Cardiopulmonary Exercise Testing for Evaluating Patients with Unexplained Exertional Dyspnoea: Potential Role in Risk Stratification?

Dear Editor,

Dyspnoea is a common complaint, the cause of which often remains elusive after comprehensive evaluation. Cardiopulmonary exercise testing (CPET) provides a global assessment of the integrative exercise response involving the pulmonary, cardiovascular, neuropsychiatric, haematopoietic and skeletal muscle systems. CPET is recommended early as a diagnostic tool for evaluation of unexplained dyspnoea.[1] Despite this, CPET is underused[2] and there is a paucity of literature regarding its practical usefulness for stratifying the need for further investigations. This study, therefore, aimed to evaluate the usefulness of CPET in risk-stratifying patients with unexplained dyspnoea by following up on their progress over 2 years.

Materials and Methods

Subjects

This study was a single-centre retrospective study of all consecutive patients who had CPET performed for the indication of "unexplained exertional dyspnoea for investigation" between the period of January 2009 to December 2010 (inclusive). The indication for CPET was based on the physician's discretion and may include some patients who were not responding to treatment based on clinical diagnoses. The study was approved by the SingHealth Institutional Review Board (2011/060/C).

Baseline Data

Spirometry and maximal voluntary ventilation (MVV) were performed according to the American Thoracic Society (ATS)/American College of Chest Physicians (ACCP) guidelines (2003),[1] using a spirometer (Medgraphics, USA) for all patients before CPET.

CPET

A total of 64 patients were referred for dyspnoea of unknown cause and all patients underwent maximal symptom-limited cardiopulmonary incremental protocol on a cycle ergometer as per ATS/ACCP guidelines.[3]

Cardiopulmonary exercise testing equipment included a metabolic cart (Oxycon alpha, Jaeger, Würzburg, Germany) with an interfaced bicycle ergometer (Ergoline, Jaeger, Würzburg, Germany). Exercise values were assessed breath-by-breath and were reported as mean values calculated over 10-second intervals. The predicted peak oxygen uptake (VO_2 peak [%]) was calculated according to Hansen's equation.[4] Anaerobic threshold was determined by the V-slope method according to Beaver.[5]

All tests were reviewed by 3 pulmonologists (Ong TH, Loo CM, Koh MS) who were blinded to the patient's clinical presentation and other data. The results were interpreted in accordance with the ATS/ACCP guidelines.[3] The results were categorised into "Normal", "Cardiac limitation", "Deconditioning" , "Cardiac limitation vs deconditioning", "Gas exchange limitation" or "Ventilatory limitation". Discrepancies were discussed to reach final consensus.

Follow-up

Healthcare utilisation (admissions and emergency visits) and significant laboratory results ordered after the CPET testing or new diagnosis were recorded and reviewed by cross-checking the electronic health records over 2 years.

Statistical Methods

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range). Categorical variables were presented as numbers (%).

Results

Patient Characteristics

Out of the 64 patients, 47 completed maximal tests and were included for analysis. Patient demographics are presented in Table 1. Mean age was 36.8 (± 17.5) years and 63.8% were male. Majority of the patients were of Chinese ethnicity (91.5%). The CPET results are presented in Table 2.

Exercise Testing Results by Final Diagnosis

A total of 19 patients were categorised as "Cardiac limitation vs deconditioning" in the final diagnosis. Over a 2-year period, 10 patients had no further evaluations or healthcare utilisation. Nine patients had further evaluation, in which 1 was found to have minor coronary artery disease while another had mild pulmonary emphysema on computed tomography (CT) of the thorax.

Table 1. Demographic Characteristics and Baseline Results of Patients

Characteristics	Baseline Results* n = 47
Gender (male)	63.8% (n = 30)
Age (years)	36.8 ± 17.5
BMI (kg/m^2)	22.7 ± 3.7
Ethnicity	
Chinese	91.5% (n = 43)
Malay	2.1% (n = 1)
Indian	6.4% (n = 3)
Lung function test	
Normal	89.4% (n = 42)
Obstructive	6.4% (n = 3)
Restrictive	2.1% (n = 1)
Others (truncation in FV loop)	2.1% (n = 1)
Baseline electrocardiogram	
Normal	97.9% (n = 46)
Others (right bundle brunch block)	2.1% (n = 1)

BMI: Body mass index; FV: Flow volume
*Data represented as mean ± standard deviation or percentages.

Table 2. CPET Results of Patients (n = 47)

Characteristics	Results*
Maximum work rate (percentage predicted)	68.9 ± 18.7
Maximum VO_2 (L/min)	1367.7 ± 477.7
Max VO_2 (percentage predicted)	64.2 ± 15.2
AT (percentage predicted VO_2 max)	32.9 ± 9.2
Heart rate reserve (bpm)	33.1 ± 18.77
Oxygen pulse (percentage predicted)	81.6 ± 23.5
Maximum VE (L/min)	49.2 ± 14.8
Breathing reserve (percentage)	54.0 ± 14.8
VE/VCO_2 at AT	28.8 ± 6.2
Modified Borg scale†	5.2 ± 1.8
Reasons for termination (may have >1 reason)	
Breathlessness	44.7% (n = 21)
Leg fatigue	74.5% (n = 35)
Chest pain	2.1% (n = 1)

AT: Anaerobic threshold; CPET: Cardiopulmonary exercise testing; VCO_2: Carbon dioxide output; VE: Minute ventilation; VO_2: Oxygen uptake
*Continuous data represented as mean ± standard deviation or percentages.
†Two missing data.

There were 13 patients classified under "Deconditioning". Among these, 5 had no further evaluations while 6 had further evaluations, which were all normal.

Of the 10 patients with normal CPET, 3 had normal CT thorax and 2 had normal echocardiography.

Among the 4 patients classified in the "Cardiac limitation" group, 1 had normal CT thorax. One patient had left ventricular (LV) diastolic dysfunction in echocardiography and was found to have double-vessel coronary artery disease. One patient had moderate pulmonary hypertension and moderate tricuspid regurgitation. Her CT thorax showed arteriovenous malformation and she underwent successful embolisation. One patient had both gas exchange and cardiac limitation. He underwent several further tests including echocardiography, pulmonary function test, methacholine challenge test, diffusion test and lung volume measurement, which were all normal.

Discussion

While CPET is a recommended test for evaluating unexplained dyspnoea,[3,6] its value in risk stratification has not been explored. We found that among patients with "Normal" exercise test or abnormalities suggesting "Cardiac limitation vs deconditioning" or "Deconditioning", only 1 out of 42 (2%) subjects was found to have a minor cardiac problem. None of these patients had healthcare utilisation for related problems on follow-up for 2 years. In contrast, 2 out of 4 (50%) patients with "Cardiac limitation" were found to have significant heart diseases. Therefore, based on our limited sample size, CPET may be used as a tool to stratify the need for further investigations. In patients with results showing "Normal", "Cardiac limitation vs deconditioning" or "Deconditioning", it seemed reasonably safe to limit further investigations.

To our knowledge, none of the previous studies on CPET have evaluated its value in prognosticating outcome in the longer term. Martinez et al[5] examined the role of CPET in 50 patients with dyspnoea that was unexplained by routine evaluation (history, physical examination, chest x-ray, full blood count and thyroid function test) and they concluded that CPET was useful in identifying a cardiac or pulmonary cause but insensitive in distinguishing cardiac disease from deconditioning. Their study differed from ours with respect to the short median follow-up of 9.1 months (range, 2.5 to 80 months) and lack of information about healthcare utilisation or long-term outcomes. De Paso et al[7] evaluated 72 patients with unexplained dyspnoea and subjected patients to diffusion test, ventilation-perfusion scan and echocardiogram. Definite cause of dyspnoea was not found in 14 patients (19%) for which only 2 patients had CPET performed and both were normal. Although patients were followed-up for mean of 5 years (range, 1 to 8 years), the numbers were too small to make any conclusion.

The main limitation of our study lies in its retrospective nature and small sample size. Our study population also comprised predominantly younger patients (median age: 32 years) when compared to the Martinez's study (median

age: 55 years) as the main source of referral came from our armed forces for evaluation of national servicemen with dyspnoea. Therefore, this may affect the external validity of our study. The strength of our study lies in the standardised reporting of CPET by 3 pulmonologists in blinded fashion and a 2-year follow-up period. However, we were not able to capture the data for healthcare visits to other institutions.

While CPET can prognosticate several diseases including emphysema,[8] idiopathic pulmonary fibrosis,[9] lung cancer,[10] hypertrophic cardiomyopathy,[11] and chronic heart failure,[12] its value in unexplained dyspnoea is largely unexplored.

Conclusion

In patients with unexplained dyspnoea and CPET results showing "Normal", "Cardiac limitation vs deconditioning" or "Deconditioning", it seemed reasonably safe to limit further investigations for their symptom of dyspnoea. Larger prospective studies are required to confirm the findings.

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