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Factors influencing exercise performance in thoracic cancer

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Summary

Background: Patients with incurable thoracic cancer often complain of a reduced ability to exercise, but the cause of this has been little studied. Thus, we have explored how various physiological and psychological factors relate to exercise performance in this group.

Methods: Inspiratory muscle strength, peripheral muscle power, lung function and mastery over breathlessness were assessed using sniff nasal inspiratory pressure, leg extensor power, simple spirometry and the mastery domain of the Chronic Respiratory Disease Questionnaire respectively. Exercise performance was assessed using the Incremental Shuttle Walking Test (ISWT) during which patients wore a K4 b^2 system permitting measurement of resting and breakpoint heart rate, minute ventilation (VE) and oxygen uptake (VO_2). Relationships between ISWT distance and the four factors were determined using correlation and β regression coefficients.

Results: Forty-one patients (21 male, mean (SD) age 64 (8) years) walked a median [IQR] of 320 [250–430] metres and reached a mean (SD) of 76 (10), 77 (25), and 48 (14) of their percent predicted maximum heart rate, VO_2, and VE respectively. Exercise performance was significantly associated only with inspiratory muscle strength ($r = 0.42$, $P < 0.01$) and peripheral muscle power ($r = 0.39$, $P = 0.01$). These factors were also significant determinants of exercise performance (β coefficients [95%CI] 1.77 [0.53, 3.01] and 1.22 [0.31, 2.14] respectively).

Conclusion: Of the factors examined, only inspiratory and peripheral muscle performance were significantly related to and predictive of exercise performance. Rehabilitation interventions which include inspiratory and peripheral muscle training are worth exploring further in this group of patients with thoracic cancer.

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Introduction

Patients with incurable thoracic cancer often complain of a reduced ability to exercise which can impede levels of physical activity, independence and quality of life.[1,2] It is generally assumed that this mainly results from the cancer interfering with the normal ventilatory function of the lungs, chest wall or diaphragm, particularly as exertional breathlessness is also common.[3–5] However, there has been little formal study in this group and this assumption may or may not be correct. For example, in patients with chronic obstructive pulmonary disease, who also have impaired ventilation and experience breathlessness, quadriceps muscle strength is the strongest predictor of exercise performance.[6,7]

Our group is interested in developing rehabilitation interventions for patients with incurable thoracic cancer, to be offered soon after diagnosis, alongside or following initial anticancer therapy, with the aim of maintaining reasonable levels of physical activity and independence for as long as possible. Identifying appropriate interventions will be informed by a greater understanding of the factors which influence exercise performance. Thus, this study examines how inspiratory and peripheral muscle function, simple spirometry and feeling of mastery relate to exercise performance in this group of patients.

Methods

Patients with incurable thoracic cancer and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 reporting a subjective reduction in ability to undertake their usual activities since their diagnosis of cancer were recruited from outpatient clinics at Nottingham University Hospitals NHS Trust. Patients were excluded if a palliative intervention was appropriate to improve their exercise capacity, e.g. drainage of a pleural effusion, they had ischaemic heart disease, pain affecting their ability to walk, or if they had received chemotherapy or radiotherapy within the last 4 weeks. Those with chronic obstructive pulmonary disease (COPD) were included if this was clinically stable and not considered to be responsible for their recent decrease in exercise capacity. The dose of any drugs that may have affected the ability to exercise had to have been stable for at least one week. All provided written informed consent and the study was approved by the Hospital Ethics Committee (EC99/45).

Measurements

Inspiratory muscle strength

Assessed by measuring sniff nasal inspiratory pressure (SNIP) with the patient standing, using a modified PK Morgan Pmax monitor (PK Morgan, Rainham, Kent, UK). With a closed mouth, the patient takes 10 short, sharp sniffs using maximal effort with one nostril occluded by a nasal pillow attached to a syringe barrel which is connected via a line to the pressure transducer. The highest value obtained was expressed as a percentage of the predicted normal value, adjusted for age and sex, and used for analysis.[8–10]

Peripheral muscle power

Assessed using a purpose built leg extensor power (LEP) rig, consisting of a seat and a footplate connected through a lever and a chain to a flywheel.[11] The patient, in a seated position with folded arms, applies maximum force with their dominant leg to push the footplate away from 60° knee flexion into full extension and accelerate the flywheel from rest. The final angular velocity of the flywheel is measured by an opto-switch and used to calculate average leg extensor power, expressed as Watts/kilogram body weight (W/kg). After 2–3 practice attempts for familiarisation purposes, 10 pushes were undertaken with standardised verbal encouragement and the maximum value used for analysis. In a large sample of healthy older ($\geq$50 years) men and women, mean (SD) values of 3.1 (1.1) and 2.0 (0.8) W/kg respectively have been recorded, with power declining with age.[12]

Simple spirometry

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured as the best of three measurements within 100 ml using a dry wedge spirometer (Vitalograph Type R Spirometer, Buckingham UK) with the patient seated. Results were expressed as absolute (Litres, L) and percent predicted values, adjusted for age and sex, and the FEV_1:FVC ratio calculated.

Mastery

Assessed using the Chronic Respiratory Disease Questionnaire (CRDQ). This consists of 20 items covering four dimensions: dyspnoea, fatigue, emotion and mastery. Four questions make up the mastery dimension, with answers selected from a 7-point categorical scale. Each answer is scored numerically and summated to give a total score for the dimension. Scores range from 4 to 28, with a higher score indicating greater level of mastery.[13]

Exercise performance and ventilation, oxygen uptake, heart rate, blood gases and symptoms limiting exercise

Exercise performance was assessed using the Incremental Shuttle Walking Test (ISWT; Department of Respiratory Medicine, Glenfield Hospital, Leicester, UK).[14] The patient walks around a 10 m 'shuttle' course defined by two marker cones at a speed dictated by audio signals from a calibrated tape cassette. The test speed increases every minute until the patient reaches their breakpoint, defined as the point at which the patient is unable to continue or cannot maintain the required walking speed. Testing was also stopped if the patient exceeded their maximum predicted heart rate. The total distance walked to the last fully completed 10 m shuttle was recorded.

Ventilation, oxygen uptake and heart rate were measured using a COSMED K4 b^2 (COSMED, Rome, Italy).[15] This lightweight (800 g, including battery) portable telemetric gas analysis system is worn by the patient in a harness. Respiratory flow and volume are measured by the patient breathing through a tightly fitting facemask containing a 28 mm diameter bi-directional digital turbine flowmeter (resistance, flow range, ventilation range, volume resolution, accuracy of $<$0.7 cm H_2O L s^{-1} at 12 L s^{-1}, 0–20 L s^{-1}, 0–300 L min^{-1}, 4 mL, $\pm$2% respectively). Oxygen uptake is assessed breath by breath using a thermostated oxygen analyser (range, accuracy, response time 7–24%, 0.02%, <160 msec respectively). Before use, the flowmeter and oxygen analyser were calibrated using a 3 L syringe and cylinder air respectively in accordance with the manufacturer's instructions.

Heart rate was measured using a wireless double electrode heart rate monitor on a chest belt (HR Polar transmitter, Polar Electro UK Ltd, Warwick, UK) fastened around the lower chest at the level of the fifth intercostal space. During the study, intermittent problems with the heart rate monitor telemetry were encountered; these persisted even with replacement belts, and were probably due to electromagnetic interference. Subsequently, as a back up, patients also wore a wrist pulse oximeter (Pulsox 3i, Minolta, Osaka, Japan) to measure heart rate if necessary via a finger probe sited on the index finger.

The K4 b^2 and its software (COSMED data management software v8.1) provide continuous data which, via telemetry, is accessible on a remote computer in real time. Ventilation (V_E; L min^{-1}), oxygen uptake (VO_2; mL min^{-1} kg^{-1}) and heart rate (beats min^{-1}) at rest and at breakpoint of the ISWT, expressed as absolute and percent of maximum predicted values, were used for analysis.

Blood pH, PaO_2 and $PaCO_2$ were analysed using a portable blood gas machine (Osmetch Opti CCA, GMI, Minnesota, USA). Arterialised capillary blood was collected from a finger tip using a lancet and capillary tube at rest and at breakpoint. If necessary, this was facilitated by prior immersion of the patient's hand in warm water.

At breakpoint, patients were asked to report the main symptom(s) limiting exercise as 'breathlessness alone', 'leg fatigue alone', 'breathlessness and leg fatigue equally' or 'other', and to rate the severity of their breathlessness or leg fatigue by pointing to a modified Borg scale,[16] reproduced in large print on a board held by one of the researchers.

Protocol

Patients were given written instructions to avoid caffeinated drinks within 1 h, large meals within 2 h, and excess alcohol the night before the test. They were asked to take their usual medication as prescribed and advised to wear comfortable walking shoes. The study was conducted uninterrupted in a large room.

Drug use and smoking history were noted and a 12-lead electrocardiogram was performed to exclude unexpected cardiac pathology. Height and weight were recorded. Patients underwent tests of simple spirometry, sniff nasal inspiratory pressure (SNIP), leg extensor power and completed the mastery questionnaire. A 5 min rest period was allowed between each assessment for recovery. The K4 b^2 mask and harness were then fitted and the patient sat resting for 5 min and listened to pre-recorded instructions on how to complete the ISWT from the supplied tape cassette. An initial ISWT was undertaken for familiarisation purposes. After completing the walk, patients were seated until breathlessness scores and heart rate had returned to baseline values. The K4 b^2 equipment was removed and the patient rested for 1 h, during which they were permitted one (non-caffeinated) drink. A second ISWT was then undertaken, with arterialised capillary blood gases obtained immediately before and after the walk. On completing the walk, patients sat until breathlessness scores and heart rate had returned to baseline values.

Statistical analysis

Data were described by mean (standard deviation, SD) and median [interquartile range, IQR] as appropriate. Pearson's correlations were used to determine correlations between exercise performance and inspiratory muscle strength, peripheral muscle power, FEV_1 and FVC. Spearman's rank was used to determine correlations between exercise performance and mastery domain score. Simple linear regression was used to further explore the relationship between these variables and exercise capacity, with β regression coefficients and their 95% confidence intervals reported. All calculations were performed using the Statistical Package for Social Sciences (SPSS) v17.0 and P values of <0.05 were regarded as statistically significant.

Results

Participants

Of 79 eligible patients approached, 41 were recruited and completed the study (Fig. 1). Measurements were completed in full except for blood gases, with paired resting and breakpoint samples unavailable in eight patients. Generally this was due to difficulty in collecting a timely and sufficient sample of blood into the capillary tube despite use of warm water, 'milking' the finger and repeated stabs with the lancet; in two instances, the portable blood gas machine failed despite an adequate sample, and two patients declined to have the sample undertaken (Fig. 1).

Participants (21 male) had a mean (SD) age of 64 (8) years and a median (range) ECOG performance status of 1 (0–2); 26 had non-small cell lung cancer (NSCLC), 11 mesothelioma and four small cell lung cancer. Mean (SD) body mass index was 25.4 (3.8) kg/m^2 and percentage

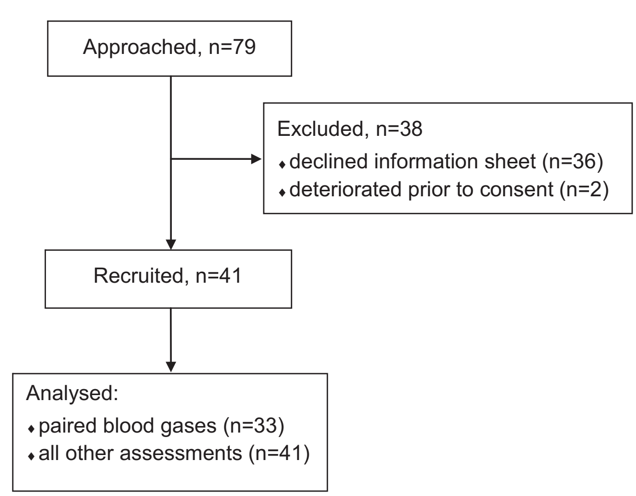

Figure 1 Study flow chart.

weight loss from a pre-illness stable baseline was 1 (11). Six and one participants respectively were taking regular or 'as required' inhaled bronchodilators, although only five had a documented diagnosis of COPD (Table 1). To date 33 patients have died with a median [IQR] survival of 47 [29–77] weeks.

Table 1 Patient details. Mean (SD) or number of group unless specified otherwise.

Age, years	64 (8)
Gender, male:female	21: 20
Diagnosis	
Non-small cell	26
Mesothelioma	11
Small cell	4
ECOG performance status	
0/1/2	16/21/4
Disease extent	
Local/advanced	21/20
Metastases	
Lymph nodes/lung/bone/ liver/adrenal	12/6/4/2/1
Previous treatments	
Palliative chemotherapy	26
Palliative radiotherapy	10
Radical radiotherapy	1
Cigarette smoking status	
Ex smoker	27
Current	7
Never	7
Relevant comorbidities	
COPD	5
Osteoarthritis	3
Hypertension	4
Diabetes	4
Recent pulmonary embolism	1
Current medication	
Inhaled corticosteroid	5
Inhaled bronchodilator	2
Oral corticosteroid	2
Diuretic	2
Low molecular weight heparin	1
Anthropometry	
Height, cm	169 (10)
Weight, kg	73 (14)
Body mass index, kg m^2	25.4 (3.8)
Inspiratory muscle strength	
Actual, cmH_2O	58 (32)
% Predicted	63 (32)
Leg extensor power	
Watts	90 (43)
Watts/kg	1.23 (0.52)
Spirometry	
FEV_1, L	1.62 (0.59)
FEV_1 % predicted	60 (19)
FVC, L	2.15 (0.73)
FVC % predicted	64 (18)
FEV_1:FVC%	0.75 (0.11)
$<$70%	25
$\geq$70%	16
Mastery score, median [IQR]	25 [21–27]

Exercise performance

Patients walked a median [IQR] distance of 320 [250–430] metres over a mean (SD) test duration of 358 (95) seconds and final test walking speed of 5.11 (0.99) km h^{-1}. The group reached a mean (SD) of 76 (10), 77 (25) and 48 (14) of their percent predicted maximal heart rate, peak oxygen uptake, and ventilation respectively (Table 2). Reasons given for stopping were shortness of breath alone (28), shortness of breath and leg fatigue equally (9) and leg fatigue alone (3). One patient reported general fatigue as their limiting symptom (Table 2). For the group as a whole, breathlessness was rated higher than leg fatigue at breakpoint with median values of 3 'moderate' and 0 'none at all' respectively.

Factors associated with exercise performance

Exercise performance was moderately and significantly correlated with inspiratory muscle strength (r = 0.42, P = 0.01) and peripheral muscle power (r = 0.39, P = 0.01), but not spirometric values or mastery domain score (Table 3). Simple linear regression of the factors revealed only inspiratory muscle strength and peripheral muscle power to be significant determinants of exercise performance, with regression coefficients [95% CI] of 1.77 [0.53, 3.01] and 1.22 [0.31, 2.14] respectively (Table 3).

Discussion

This study is the first to explore how a number of physiological and psychological factors influence exercise performance in a progressive walking test in patients with

Table 2 Mean (SD) physiological measurements.

	At rest	Breakpoint
Heart rate		
Beats per minute	81 (15)	118 (15)
% Predicted maximum	52 (10)	76 (10)
Oxygen uptake		
VO_2, mL kg^{-1} min^{-1}	5.0 (2.4)	18.3 (6.2)
% Predicted maximum	21 (10)	77 (25)
Ventilation		
L min^{-1}	14.4 (6.7)	37.5 (14.7)
% Predicted maximum	19 (8)	48 (14)
Reason for stopping		
Breathlessness	–	28
Breathlessness and leg fatigue	–	9
Leg fatigue	–	3
General fatigue	–	1
Borg Scores, median [IQR]		
Breathlessness	0 [0–0]	3 [2–4]
Leg fatigue	0 [0–0]	0 [0–3]
Blood gases		
O_2, kPa	9.3 (3.1)	9.8 (2.9)
O_2, mmHg	69.6 (23.5)	73.3 (21.7)
CO_2, kPa	5.2 (1.0)	4.9 (0.9)
CO_2, mmHg	38.9 (7.2)	37.2 (6.6)

Table 3 Correlations between exercise performance and baseline measurements.

Baseline measurement	r	β [95% CI]	P
Inspiratory muscle strength	0.42	1.77 [0.53, 3.01]	0.01
Peripheral muscle power	0.39	1.22 [0.31, 2.14]	0.01
% Predicted FEV_1	0.22	1.50 [−0.68, 3.66]	0.17
% Predicted FVC	0.21	1.54 [−0.82, 3.90]	0.20
Mastery domain score	0.21	5.74 [−3.40,14.87]	0.18

incurable thoracic cancer. We found that in a group with a reasonable performance status and limited weight loss, who mainly experience breathlessness as the symptom limiting exercise, inspiratory muscle strength and peripheral muscle power helped predict exercise performance, but not spirometric values or mastery. Further, breakpoint values did not suggest that cardiac factors or hypoxaemia were factors limiting exercise.

There are no directly comparable studies to ours. Patients with other cancers have been compared to matched healthy volunteers during treadmill exercise.[5,17] Exercise performance was found to relate to inspiratory muscle strength ($r = 0.40$, $P < 0.01$) in patients with various cancers presenting with unexplained breathlessness on exertion,[5] and to peripheral muscle mass ($r = 0.42$, $P < 0.01$) in patients with pancreatic cancer.[17] With less peripheral muscle mass, the anaerobic threshold is reached at lower workloads, resulting in a reduced exercise capacity.

We found breathlessness, rather than leg muscle fatigue, to be the most common symptom limiting exercise. This could suggest that inspiratory muscle weakness plays a particular role in the generation of breathlessness in this setting, i.e. neuro-mechanical uncoupling occurs as the ventilatory pump becomes unable to match the increased demands of exercise.[18] On the other hand, peripheral muscle could also contribute to breathlessness as it may directly influence the ventilatory response to exercise via the ergoreflex.[19] This reflex is enhanced in the presence of a reduced peripheral muscle mass (more work per unit volume) or muscle dysfunction (more rapid accumulation of waste metabolic products) and is considered to contribute to the increased ventilatory response to exercise and breathlessness in patients with heart failure.[19] The role of leg muscle fatigue may become more relevant with greater degrees of muscle wasting. In a hospice setting, of patients with various cancers with breathlessness on exertion, about half reported leg muscle fatigue as the symptom limiting exercise.[20]

There are a number of limitations to the study. The group was heterogeneous, including both lung cancer and mesothelioma, whose disease may impact differently on lung, chest wall or diaphragm function. However, comparison of both groups revealed no significant difference in any of the factors studied at baseline (data not shown). Further, exclusion of mesothelioma made little difference to the associations between exercise performance and inspiratory muscle strength ($r = 0.42$, $P = 0.01$) or peripheral muscle power ($r = 0.44$, $P = 0.01$). Recruitment took some time because of various factors, including difficulty in finding suitable patients. Many were ineligible because of concurrent ischemic heart disease and other comorbidities and this may limit the generalisability of our findings. Our data for numbers excluded was incomplete; however, the presence of multiple comorbidities was the main reason why three-quarters of patients with advanced NSCLC screened for a study exploring the safety and feasibility of cardiopulmonary exercise testing were ineligible.[21] We did not examine other factors which may help predict exercise performance, e.g. left ventricular function.[22] The use of the K4 b^2 allowed us to measure various parameters during a walking test, a more familiar form of exercise than treadmill or cycle testing, and to demonstrate that comparable mean absolute and percent predicted values of VO_2 at breakpoint are reached as in patients with advanced NSCLC undergoing cycle ergometry (17 mL kg^{-1} min^{-1} and 67% respectively).[21] However, the K4 b^2 is expensive (about £18k/$30k), needs off-site servicing every 6 months, and requires training in its set up, calibration and use. Further, some patients found the tight fitting face mask uncomfortable. We used SNIP as a simple, non-invasive assessment of inspiratory muscle strength. However, it can underestimate strength because it is dependent on volition, and also because of reduced transmission of pressure from the oesophagus to the nose in patients with obstructive airways disease.[23] Capillary blood gases tend to underestimate oxygen values,[24] but were used mainly to exclude falling levels at breakpoint. Practical difficulties in obtaining a sufficient sample led to an incomplete data set, but this did not suggest a decrease with exertion.

We purposely recruited patients with a reasonable performance status as we consider that it is this group for whom proactive rehabilitation therapies have the greatest potential to improve, maintain or slow the decline in exercise ability. It is also pragmatic, as less fit patients are less likely to be capable or willing to undertake and complete a therapeutic exercise programme. Nonetheless, new approaches are likely to be required as currently only about half of patients with or cured of cancer offered an exercise programme will complete one.[25,26] One approach our group is exploring is neuromuscular stimulation of the quadriceps muscles. Having completed a pilot study,[27] we are now examining its use alongside palliative chemotherapy.

In conclusion, of the factors examined, only inspiratory and peripheral muscle performance were significantly related to and predictive of exercise performance in patients with thoracic cancer and a reasonable performance status. This suggests that rehabilitation interventions which include inspiratory and peripheral muscle training are worth exploring further in this group.

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Conflicts of interest

None declared.

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