The clinical utility of cardiopulmonary exercise testing: results of a university hospital

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Abstract

Objective: To determine the main reasons for cardiopulmonary exercise test (CPET) referrals in our hospital over the last two years; to evaluate clinical usefulness of CPET.

Methods: We included 207 patients between 17 and 76 years of age. For every patient, we measured electrocardiography (ECG), arterial blood gases, spirometry, maximal voluntary ventilation (MVV) and diffusing capacity. CPET was then performed; using a treadmill, according to the modified Bruce protocol; then spirometry and diffusing capacity were repeated.

Results: The most common reason for sending patients for CPET was dyspnea during exertion (85%), then preoperative assessment of lung cancer patients (11.6%), and preoperative assessment of heart transplant candidates (3.4%). After CPET in a dyspnea group, 33.5% had normal findings, 22.2% had pulmonary limitation, 31.8% had non-pulmonary pathology, and 12.5% reached submaximal effort due to subjective problems (poor condition, feeling discomfort) but no objective reasons to stop. From a lung cancer group, 25% were deemed unsuitable surgical candidates, and 14.29% of a heart transplant group was recommended immediate surgery, the remainder needed re-evaluation.

Conclusion: Dyspnea of unknown cause is optimally investigated with CPET, allowing us to differentiate between the major causes of limitation (lung, heart, cardiovascular, muscular) and, within each area, the specific causes of limitation. The most common diagnoses after CPET are pulmonary and cardiac diagnoses. CPET helps us to detect concurrent cardiovascular disease at respiratory impaired patients. CPET is the gold standard for evaluation of morbidity and mortality risk of lung cancer surgery and for selection of patients for heart transplant.

Key words: CPET; Dyspnea; Oxygen consumption; Preoperative assessment

Introduction

Exercise intolerance is defined as the inability to successfully complete a physical task that a normal subject would find tolerable. Exercise intolerance is the main problem in pulmonary and cardiac disease. Measurements of lung function (FEV1, forced expiratory volume in one second; and DLCO, pulmonary diffusing capacity of the lung for carbon monoxide) and cardiac function (left ventricular ejection fraction, EF) obtained at rest are poorly predictive of the degree of exercise intolerance. Because of this, it is necessary to directly assess an individual’s exercise intolerance and, where possible, establish the cause. The gold standard approach for this is cardiopulmonary exercise testing (CPET) [1].

Abnormalities of the heart might cause pulmonary symptoms with abnormalities in lung gas exchange during exercise and similarly pulmonary disorders might result primarily in abnormalities in cardiovascular response to exercise [2].

CPET requires sophisticated equipment and should be performed only by laboratories with strict quality control, experienced physiological direction, appropriate medical supervision and considerable experience in conducting such tests. CPET is a relatively safe investigation, however it does bear a finite risk of death (2-5 per 100,000 clinical exercise tests)[3]. Experience is very important for the interpretation of the findings obtained by CPET [4].

In practice, CPET is used to answer specific clinical questions which have not been answered by more basic investigations including detailed history, physical examination, chest X-ray, resting pulmonary function tests (PFT) and a resting electrocardiogram (ECG). It is never the first line investigation and caution must be exercised to ensure that the benefit of performing CPET always outweighs the risk.

The measurements include oxygen consumption (VO2), minute ventilation (VE), the amount of
exhaled carbon dioxide at a given time (VCO\(_2\)), ventilator equivalent for carbon dioxide (VE/VCO\(_2\)), ventilator equivalent for oxygen (VE/VO\(_2\)), anaerobic threshold (AT, the level of oxygen consumption at which lactic acid production can be detected), dead space and physiological dead space (VD, consisting of anatomical dead space, i.e. volume of the upper airways, trachea and bronchus, and alveolar dead space, i.e. volume of alveoli that are ventilated but without perfusion or with poor perfusion), and the dead space to tidal volume ratio (VD/VT) which is an index of the relative inefficiency of gas exchange and elimination of CO\(_2\). Measurements also include heart rate (HR), pulse oximetry (SpO\(_2\)), blood pressure (BP), ECG, oxygen uptake per heart beat (O\(_2\)-pulse), respiratory exchange ratio (RER), breathing reserve (BR), and heart rate reserve (HRR).

The aims of this research are: (1) to determine the main reasons for sending patients for CPET in our hospital during last two years; (2) to evaluate the clinical usefulness of CPET.

**Patients and methods**

Two hundred and seven patients, 106 female (51.21%) and 101 male (48.79%), between 17 and 76 years of age, who were referred for CPET by their physician or a specialist during the last 2 years, were included in this research. Specific questions persisted after consideration of basic clinical data and because of that patients were referred for CPET. All the patients came to the CPET with detailed history, physical examination, chest X-ray, resting PFT and resting ECG which were done by their physician or other specialist. Some of them also had echocardiography findings.

In all patients, the following were measured at rest: ECG, arterial blood gases, spirometry, maximal voluntary ventilation (MVV), DLCO. A resting 12-lead ECG should be obtained; before the CPET begins the electrodes are moved to modified positions so that better waveforms can be recorded during activity. A BP cuff is placed so that BP measurements can be taken throughout the CPET. Breath gas analyzers should be placed into the patient’s mouth. CPET was then performed. An impressive number of variables were measured during CPET: external work (WR), metabolic gas exchange (VO\(_2\), VCO\(_2\), RER, AT), pulmonary gas exchange (SpO\(_2\), VE/VCO\(_2\), VE/VO\(_2\), end-tidal oxygen-PETO\(_2\), end-tidal carbon dioxide-PETCO\(_2\), arterial oxygen pressure-PaO\(_2\), VO\(_2\) pulse, arterial carbon dioxide pressure-PaCO\(_2\), standard HCO\(_3\)), cardiovascular (HR, ECG, BP, O\(_2\)-pulse), ventilatory (VE, VT, BR, respiratory frequency-fr), and general symptoms (dyspnea, fatigue, chest pain); followed by spirometry and diffusing capacity after CPET. Spirometry and diffusing capacity were carried out according to ERS/ATS (European Respiratory Society/American Respiratory Society) guidelines [5, 6]. All the measurements were done on Sensor Medics V\(_{\text{max}}\) device, using a treadmill, according to the modified Bruce protocol. This protocol begins with a speed of 2.7 km/h and grade 0% for the first 3 min, then 3 min at 2.7 km/h and grade 5%, then a further 3 min at 2.7 km/h, grade 10%. From this point on, the speed is increased in increments of 1.3 km/h and grade 2% every 3 min until the treadmill reaches 15% grade and 8 km/h. After that, the speed is increased by 0.8 km/h every 3 minutes. All the tests were performed, with continuous monitoring of ECG, BP and oxygen saturation. The interpretation of CPET findings is carried out according to the ATS/ACCP (American Thoracic Society/American College of Chest Physicians) statement on cardiopulmonary exercise testing [3] and reference values for CPET in healthy volunteers [7]. For functional evaluation and disability, patients should be tested with their optimal medication regimen (all patients with beta-blocker medications and anti-hypertensive drugs were included in the study) [3, 7]. On the day of testing the only one thing the patients didn’t use are short acting bronchodilatators, and current smokers didn’t smoke.

Basic strategy for the interpretation of peak CPET results begins with consideration of patient information and reasons for testing, also with analysis of VO\(_{\text{2max}}\) and subsequent simultaneous assessment of HR, VE, and SpO\(_2\). The AT may be helpful at this point. Determination of physiologic limitation is accomplished by analysis of BR and HRR [3]. The first question is whether the peak VO\(_2\) is decreased or normal, and whether it has reached the AT. Wasserman et al. describe a useful flowchart approach to interpretation based on measured VO\(_2\) peak and AT [2].

If a normal peak VO\(_2\) is present and the patient complains of intolerance efforts, it should considered the issue of obesity, early cardiovascular or lung disease, or finding the existence of orderly excessive worries about his health. Here are monitored parameters at maximum: O\(_2\)-pulse, respiratory gases, ECG, VO\(_2\) pulse, parameters of PFT.
Table 1. Results after CPET for 176 patients with dyspnea

<table>
<thead>
<tr>
<th>Referral diagnosis (mean age in years)</th>
<th>Normal findings</th>
<th>Pulmonary limitation</th>
<th>Cardiac limitation</th>
<th>Obesity</th>
<th>Muscular skeletal disorders</th>
<th>Anemia</th>
<th>Achieve poor effort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea (32.44)</td>
<td>37</td>
<td>14</td>
<td>7</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>COPD (72.20)</td>
<td>3</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Prolonged cough (65.67)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>State after surgery/carcinoma (74.4)</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>State after pulmonary embolism (54.25)</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Chronic pneumonia (59.34)</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Primary pulmonary hypertension (24.33)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asbestosis (60.5)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease (62.38)</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Connective Tissue disease (59.67)</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Asthma (45)</td>
<td>8</td>
<td>5</td>
<td>–</td>
<td>9</td>
<td>5</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>Number of patients</td>
<td>59</td>
<td>28</td>
<td>8</td>
<td>3</td>
<td>22</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>

Obstructive pulmonary disease (obs. pulm. dis.): BR low, HRR high, VD/VT-abnormal, fr < 50, FEV1/VC low; mild respiratory acidosis at peak VO2 (if fr < 50; restrictive lung disease, VC low); Pulmonary vascular disease (pulm. vasc. dis.): low peak VO2, low AT, BR normal, VE/VCO2 high, VC normal, VD/VT high, low non-changing O2 pulse; Left ventricular failure (LV fail.): low peak VO2, AT not determined, VD/VT abnormal, BR normal, not decreasing PaO2, O2 pulse low, VE/VCO2 high; Exercise hypertension (ex. hyp.): low peak VO2, AT not determined, VD/VT high, HRR high, change in VO2/change in WR low; Myocardial ischemia (myoc. isch.): low peak VO2, normal AT, BR normal, ECG abnormal, chest pain, low O2 pulse; Obesity: normal peakVO2, normal ECG and arterial blood gases, O2 pulse at peakVO2, body mass index-BMI > 30; Muscular skeletal disorders: low peakVO2, normal AT, BR normal, ECG normal, VD/VT normal, HRR high, HCO3 low; Anemia: low peak VO2, AT not determined, VD/VT normal, HRR normal, hematocrit low, metabolic acidosis at peak VO2, O2 pulse low; Achieve poor effort: low peak VO2, AT not determined, VD/VT normal, HRR high, ECG normal BR high, only slight decrease in HCO3.

If we have low peak VO2 and AT is not determined, then we considered heart disease, pulmonary vascular disease, lung disease, peripheral arterial disease, anemia, chronic metabolic acidosis, and poor effort (follow the parameters of HRR, BR, PFT, PaO2, BP, disturbances in the ECG).

If the VO2 peak is low and AT is determined then it was seen whether AT is normal or low? During normal AT lung disease, myocardial ischemia, poor effort or muscular skeletal disorder (monitored parameter BR, PFT, and ECG) was considered. If AT is low it could be peripheral circulatory disorders, pulmonary vascular disease, heart disease, lung disease with O2 flow problem, and chronic metabolic acidosis (follow the parameters of lung function, hematocrit, O2 saturation, arterial-alveolar O2 difference).
Results

The most common reason for sending patients for CPET was dyspnea during exertion (176/207), followed by preoperative assessment of lung cancer patients (24/207), and evaluation for heart transplantation (7/207).

One hundred and seventy six patients (85%) were referred for CPET due to dyspnea during exertion. In this group, 88 patients had normal spirometry values and no ECG pathology. They were not taking any medication and dyspnea during exertion was their only complaint. Fifty five patients also had exertional dyspnea, but their spirometry values and/or ECG and/or chest X-ray were abnormal. These patients already had a diagnosis and were undergoing drug treatment, but despite therapy, still experienced dyspnea during exertion. Thirty three patients had suspected asthma and dyspnea during exertion. Their spirometry values and ECG were normal and their only therapy is salbutamol as needed. Bronchoprovocation was not performed on these patients.

From 176 patients; 59 patients (33.75%) had normal findings on CPET (either psychogenic dyspnea or no identifiable disease). In 39 patients (22.2%) the cause of dyspnea was pulmonary. Fifty six patients (27%) had non pulmonary causes (cardiac limitation, 39; obesity, 10; musculoskeletal disorders, 5; and anemia, 2 patients). Twenty two patients (12.5%) gave inadequate effort during testing, due to subjective problems (poor condition or unexplained feeling of discomfort), however there was no objective indication to stop the testing. Results after CPET are presented in Table 1.

Twenty four patients with lung cancer (11.6%) were sent for CPET as part of preoperative evaluation of morbidity and mortality risk of lung cancer surgery. Six of them were deemed unsuitable surgical candidates on the basis of VO_{2max} analysis, because VO_{2max} was < 15 ml/kg/min and the percentage of predicted VO_{2} peak is < 56%. Three patients (12.5%) were referred for surgery, even though VO_{2} peak was < 15 ml/kg/min, but predicted VO_{2} peak was between 61-71%. Also, one patient had a VO_{2} peak of 17.5 ml/kg/min, but predicted VO_{2} peak was 59%. He was referred for resection of one lobe. The distribution of patients in this study according to the predicted value is shown in Tables 2 and 3.

Seven patients (3.4%) were referred for CPET as part of preoperative evaluation for heart transplant. One of them was referred for immediate surgery. In three cases, the heart failure survival score needed to be repeated. The last three were recommended to continue medical therapy (Table 4).

Table 2. Twenty four patients with lung cancer who were sent for CPET as part of preoperative evaluation of morbidity and mortality risk of lung cancer surgery

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Peak VO_{2} (ml/kg/min)</th>
<th>% predicted values VO_{2}</th>
<th>Number of patients for operation</th>
<th>Number of patients (no recommendation for operation)</th>
<th>Risk evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>&lt; 15</td>
<td>13-71</td>
<td>3</td>
<td>6</td>
<td>higher risk for morbidity and mortality for lung resection</td>
</tr>
<tr>
<td>9</td>
<td>15.4-18.6</td>
<td>59-84</td>
<td>9</td>
<td>0</td>
<td>intermediate risk</td>
</tr>
<tr>
<td>6</td>
<td>19-31</td>
<td>76-109</td>
<td>6</td>
<td>0</td>
<td>low risk</td>
</tr>
</tbody>
</table>

VO_{2} = oxygen consumption

Table 3. Distribution of patients with lung cancer according to percentage of predicted VO_{2}

<table>
<thead>
<tr>
<th>VO_{2} (% predicted values)</th>
<th>Number of patients</th>
<th>Statistical evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 75%</td>
<td>10</td>
<td>complication free</td>
</tr>
<tr>
<td>&lt; 60%</td>
<td>7</td>
<td>higher morbidity</td>
</tr>
<tr>
<td>61-74</td>
<td>7</td>
<td>Intermediate risk of complications</td>
</tr>
</tbody>
</table>

VO_{2} = oxygen consumption
Table 4. Seven patients referred for CPET as part of preoperative evaluation for heart transplant

<table>
<thead>
<tr>
<th>VO₂ ml/kg/min</th>
<th>VO₂ (%predicted values)</th>
<th>Number of patients</th>
<th>Decision after CPET</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>24</td>
<td>1</td>
<td>evaluate for transplant</td>
</tr>
<tr>
<td>10 until 14</td>
<td>37-51</td>
<td>3</td>
<td>heart failure survival score</td>
</tr>
<tr>
<td>&gt; 14</td>
<td>51-57</td>
<td>3</td>
<td>continue medical therapy</td>
</tr>
</tbody>
</table>

VO₂ = oxygen consumption

Discussion

The most common complaint referred for CPET is dyspnea. Fifty nine patients (33.75%) had normal findings on CPET, and in the remaining patients, the most common causes were pulmonary and cardiac limitations. The most normal findings (37 patients) were in the group which had normal finding at rest and didn’t take any medication. As we see in Table 1 this is the youngest group (in this group were some athletes who were sent by their sports club because of dyspnea in exertion). The most frequent pulmonary limitation is obstructive pulmonary disease and in cardiac limitation is exercise hypertension. Similar results were obtained by Martinez et al [8] in their group of 50 patients with dyspnea. After CPET, they found in 16/50 patients (32%) either psychogenic dyspnea or no identifiable disease. In the remaining patients, the most common cause was pulmonary limitation, then obesity, then cardiac limitation. These authors noted that CPET was useful in identifying a cardiac or pulmonary process [8]. A completely normal study does not exclude early disease but should serve to reassure the patient that a major disorder is likely not present [9].

Pratter et al [10] studied a group of patients with dyspnea. After CPET, 53% of diagnoses were respiratory and 47% of diagnoses were non-respiratory [10]. Patients often reported dyspnea during exertion which should be further analyzed as a problem of heart or lung disease. It is interesting that almost half of the patients who were sent for CPET as suspected asthma-dyspnea, had cardiac limitation. Some of our patients after CPET had two diagnoses. Among patients undergoing exercise testing for evaluation of impairment due to lung disease, high rates of comorbid cardiovascular disease have been identified, so that attribution of symptoms and impairment is one of the purposes of exercise testing in this context. Respiratory impaired patients appear to be at risk for undetected concurrent cardiovascular disease [11].

CPET helps us to differentiate between the major causes of limitation (lung, heart, cardiovascular, muscular) and, within each area, the specific causes of limitation. Dyspnea of unknown cause is optimally investigated with CPET [12]. In many series of unexplained dyspnea, CPET is infrequently used. In 100 consecutive patients evaluated at a tertiary referral center for chronic dyspnea, CPET was used in the evaluation of only 15 patients [9].

The British Thoracic Society [13] and American College of Chest Physician guidelines [14] for selection of patients for lung cancer surgery suggest that a patient of borderline operability should undergo exercise testing to measure maximum oxygen transport at peak exercise. If VO₂ peak is < 15 ml/kg/min, the patient is regarded as high risk for surgery. Some authors preferred the percentage of predicted VO₂ peak and its relationship to surgical outcome. They found that percentage of predicted VO₂ peak was significantly more sensitive than the absolute value. A value > 75% was an excellent predictor (> 90%) of an uneventful operation, whereas a value of < 43% was a contraindication to any lung resection surgery, and values of < 60% were a contraindication for resections involving more than one lobe [15]. Two additional studies [16, 17] also corroborated the use of percentage of predicted VO₂ peak. Both studies showed that values of < 50% were associated with a high risk of death related to cardiopulmonary causes and complications.

Selection of patients for heart transplant in the current era of heart failure therapy is made on the basis of peak VO₂ (ml/kg/min). If peak VO₂ < 10 that patient is considered for transplant, however, if peak VO₂ > 14 continuation of medical therapy is indicated; if peak VO₂ is between 10-14, then heart failure score should be assessed. On the basis of this score, patients are grouped into three levels: high risk (consider for transplant because beta-blockers are not tolerated), medium risk (beta-blockers tolerated), low risk (must continue medical therapy and reassess in 1 year) [1]. In our study, patients were grouped according to these criteria, and only one patient was considered for transplant, all others needed re-evaluation. However, peak oxygen uptake is affected by a person’s age, gender,

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and weight and if heart failure patients achieve greater than 50% of their predicted VO$_{2\text{max}}$ some authors can safely defer transplantation. Survival in patients who achieved ≤ 50% predicted VO$_{2\text{max}}$ was significantly lower than in those who achieved more than 50% predicted VO$_{2\text{max}}$ at one (74 vs 98%) and two years (43 vs 90%). Multivariate analysis suggested that this parameter was the most significant predictor of cardiac death or status 1 transplant priority.

Use of the percent predicted VO$_{2\text{max}}$ provided additional prognostic information to the absolute peak VO$_2$, but also other clinical parameters have been combined into validated prediction models such as the Heart Failure Survival Score (HFSS)[18]. The discrimination between the low-, medium-, and high-risk groups of the HFSS is retained with the survival shifted upward, consistent with improved survival in patients receiving beta-blockers. As medical and device therapies have advanced during the last 15 years, the cutoff value to define transplant candidacy has been lowered from a peak VO$_2$ < 14 to < 12 ml/kg/min [19].

There is mounting evidence that tolerance is a very good indicator of the risk of mortality in healthy individuals, as well as in many cardiovascular and pulmonary diseases. Guidelines for heart transplantation are based on CPET-derived indices; peak VO$_2$ value < 10 is one of the criteria for determining urgency of transplantation [4].

CPET is also an important tool for evaluating the degree of effort intolerance in patients with pulmonary diseases (chronic obstructive pulmonary disease-COPD, interstitial lung disease, pulmonary vascular disease, cystic fibrosis). Prognostic stratification is one of the main indications for CPET in patients with pulmonary diseases. Generally, in preoperative preparation, especially in surgery for heart and lung transplantation, CPET is recommended for preoperative evaluation of the degree of risk for morbidity and mortality [20, 21].

CPET can provide an objective measure of exercise capacity; identify the mechanisms limiting the tolerance of effort. It is also useful in monitoring disease progression or response to treatment [22].

In conclusion, this research shows that the most common complaint referred to CPET is dyspnea (85%). Dyspnea of unknown cause is optimally investigated with CPET, allowing us to differentiate between the major causes of limitation (lung, heart, cardiovascular, muscular) and within each area, the specific causes of limitation. It is never a first line investigation. The goal of CPET is to induce a level of exercise stress in order to expose underlying disorders which are not apparent at rest. The most common diagnoses after CPET are pulmonary and cardiac diagnoses (44.4%). CPET helps us to detect concurrent cardiovascular disease at respiratory impaired patients. CPET is the gold standard for evaluation of morbidity and mortality risk of lung cancer surgery and for selection of patients for heart transplant.

For 89.4% of our patients the clinical problem was solved (either a diagnosis was reached, or a referral for operation or recommendation for further drug treatment can be made); only 10.6% (22/207) of cases were not solved because they reached a poor effort due to subjective problems (poor condition or unexplained feeling of discomfort in absence of objective parameters to stop the test), thus, requiring the test to be repeated. CPET is evidently a very sophisticated and useful test, giving us valuable data that can help us greatly in solving the clinical problems of our patients.

Competing interests
The author stated that this particular work was not commercially sponsored or supported by any grant, and that it is the author’s own work (without co-authors). The author declared to have no conflicts of interest.

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