Original Article

Cardiopulmonary Exercise Testing for Unexplained Breathlessness in a Indian Tertiary Care Centre

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Abstract

Background. Cardiopulmonary exercise testing (CPET) is a non-invasive, objective and provides relevant information for clinical decision making. The purpose of the present study was to evaluate the cause for unexplained breathlessness by performing cardiopulmonary exercise testing.

Methods. We carried out a retrospective analysis of CPET performed for 51 patients with unexplained breathlessness over a one-year period. Cardiopulmonary exercise testing was done by maximum symptom limited incremental protocol on a treadmill.

Results. The mean age was 45 years (range 20-74 years). Mean body mass index (BMI) was 26.4; 7 (14%) subjects had a normal BMI, 12 (23%) were overweight, 30 (59%) were obese and 2 (4%) were underweight. Thirty-one (61%) patients achieved anaerobic threshold (AT). Based on the AT percentage criteria, 4% were classified as diseased, 17% as deconditioned, 20% as sedentary and 20% as normal. Fourteen (27%) patients had $\dot{V}O_2$ max >80% predicted. In the final analysis, 11 (22%) patients had ventilatory limitation, 16 (31%) had cardiovascular, 9 (17%) had mixed pulmonary and cardiac, 3 (6.5%) had musculoskeletal limitation and 3 (6.5%) had obesity as exclusive cause for breathlessness. Nine (17%) had normal studies with abnormal perception of breathlessness and they were advised to gradually increase their exercise levels.

Conclusions. Cardiopulmonary exercise testing is a useful tool in the evaluation of dyspnoea disproportionate to clinical findings and standard tests. Although CPET points out the organ causing dyspnoea, organ specific investigation is required to plan the management. **[Indian J Chest Dis Allied Sci 2017;59:119-123]**

Key words: Cardiopulmonary exercise testing, Dyspnoea, Oxygen consumption, Exercise tolerance, Anaerobic threshold.

Introduction

Dyspnoea is a common and often debilitating symptom that affects up to 50% of patients admitted to tertiary care hospitals and a quarter of patients seeking care in ambulatory settings. Dyspnoea has been defined as a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.[1] Population-based studies have shown a prevalence of 9% to 13% for mild to moderate dyspnoea among community-residing adults[2-4]; 15% to 18% among community-residing adults aged 40 years or older,[3,5,6] and 25% to 37% of adults aged 70 years and older.[7] This is responsible for substantial disability and millions of patient visits each year. Breathlessness is an extremely common symptom occurring as the third most frequent complaint (following fatigue and back pain) from outpatients evaluated in medical clinics.

In some individuals with exercise intolerance, the only finding is a disproportionate or exaggerated perception of symptoms (e.g. dyspnoea, leg effort) with no evident physiological abnormality. Unexplained exertional dyspnoea or fatigue is usually assessed by resting tests, such as pulmonary function tests and echocardiogram. These routinely performed tests can at times be non-diagnostic and pose a significant diagnostic challenge to physicians as these symptoms are often relatively mild, poorly characterised, or insidious. Cardiopulmonary exercise testing (CPET) is a valuable tool in this regard, providing the clinician with evidence that the patient-perceived symptoms are not due to significant cardiovascular or respiratory diseases. CPET allows to study the responses of cardiovascular and ventilator systems to a known exercise stress through the measurement of gas exchange at the airway. It can also be particularly helpful in the evaluation of patients in whom an initial evaluation is unrevealing

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or patients in whom multiple problems may contribute to dyspnoea.[8] Previous studies have not included CPET in all the patients with unexplained dyspnoea. So, we present our experience using graded, comprehensive CPET in a group of patients with unexplained dyspnoea.

Material and Methods

Study Design and Population

This study was a retrospective analysis of patients referred for cardiopulmonary exercise testing between August 2012 and July 2013, to identify the cause for unexplained breathlessness. Institutional Review Board (IRB) approval was obtained for this study. Fifty-one patients had been referred to pulmonary function laboratory for evaluation of unexplained breathlessness. They had symptoms out of proportion to clinical findings and initial evaluation. For example, if patient had mild obstruction in baseline spirometry but severe dyspnoea limiting daily activities, they were subjected to CPET. A short questionnaire was administered to rule out contraindications for CPET and to identify the risk factors for coronary artery disease, such as smoking history, cholesterol, chest pain, hypertension, overweight, and family history. This also included questions related to cardiopulmonary and major systemic diseases and current therapy. Subjects with a discrepancy between their persistent unexplained symptoms and their detailed clinical history, physical examination, pulmonary function tests, radiologic imaging, electrocardiogram (ECG) and blood test underwent CPET.

Exercise Testing

Symptom-limited CPET was performed on a treadmill ergometer using modified Balke protocol[9] with a grade range of 0–24% and speed range of 0–22 km/hour. Ventilatory expired gas analysis was performed using a metabolic cart (Jaeger master screen CPx, Version 5.01.10, Germany). The metabolic cart was calibrated before each test.

Standard 12-lead electrocardiography was obtained at rest, each minute during exercise and 10 minutes following exercise.[10] Blood pressure was measured using a standard cuff sphygmomanometer at rest and during peak exercise. Oxygen saturation was measured using pulse oximetry. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation (VE), and other cardiopulmonary variables were measured by breath-by-breath method averaged 7 breaths as per the guidelines of the Joint statement of the American Thoracic Society (ATS)/American College of Chest Physicians (ACCP).[11] Anaerobic threshold was determined by V slope method, ventilatory equivalents method and when the respiratory gas exchange ratio (RER) consistently exceeded 1.[12,13] Pre-exercise spirometry was done according to guidelines of American Thoracic Society/European Respiratory Society task force.[14] Maximal voluntary ventilation (MVV) was obtained by multiplying forced expiratory volume in the first second (FEV_1) with 35. As per consensus statement 2009, body mass index (BMI) can be categorised as underweight (<18 kg/m^2), normal (18-22.9 kg/m^2), overweight (23-24.9 kg/m^2), and obese (>25 kg/m^2).[15] Test was terminated on volitional exhaustion, such as dyspnoea and fatigue.

Statistical Analysis

All data were analysed using Statistical Package for Social Sciences (SPSS) version 17. Data are presented as mean ± standard deviation for each limitation, such as cardiac, ventilatory, normal, musculoskeletal, respiratory and cardiac, and obesity. The $\dot{V}O_2$ max during exercise was the prime variable to be examined because it establishes whether the patient's physiologic responses allow normal maximal aerobic function. Peak oxygen consumption ($\dot{V}O_2$), peak oxygen pulse, peak exercise VE, peak exercise breathing frequency, breathing reserve, ventilatory equivalence for carbon dioxide (VE/$\dot{V}CO_2$) at anaerobic threshold were compared across different limitations using Kruskal-Wallis test as the distribution was skewed within each of the limitation. A p-value <0.05 was considered statistically significant.

Results

Mean age of the subjects was 45 years (range 20-74 years). Mean body mass index was 26.4±4.3; 7 (14%) subjects had a normal BMI, 12 (23%) were overweight, 30 (59%) were obese and 2 (4%) were underweight. FEV_1 was <80% predicted in 30 (59%) patients. Baseline characteristics of the patients are shown in table 1.

Table 1. Baseline characteristics

Variable	Mean±SD	Range
Age (years)	44.9±12.8	20 - 74
Gender (male: female)	26:25	
BMI (kg/m^2)	26.4±4.3	15.15 - 36.15
FVC (% predicted)	76.2±17.2	35.6 - 111.3
FEV_1 (% predicted)	73.2±19.5	22.1 - 107.7
FEV_1/FVC (%)	78.59±10.55	40.84 - 95.4

Definitions of abbreviations: SD=Standard deviation; BMI=Body mass index; FVC=Forced vital capacity; FEV_1=Forced expiratory volume in the first second

Seven patients were known to have diabetes mellitus, 13 had hypertension and 23 had dyslipidemia. Forty-four (86%) patients achieved >80% target heart rate. Fourteen (27%) patients had $\dot{V}O_2$ max >80% predicted. Thirty-nine (76%) patients worked to a load of >80% predicted. Thirty-one (61%) patients achieved anaerobic threshold. Based on the anaerobic threshold percentage criteria, 4% were classified as diseased, 17% as deconditioned, 20% as sedentary and 20% as normal. CPET parameters are displayed in table 2. The cardiopulmonary profile of the subjects who underwent CPET is shown in table 3. Aetiology of dyspnoea observed on the basis of different CPET response patterns[11,16,17] is presented in table 4.

Table 2. Cardiopulmonary exercise testing parameters

Variable	Mean±SD	Range
Peak $\dot{V}O_2$ (% predicted)	71.98±17.36	35 - 115
Peak $\dot{V}O_2$ (mL/kg/min)	20.54±5.05	12.9 - 34.7
Peak O_2 pulse (% predicted)	77.26±16.08	48 - 113
Peak exercise $\dot{V}E$ (L/min)	50.61±14.94	26 - 86
Peak exercise breathing frequency (breaths/min)	43.29±9.74	24 - 69
$\dot{V}E/\dot{V}CO_2$ at AT	32.03±4.57	21.9 - 42.8
Breathing reserve, % of MVV	31.67±4.48	22 - 43

Definition of abbreviations: $\dot{V}O_2$=Oxygen consumption; O_2=Oxygen, VE=Minute ventilation; VE/VCO_2=Ventilatory equivalent for carbon dioxide, AT=Anaerobic threshold, MVV=Maximal voluntary ventilation

Table 4. Definitions for limitation [11,16,17]

Limitation	Features
Ventilatory limitation	$\dot{V}O_2$ peak <80% predicted Breathing reserve <20%
Cardiovascular limitation	Normal PFT* $\dot{V}O_2$ peak <80% predicted AT <60% of $\dot{V}O_2$max Oxygen pulse <80% predicted Shape of O_2 pulse-flattened Abnormal ECG changes
Mixed respiratory and cardiological	$\dot{V}O_2$ peak <80% predicted AT <60% of $\dot{V}O_2$max Oxygen pulse <80% predicted Shape of O_2 pulse-flattened Breathing reserve <20% Normal or reduced heart rate reserve
Musculoskeletal	Increased lactic acidosis at peak exercise Leg fatigue
Obese	Increased respiratory rate Increased minute ventilation $\dot{V}E/\dot{V}CO_2$ at AT <34 Peak $\dot{V}O_2$/body weight values are low A significant difference in peak $\dot{V}O_2$ between ideal and actual body weight

Definition of abbreviations $\dot{V}O_2$=Oxygen consumption; PFT=Pulmonary function testing; AT=Anaerobic threshold O_2=Oxygen, ECG=Electrocardiogram; $\dot{V}E$=Minute ventilation; $\dot{V}E/\dot{V}CO_2$=Ventilatory equivalent for carbon dioxide

Table 3. Cardiopulmonary exercise testing results of different limitations

Parameters	Ventilatory	Normal	Cardiac	Respiratory and Cardiac	Musculoskeletal	Obesity	p-value
Peak $\dot{V}O_2$ (% predicted)	80.21±19.46	80.67±16.14	62.94±12.74	65.22±17.96	81.00±16.52	75.25±10.44	0.031
Peak O_2 pulse (% predicted)	86.00±16.63	87.78±12.43	69.13±12.14	69.33±18.65	83.00±13.00	75.10±3.65	0.003
Peak exercise $\dot{V}E$ (L/min)	51.55±13.87	50.67±11.60	50.19±17.74	45.56±13.50	63.00±23.51	52.00±9.00	0.798
Peak exercise breathing frequency (breaths/min)	48.27±13.14	46.44±4.79	39.69±10.53	45.44±4.39	38.33±2.51	33.33±3.51	0.043
Breathing reserve (% of MVV)	11.63±12.13	27.55±13.99	36.04±22.62	14.01±21.72	46.27±5.46	31.14±19.02	0.013
$\dot{V}E/\dot{V}CO_2$ AT	31.42±5.26	31.32±2.41	31.70±6.07	32.53±3.30	31.35±0.49	—	0.945

Definition of abbreviations: $\dot{V}O_2$=Oxygen consumption; O_2=Oxygen, $\dot{V}E$=Minute ventilation; $\dot{V}E/\dot{V}CO_2$=Ventilatory equivalent for carbon dioxide; MVV=Maximal voluntary ventilation; AT=Anaerobic threshold

In the final analysis, 11 (22%) patients had ventilatory limitation, 16 (31%) had cardiovascular limitation, 9 (17%) had mixed pulmonary and cardiac limitation and 3 (6.5%) had musculoskeletal limitation and 9 (17%) had normal studies. Seven patients had obesity as the cause for breathlessness, out of which 3 (6.5%) had obesity as exclusive cause for breathlessness. More than half the diagnosis were non-respiratory.

The dominant symptom at peak exercise were dyspnoea in 44 (86.3%) patients, leg fatigue in 6 (11.8%) patients and both dyspnoea and leg fatigue in one patient.

Discussion

Cardiopulmonary exercise testing was useful in elucidating the nature of symptoms among patients with unexplained breathlessness and provided a clear assessment of the mechanism of dyspnoea which was not adequately obtained by other standard techniques. CPET is a useful tool in the integrated evaluation of common problems, such as unexplained dyspnoea on exertion and limitation of exercise tolerance.[8] It was normal in all patients with non-physiologic dyspnoea and limited subsequent testing. Subjects who had normal studies with abnormal perception of breathlessness were reassured and advised to gradually increase their exercise levels. In those patients identified to have cardiovascular and ventilatory limitation, we were able to show ventilation-perfusion mismatch. We were not able to correlate left ventricle diastolic dysfunction in patients with cardiovascular limitation due to non-availability of echocardiography in all the patients. Although CPET points out the organ causing dyspnoea, organ specific investigation is required to plan the management.

Cardiopulmonary exercise testing provides indices of the functional reserves of the organ systems involved in the exercise response, with inferences for system limitation at peak exercise. It is thought to be the "gold standard" for evaluating the causes of exercise intolerance in patients with pulmonary and cardiac diseases.[18] Pratter *et al*[18] described their experience with patients presenting to a pulmonary clinic with chronic breathlessness. Pulmonary disorders were believed to be the cause of symptoms in 75% of patients, and in 10% the cause was believed to be of cardiac origin. A variety of other extra-pulmonary and extra-thoracic causes made up the rest. The authors emphasised the utility of bronchoprovocation testing in the evaluation of these patients. CPET was performed in only 18% and was believed to be most useful in diagnosing psychogenic dyspnoea or deconditioning. It is of interest that in our study, we included all the subjects with unexplained dyspnoea to undergo CPET to elucidate the cause.

DePaso *et al*[19] reported their experience of 72 patients with dyspnoea unexplained by history, physical examination, and simple spirometry. Pulmonary causes accounted for the symptoms in 36% with cardiac causes accounting for 14%. Hyperventilation was believed to account for 19%. The remaining patients suffered from a variety of extra-thoracic and intra-thoracic disorders. Almost 20% had no explanation for their symptoms. The authors point out that a standardised evaluation protocol was not used nor was bronchoprovocation routinely performed. Only 15 CPETs were performed, and of these only 13% were believed to have directed further evaluation or treatment. They concluded that although a cause could be identified in most patients, no sequence of diagnostic testing could be recommended. With the inferred results from CPET, we referred subjects to the respective department for further testing.

Martinez *et al*[8] evaluated 50 patients with a chief complaint of dyspnoea unexplained by routine evaluation. Seven of 50 patients had cardiac limitation; 17 had pulmonary limitation, 14 had obesity and/or deconditioning, 1 had gastro-oesophageal reflux, and 16 patients had either psychogenic dyspnoea or no identifiable disease. Five patients had more than one clinical diagnosis. Thirty percent of patients with either no disease or a psychogenic cause for symptoms on the basis of CPET results responded to simple reassurance, psychotropic medication, or psychotherapy. There are differences in the baseline characteristics of the subjects in our study. Based only on CPET results, 11 patients had ventilatory limitation, 16 had cardiovascular limitation, 9 had mixed pulmonary and cardiac limitation, 3 had musculoskeletal limitation and 9 had normal studies. There was no follow-up as this was a retrospective study.

A spectrum of exercise responses can be seen in obese patients. Exercise capacity may be normal or low and it will be even lower with significant obesity when expressed per kilogram of actual body weight $\dot{V}O_2$max/kg). The increased metabolic requirements of moving the excess weight during exercise results in a disproportionately increased $\dot{V}O_2$, heart rate, and $\dot{V}E$ at any given level of work. Once other causes of dyspnoea are excluded, obese patients should be enrolled in a weight reduction/aerobic training programme and monitored for symptom improvement.[20] A reduced $\dot{V}O_2$/kg plus a normal $\dot{V}O_2$ max without cardiorespiratory dysfunction was considered consistent with obesity-related dyspnoea.[17,21] CPET provides indices of the functional reserves of the organ systems involved in the exercise response, with inferences for system limitation at peak exercise.[22]

Conclusions

For patients with unexplained dyspnoea and for whom initial test results are non diagnostic, the weight of evidence suggests that CPET is a useful tool in identifying the following: cardiac and/or pulmonary causes, mitochondrial myopathy and psychological factors (hyperventilation, panic, anxiety syndromes, etc.) or deconditioning. Results from CPET may efficiently direct further diagnostic testing to target the suspected organ system involved. Early use of it in the assessment of unexplained dyspnoea may provide reassurance about exercise capacity and reduce or avoid many invasive and expensive investigations in these patients. We would recommend cardiopulmonary exercise testing to be incorporated into routine investigation in the evaluation of dyspnoea disproportionate to clinical findings and standard tests.

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