

# Cardiopulmonary exercise testing in differential diagnosis of dyspnea

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## INTRODUCTION

**D**yspnea is a common exercise-induced symptom whose treatment is often improperly because the pathophysiology causing the exercise intolerance is not well understood. The most important requirement for exercise performance is transport of oxygen to support the bioenergetic processes in the muscle cells (including, of course, the heart) and elimination of the carbon dioxide formed as a product of exercise metabolism. Thus, appropriate cardiovascular and respiratory responses are required and the patient's symptoms should be sought for in terms of a gas exchange defect between the cells and environment. The defect may be in the lungs, heart, peripheral or pulmonary circulation, hemoglobin content and quality, metabolic disorders, psychogenic disorders or the muscles themselves, or there could be combinations of these defects. Cardiopulmonary exercise testing (CPET) allows the simultaneous study of the responses of the cardiovascular and ventilatory systems through the measurement and the integrative interpretation of a lot of parameters (1). □

## PARAMETERS

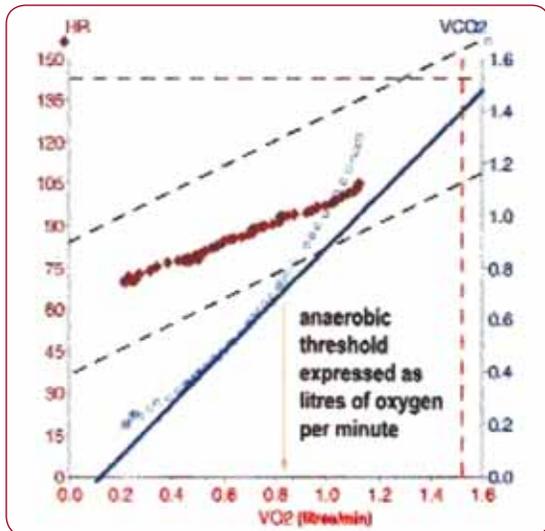
**E**xercise capacity can be quantified clinically by measurement of oxygen uptake ( $\text{VO}_2$ ), carbon dioxide production ( $\text{VCO}_2$ ) and minute ventilation (VE). These parameters are measured during exercise with rapidly responding gas analyzers capable of breath-by-breath determination of  $\text{O}_2$  and  $\text{CO}_2$  concentrations.

**The maximal  $\text{VO}_2$**  represents the highest  $\text{VO}_2$ , averaged over a 20-30 seconds, achievable as evidenced by failure for  $\text{VO}_2$  to increase despite increasing work rate; it is calculated as a product of highest cardiac output and difference between arterial and venous  $\text{O}_2$  content. At normal subjects  $\text{VO}_2$  has a linear increase at exercise and the maximal oxygen uptake usually reaches a plateau despite increasing workload. Many investigators reported that peak  $\text{VO}_2$  decrease with age and it is smaller in women than in men. Now, due to a lot of studies in this area, there are nomograms available to predict  $\text{VO}_2$  max depending on age, sex, high and weight (2).

**The ventilatory threshold (VT)**, formerly called anaerobic threshold is another index used to estimate exercise capacity (3). It is de-

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**FIGURE 1.** Determination of the anaerobic threshold by the point where the rate of increase in carbon dioxide output ( $VCO_2$ , ml/min) exceeds that of oxygen uptake ( $VO_2$ , ml/min). HR = heart rate (13)

defined as the highest  $VO_2$  that can be sustained without developing a lactic acidosis, a response that is generally seen at 60 to 70 percent of  $VO_{2max}$ . It has been suggested that the VT might be more predictive than the peak  $VO_2$  because it is less prone to error. In one report of 223 consecutive patients with heart failure, a  $VT < 11$  ml/kg/min was more predictive of six month mortality than a peak  $VO_2 < 14$  ml/kg/min (4). **Tidal Volume (VT)** is the volume of gas inspired and expired during one respiratory cycle. **Minute ventilation (VE)** is the volume of gas exhaled per minute, so is the product between VT and respiratory frequency. It's usually about 5-6l/min, but could rise at patients with high production of  $CO_2$ . A valuable estimating the degree of mismatching of ventilation to perfusion during exercise is the physiological dead space/tidal volume ratio ( $VD/VT$ ). At rest, the physiological dead space volume is normally about one-third of the Tidal Volume and it is reduced to about one-fifth during exercise. A possible alternative in patients who cannot achieve  $VO_{2max}$  is measurement of ventilatory efficiency, the  $VE/VCO_2$  ratio in early exercise (5). Heart failure is associated with an increase in VE (due to increased dead space ventilation) and an increase in  $VCO_2$  relative to  $VO_2$  (because of bicarbonate buffering of lactic acid). A metaanalysis of more reports concluded that a  $VE/VCO_2$  slope above 34 associated with severe heart failure, reduced survival during 18

month follow up of patients with heart failure, but it is also negative predictive of outcome in patients with preserved exercise capacity and  $VO_{2max} > 18$  ml/kg/min.  **$O_2$ pulse** is a report between  $O_2$  uptake and heart rate ( $VO_2/HR$ ); its values are dependent of stroke volume and its slope is linear. A higher  $VO_2/HR$  than predicted indicates better than average cardiorespiratory function, whereas a response with a lower  $VO_2/HR$  indicates poorer than average cardiorespiratory function.  **$O_2/WR$**  is another parameter which shows us the oxygen cost of performing work and which is the aerobic contribution to exercise. Low value suggests high anaerobic contribution and most patients with circulatory diseases (pulmonary, cardiac or peripheral) have  $\Delta VO_2/\Delta WR$  reduced. **Maximal voluntary ventilation** is a parameter calculated at rest, either direct, from a 12 seconds maneuver of rapid and deep breathing, or indirect by multiplying the **FEV<sub>1</sub>** (forced expiratory volume in 1 second) by 40 (respiratory rate per minute) (6). Normal values for MVV are available. The **breathing reserve (BR)** is expressed as either the difference between the maximal voluntary ventilation (MVV) and the maximum exercise ventilation (VE) in absolute terms, or this difference as a fraction of the MVV. Normal males have a BR of at least 11 l/min or 10-40% of the MVV. A low BR is characteristic of patients with primary lung disease (the smallest BR occurs in obstructive lung disease) and a high BR occurs when cardiovascular or other diseases limit exercise performance.

The cardiopulmonary exercise test is normally reported from a montage of nine graphs containing 15 plots, known as the 'nine panel plot'. This panel covers the majority of information obtained from the test. □

## DISORDERS LIMITING EXERCISE

### Hyperventilation/psychogenic disorders

Patients with psychogenic causes of dyspnea often have normal or near-normal exercise tolerance. In contrast to the gradual increase in respiratory frequency during progressive exercise in healthy persons, patients who have hyperventilation syndrome may have an abrupt onset of regular, rapid, shallow breathing that is disproportionate to the level of metabolic stress, with development of respiratory alkalosis. Hyperventilation might also start at rest, in anticipation of the exercise. Patients with hyperven-

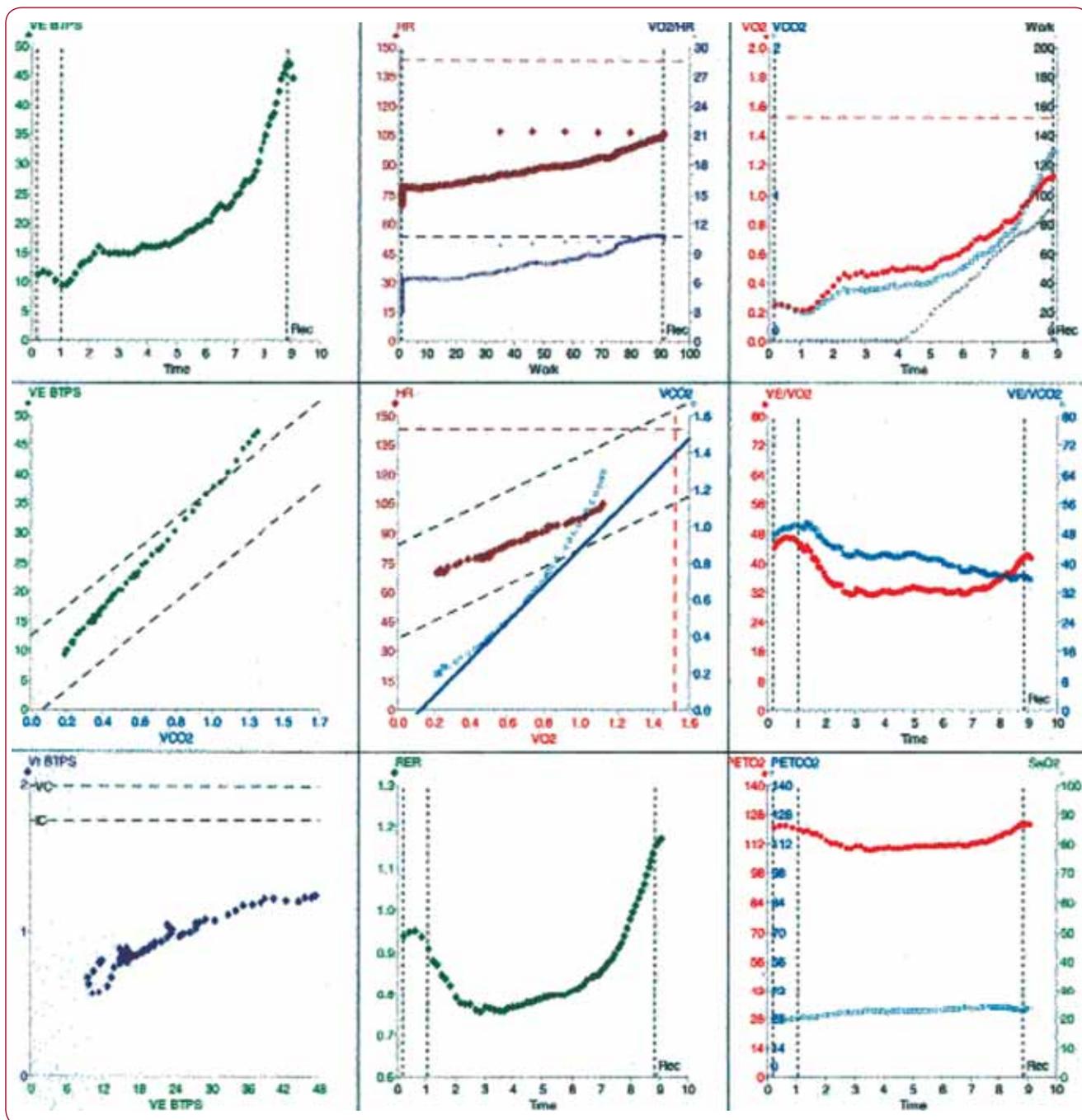


FIGURE 2. The “nine panel plot” (13)

tilation syndrome can have a variety of psychogenic disorders and they commonly complain of “asthma-like” symptoms of dyspnea.

**Obesity**

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 kilo-

gram of actual body weight ( $VO_{2max}/kg$ ). The increased metabolic requirements of moving the excess weight during exercise results in a disproportionately increased  $VO_2$ , heart rate, and VE at any given level of work. Obese subjects require increased  $VO_2$  to do a given work, so, obesity displaces the  $VO_2$ /work rate relationship upward, by approximately 5,8ml/min per kg of body weight, but the slope is unchanged (7). Coronary ischemia and diastolic

dysfunction are commonly associated with obesity and must be carefully excluded during CPET evaluation. Once other causes of dyspnea are excluded, obese patients should be enrolled in a weight reduction/aerobic training program and monitored for symptom improvement.

### Cardiac ischemia

Patients with a cardiac ischemia response pattern on CPET may have coronary disease or reduced oxygen delivery resulting from significant anemia. Exercise capacity is reduced, and anaerobic threshold is low as a result of the early onset of lactic acidosis. During exercise, heart rate is elevated and oxygen pulse is low, which is a surrogate marker of inadequate stroke volume augmentation during exercise, consecutively results a steepening of the heart rate- $\dot{V}O_2$  relation as the maximum work rate is approached (8). In these patients the rate of rise of  $\dot{V}O_2$  is slow relative to the increase in work rate. Changes in the ECG consistent with myocardial ischemia during exercise, combined with concurrent failure of  $\dot{V}O_2$  to increase normally diagnoses exercise induced myocardial ischemia. Ample ventilatory reserve is generally present and the  $\dot{V}E/\dot{V}CO_2$  at the VT is normal, which rapidly make us aware that the  $O_2$  flow problem is not pulmonary.

### Heart failure

Limitation of exercise capacity is one of the cardinal manifestations of heart failure, varying

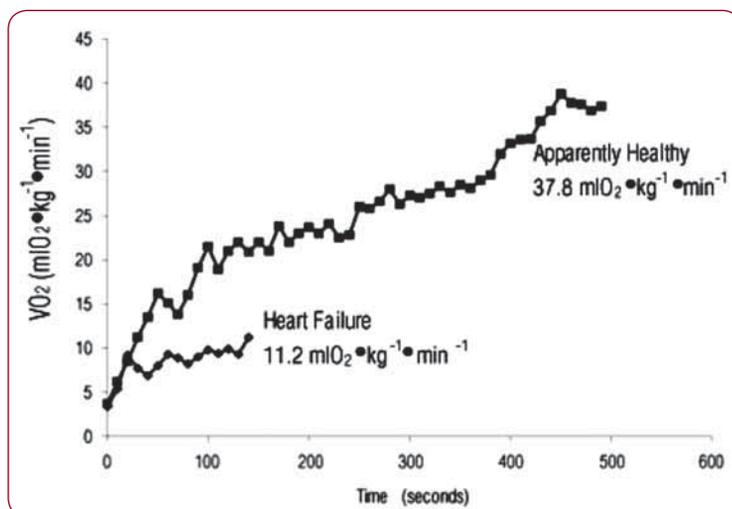


FIGURE 3. Oxygen consumption comparison during symptom-limited CPET: apparently healthy vs. heart failure (14)

directly with the severity of the disease and it occurs even in mild heart failure. Since HF patients often do not attain a true  $\dot{V}O_{2max}$ , the term peak  $\dot{V}O_2$  is often used. The peak  $\dot{V}O_2$  provides the most objective assessment of functional capacity in patients with HF, but its interpretation requires that the patient achieve the ventilatory threshold. The severity of HF is considered to be:

- none to mild, when  $\dot{V}O_2 > 20$  ml/kg/min and  $VT > 14$  ml/kg/min (class A)
- mild to moderate, when  $\dot{V}O_2 = 16-20$  ml/kg/min and  $VT = 11-14$  ml/kg/min (class B)
- moderate to severe, when  $\dot{V}O_2 = 10-15$  ml/kg/min and  $VT = 8-11$  ml/kg/min (class C)
- severe, when  $\dot{V}O_2 < 10$  ml/kg/min and  $VT < 8$  ml/kg/min (class D) (9).

The heart rate increase disproportionate given the slower increase of  $\dot{V}O_2$  resulting in a steepening of the HR- $\dot{V}O_2$  relation. HF is also associated with an increase in  $\dot{V}E$ , an increase in  $\dot{V}CO_2$  relative to  $\dot{V}O_2$  and an increase in  $\dot{V}E/\dot{V}CO_2$  slope which is also predictive of outcome for these patients. In severe HF the  $VD/VT$  becomes elevated because of ventilation-perfusion mismatching, but the BR is normal, which excludes pulmonary disease. The 2002 task force of the ACC/AHA has given a class I recommendation to the use of exercise testing with ventilatory gas analysis for the purpose of evaluating patients who are considered for cardiac transplantation (10).

### Respiratory disease

Patients with evidence of respiratory disease on CPET can demonstrate a wide variety of exercise patterns depending on the predominant mechanism of exercise limitation and disease severity, but they usually have low BR and high heart rate reserve, increase of  $VD/VT$  and  $p(a-ET)CO_2$ . In early **obstructive** lung disease, CPET responses may be normal, but exercise flow-volume loops can demonstrate expiratory flow limitation ( $FEV_1/VC$  is low). Postexercise spirometry after CPET can identify postexercise bronchospasm in patients who have occult asthma or are receiving inadequate asthma therapy. Patients with moderate to severe COPD demonstrate reduced exercise tolerance with achieving of the smallest breathing reserve, suggesting a ventilatory limitation to ex-

ercise. Anaerobic threshold may be normal, although the peak  $\text{VO}_2$  is low (11). Patients with **restrictive** lung diseases generally have reduced exercise capacity, a low peak  $\text{VO}_2$  and low anaerobic threshold. The VT increases to its maximum at a relatively low work rate and the ratio of VT to inspiratory capacity (which is low) nears a value of 1. The breathing frequency commonly exceeds 50 breaths per minute at the end of exercise. In contrast to obstructive lung diseases the  $\text{paO}_2$  decrease systematically at each work rate and not in a single step at low work rate as in COPD. Also the  $\Delta\text{VO}_2/\Delta\text{WR}$  may become reduced near peak  $\text{VO}_2$ , in contrast to COPD when it remains normal (12).

### Peripheral arterial diseases

In contrast to primary heart disease, the heart rate reserve is generally high because the patient stops the exercise (due to leg pain) before the heart can be maximally stressed. The maximum  $\text{VO}_2$  and the lactic acidosis threshold are reduced, the latter may not be even detectable. The ratio  $\Delta\text{VO}_2/\Delta\text{WR}$  is low and, in contrast to other cardiovascular disorders the ratio  $\Delta\text{VCO}_2/\Delta\text{WR}$  is also low, because the slow blood flow through the ischemic leg make that only a little part from the  $\text{CO}_2$  released locally

to be seen in the lung gas exchange. Finally, the parameters diagnostic for pulmonary disorders are normal.

### Anemia

Because anemia results in a reduced blood  $\text{O}_2$  carrying capacity, it compromises  $\text{O}_2$  delivery to the cells. Consequently, a low arterial content in  $\text{O}_2$  may be reached at a lower  $\text{VO}_2$  than normal, necessitating anaerobic mechanism for ATP generation, so metabolic acidosis and increase of lactate. A high cardiac output and heart rate are required to satisfy the tissue  $\text{O}_2$  requirement. It should be noted that the arterial blood gas tensions, the BR and the  $\text{VD}/\text{VT}$  are normal in anemia, even at maximal exercise. □

### CONCLUSION

CPET might not only distinguish between lung and cardiovascular disease, but also distinguish one cardiovascular disease from another, as a cause of exercise limitation. Coronary artery disease, chronic heart failure and peripheral vascular disease have abnormal patterns of exercise gas exchange unique to each and, therefore, can be distinguished one from other. □

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