in 1 s (FEV_1) (L)	3.2	(0.8)	2.3	(0.6)	2.8	(0.8)[b]
FEV_1:FVC ratio	0.72	(0.12)	0.80	0.09)	0.75	(0.11)
Peak exercise data						
Test duration (min:s)	8:47	(2:33)	6:38	(1:48)	7:52	(2:29)
Power (W)	143	(50)	93	(29)	122	(49)
$\dot{V}O_2$ (L·min^{-1})	1.578	(0.41)	1.040	(0.285)	1.349	(0.521)
$\dot{V}O_2$ (ml·kg^{-1}·min^{-1})	20.2	(5.8)	16.5	(5.0)	18.6	(5.7)
Metabolic equivalents of task (METs)	5.8	(1.7)	4.7	(1.4)	5.3	(1.6)
Respiratory exchange ratio	1.18	(0.15)	1.17	(0.15)	1.17	(0.15)
Minute ventilation (L·min^{-1})	58.6	(23.3)	41.0	(11.8)	51.2	(21.0)
Ventilatory reserve (%)	47.1	(18.4)	47.4	(17.7)	47.2	(17.9)
Heart rate (beats·min^{-1})	137	(24)	137	(20)	137	(22)
Oxygen pulse (ml·beat^{-1})	12.1	(3.7)	7.8	(1.6)	10.3	(3.6)
Lowest oxyhemoglobin saturation (%)	99	(89–99)	99	(90–99)	99	(89–99)
Systolic blood pressure (mmHg)	164	(19)	157	(12)	161	(17)
Diastolic blood pressure (mmHg)	102	(9)	96	(7)	100	(9)
Dyspnea (CR10 scale)	4.9	(2.6)	4.3	(1.7)	4.7	(2.3)
Leg discomfort (CR10 scale)	5.3	(2.6)	5.3	(1.9)	5.3	(2.3)
Recovery data						
Heart rate at 5 min of recovery (beats·min^{-1})	98	18	97	15	98	17
Δ Heart rate at 1 min recovery (beats·min^{-1})[c]	21	6	22	10	21	8
Systolic blood pressure (mmHg)[d]	131	10	127	7	129	9
Diastolic blood pressure (mmHg)[d]	87	5	85	8	86	6

Note: Oxyhemoglobin saturation data were not normally distributed so are reported as the median and range. Three study participants are excluded (see body of text for reasons why).

[a]Mean (*SD*) % predicted 112.0 (17.9).

[b]Mean (*SD*) % predicted 104.9 (23.2).

[c]Calculated as the heart rate at peak work rate minus the heart rate at 1 min into recovery. 43 (25 male, 18 female) of the 47 participants achieved a reduction in heart rate of >12 beats·min^{-1} at 1 min of recovery.

[d]Measured at between 3 and 6 min into recovery. Measurements taken close to 6 min represent a second measurement taken during recovery because the blood pressure had not decreased sufficiently when the first measurement was taken.

percentage of predicted $\dot{V}O_{2\,max}$ that was attained was positively correlated with the Leisure-time Activity Scores ($r_s = 0.35$, $p = 0.017$). No significant differences were observed for the percentage of predicted $\dot{V}O_{2\,max}$ attained for participants with different World Health Organisation performance status ($F = 1.1$, $p = 0.34$) or ACE-27 scores ($F = 1.0$, $p = 0.38$).

4 | DISCUSSION

The main aim of the present study was to assess the safety and feasibility of undertaking CPET with HaNC survivors up to 1-year post-treatment. Secondary aims were to compare the cardiorespiratory fitness of HaNC survivors to age and sex-matched reference

values and establish HaNC survivors' physical activity levels. The main findings were that the CPET was feasible in all but 3 (6%) of the 50 participants, with 47 (94%) of the participants volitionally terminating the test due to symptom-limited tolerance. No serious adverse events occurred. Other findings were that HaNC survivors typically exhibited considerably lower cardiorespiratory fitness than age and sex-matched norms and had low levels of physical activity.

4.1 | Safety

No adverse events were observed during the CPET or the 15 min post-CPET observation period, including no ECG irregularities or abnormal blood pressure responses. This contrasts to the 5.9% incidence of adverse events reported for 85 advanced lung and breast cancer survivors during CPET, including three positive tests for myocardial ischemia, one exercise-induced right bundle branch block, and one patient where the CPET induced hip pain following the test that was later diagnosed as lytic metastasis (Jones et al., 2007). Another study reported a 3.2% incidence of adverse events for 95 prostate cancer survivors being treated with androgen deprivation therapy, which also were related to exercise-induced ST segment depression and right bundle branch block (Wall et al., 2014). The only notable safety issue that arose in the present study was early test termination by the test administrator due to one participant experiencing muscle tremor resulting in substantial ECG artefacts. These artefacts meant that the ECG could not be properly monitored in regards accurately establishing any changes in heart rhythm or ST-T changes, which is an absolute indication for early test termination according to American College of Sports Medicine guidelines (Liguori et al., 2022). Undertaking CPET with HaNC survivors that are up to 1-year post-treatment therefore appears safe when patients with absolute contraindications to CPET according to American Thoracic Society/American College of Chest Physicians guidelines (ATS/ACCP, 2003) are excluded from testing, although further data are required to support this finding.

4.2 | Feasibility

Overall, feasibility was good with 47 of the of the 50 participants completing the CPET. One participant could not undertake the CPET because of a HaNC-related issue, in which the oro-nasal mask and mouthpiece could not be fitted properly due to facial disfigurement. To save time and resources and avoid unnecessary patient burden it may be prudent to check the feasibility of using a mask or mouthpiece before referring HaNC survivors to CPET. Alternatively, a traditional exercise stress test could be performed if a patient presents with this issue on arrival to the laboratory, since exercise stress tests do not involve assessment of minute ventilation and pulmonary gas exchange. An exercise stress test also might be preferable for patients that have had a laryngectomy, due to the considerable technical issues associated with determining minute ventilation and pulmonary gas exchange in these patients (Overstreet et al., 2015).

There were 21 different factors that participants in the present study perceived as contributing to volitional termination of the CPET. The most common major contributory factor was muscle aches in the legs, cited by 70% of the participants, followed by breathing discomfort/breathlessness (32%). Myers et al. (1992) reported 73% for general or leg fatigue and only 14% for breathlessness. The difference between studies relating to breathing could be due to random variability, although another plausible explanation is that Myers et al. (1992) used treadmill testing and involved apparently healthy participants that were, on average, 16 years younger than the cohort in the present study. Dry mouth or throat was the most common perceived barrier of 36 barriers to engagement in exercise cited by HaNC survivors, with 40% of participants perceiving them as 'often' or 'very often' being a barrier to exercise (Midgley et al., 2018). High minute ventilation and the effects of the silicone orofacial mask might predispose HaNC survivors to mouth and throat drying during a CPET, especially considering fluid cannot be ingested during this time. However, only 5 (10%) of the participants in the present study reported dry mouth and throat as a major contributory factor for CPET termination. This could be due to the relatively low CPET duration that might somewhat mitigate the risk of mouth and throat drying when compared to more prolonged bouts or exercise performed as part of a training programme. Shoulder weakness and/or pain was the sixth most common perceived barrier to exercise (Midgley et al., 2018), however, no participants in the current study cited this as a factor influencing test termination. This may be explained by the focus on lower body musculature during a cycling CPET. It is possible that performing the CPET on a treadmill would have altered these results due to the greater involvement of upper body musculature.

4.3 | CPET responses

The mean observed $\dot{V}O_{2peak}$ was 9.7 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ (34%) lower than the predicted $\dot{V}O_{2\,max}$ based on age and sex-matched reference values for apparently healthy non-smokers (de Souza e Silva et al., 2018), which was similar to the 33% lower value reported by Jones et al. (2007) for advanced lung and breast cancer survivors. The 9.7 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$ mean difference observed in the present study is equivalent to 2.8 metabolic equivalents (METs; when considering 1 MET as a standardised value of 3.5 $ml{\cdot}kg^{-1}{\cdot}min^{-1}$). Notably, each 1 MET increase in cardiorespiratory fitness is associated with a 13% and 15% reduction in all-cause mortality and cardiovascular events, respectively, in apparently healthy men and women (Kodama et al., 2009). Although the association between cardiorespiratory fitness and mortality in HaNC survivors has not been established, a strong negative association has been established in many other clinical populations and is potentially a stronger predictor of mortality than established risk factors such as smoking, hypertension, high cholesterol, and type 2 diabetes (Ross et al., 2016). Physical fitness,

as measured by the International Fitness Scale, also has been shown to be an important predictor of quality of life in HaNC survivors (Ortiz-Comino et al., 2022).

The TNM staging and whether the participant currently smoked had a significant effect on the percentage of predicted $\dot{V}O_{2\,max}$ that was attained. Notably, the mean $\dot{V}O_{2peak}$ of those with TNM stage 4 and current smokers was only 17.1 and 16.0 ml·kg^{-1}·min^{-1}, respectively. These levels of cardiorespiratory fitness are insufficient to undertake some activities of daily living and many recreational activities, especially considering these activities are invariably performed at an intensity below that which elicits $\dot{V}O_{2peak}$ (Ainsworth et al., 2011). Smoking cessation interventions are clearly particularly important in this population given their already compromised cardiorespiratory fitness unrelated to smoking. Regarding the methodological aspects of conducting CPETs with HaNC survivors, the ramp rate of the CPET should ideally be adjusted on an individual basis to account for the lower $\dot{V}O_{2peak}$ to help achieve the recommended target test duration of around 10 min (ATS/ACCP, 2003), since the ramp rate is typically determined using predicted $\dot{V}O_{2\,max}$ (ATS/ACCP, 2003). This is particularly important for those classified as TNM stage 4 and those who smoke, given their significantly lower $\dot{V}O_{2peak}$.

How many participants in the present study attained $\dot{V}O_{2\,max}$ is unknown. The term $\dot{V}O_{2peak}$ has been reported, as this indicates that no assumption has been made about participants attaining $\dot{V}O_{2\,max}$ during the CPET (Meyer et al., 2005). An important issue is that there are currently no robust methods to establish with a sufficient level of confidence that $\dot{V}O_{2\,max}$ has been attained. Traditionally, a plateau in the $\dot{V}O_2$ response at the end of the CPET has been regarded as the primary criterion (Midgley et al., 2007). The validity of this criterion is questionable, however, since many participants do not exhibit a $\dot{V}O_2$ plateau despite an apparent maximal effort (e.g., Doherty et al., 2003; Rossiter et al., 2006). One study even reported that more participants exhibited an accelerated $\dot{V}O_2$ response (27%) than plateau-like behaviour (17%) at the end of a CPET (Day et al., 2003). In the absence of a $\dot{V}O_2$ plateau, secondary criteria have been used that are based on participants attaining arbitrary thresholds for peak values of the respiratory exchange ratio, heart rate, and post-exercise blood lactate concentration (Midgley et al., 2007). Secondary criteria also have questionable validity since there is a large inherent inter-individual variation in the maximal values that individuals can attain for each of these variables and the criterion thresholds often can be satisfied well before $\dot{V}O_{2peak}$ has been attained (Midgley et al., 2009; Poole et al., 2008). Due to the limitations in establishing whether $\dot{V}O_{2\,max}$ has been attained, it could be argued that the percent predicted $\dot{V}O_{2\,max}$ values reported in the present study have questionable validity. However, it is important to appreciate that the study from which the predicted $\dot{V}O_{2\,max}$ values were derived also was subject to the same limitations in establishing whether 'true' $\dot{V}O_{2\,max}$ values were attained. The mean peak ratings of perceived exertion during the CPET of around 5 was relatively low, which could indicate that some participants gave a poor effort, since patients typically stop exercise at ratings of 5–8 (ATS/ACCP, 2003). This discrepancy might be explained by the fact that the present study used differential perceived exertion (i.e., dyspnoea and leg discomfort) rather than whole body exertion. Notably, the mean peak respiratory exchange ratio of 1.17 indicates substantial lactic acidosis and suggests a good effort when considering the cohort overall (ATS/ACCP, 2003).

4.4 | Physical activity levels

Low levels of physical activity were observed in the present study. Similarly low levels have been reported in previous studies for HaNC survivors in the United States (Rogers et al., 2006), Netherlands (Douma et al., 2020) and Sweden (Karczewska-Lindinger et al., 2021). Moreover, the physical activity levels of HaNC survivors have been found to be significantly lower post-treatment compared to pre-treatment (Sammut et al., 2016). The Health Contribution Score for each participant in the present study highlighted that 26% of the participants were categorised as active, 8% as moderately active, and 66% as insufficiently active. Based on these data, two-thirds of participants were insufficiently physically active to gain appreciable health benefits (Godin, 2011), although the real figure may be more than this. For logistical reasons, a self-reported physical activity questionnaire was used in the present study and participants tend to over self-report the amount of physical activity they perform compared to when an objective measure such as accelerometery is used to assess physical activity levels (Troiano et al., 2008). Since the least active and deconditioned people tend to reap the greatest health benefits from increases in physical activity (Celis-Morales et al., 2018), these results highlight that even modest increases in physical activity could considerably positively impact the health of most HaNC survivors.

4.5 | Strengths and weaknesses

To our knowledge, this is the first study to investigate CPET in HaNC survivors after the perioperative period and provides preliminary data on the safety and feasible of conducting a CPET within 1 year after completing treatment. The study also provides data on the cardiorespiratory fitness of HaNC survivors and adds further data to the literature regarding the physical activity levels of HaNC survivors. The study included a modest sample size of 50 participants, however, and further research is required to add more published data on the safety and feasibility of the CPET in HaNC survivors.

In conclusion, although previous research has reported that HaNC specific issues are perceived by many HaNC survivors as major barriers to exercise, only 1 of the 50 participants in the present study could not undertake the CPET due to a HaNC specific issue. HaNC specific issues were, however, perceived as major contributors to test termination for seven of the participants, although it is unclear how much this affected the participants' exercise tolerance. For most HaNC survivors, CPET appears safe and feasible, however,

calculations of the target test time should be adjusted to account for smoking status, TNM staging, and physical activity levels to help ensure adequate CPET data are obtained to promote quality assurance in test interpretation. The poor physical fitness of most of the participants highlights the need for greater efforts to promote physical activity in HaNC populations.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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