DOI: https://doi.org/10.20883/jms.349

A thousand words about the cardiopulmonary exercise test in respiratory system diseases

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ABSTRACT

The cardiopulmonary exercise test (CPET) is designed to measure some physiological variables related to the function of the cardiovascular and respiratory systems during exercise. Usually, the CPET is performed either on a treadmill or a cycle ergometer. In this mini-review, we describe a set of parameters which are most commonly used to quantify CPET. We also summarize clinical indications for this test and interpretation of the obtained results in patients with respiratory system diseases. The CPET, if made appropriately, may deliver valuable information helpful in the diagnosis, e.g., of unexplained dyspnea, and prognosis, e.g., in chronic obturatory pulmonary disease, pulmonary hypertension, or interstitial lung diseases.

Keywords: respiratory diseases, cardiopulmonary exercise test, VCO_2, VO_2.

Cardiopulmonary exercise test (CPET) is a non-invasive method that combines progressive exercise stress with measures of the function of the cardiovascular and respiratory system [1–3]. During this test, a set of signals is continuously monitored, for instance: ECG, arterial blood pressure, oxygen saturation (sO_2), breathing rate, tidal volume, carbon dioxide output (VCO_2) or oxygen uptake (VO_2) [1–9]. The complex information delivered by CPET goes beyond the lungs, airways, and heart. CPET results also depend on the neuropsychological factors, hemoglobin concentration (e.g., anemia) and quality (e.g., thalassemia), peripheral circulation, the function of leg muscles and even mitochondria [1–3, 5–7]. For these reasons, it is believed that CPET gives an insight into integrative responses of several systems involved in the exercise physiology.

Many patients with respiratory or cardiac diseases complain about dyspnea which starts, evolves or exacerbates on exertion. Employing diagnostic tests performed at rest is misleading in such individuals. Therefore, using a controlled exercise in clinical conditions to provoke and reproduce patient's symptoms is commonly accepted. In contrast to the standard exercise test with ECG, the CPET provides much more useful physiological and clinical information [1–3, 5–10]. This test permits to evaluate a patient at the submaximal or even maximal exercise, until limiting symptoms or exhaustion appear.

During the CPET, patients either walk or run on a treadmill or sit and ride a cycle ergometer [3]. A set of ECG electrodes, a sO_2 sensor, a brachial cuff for blood pressure monitoring, and a mouthpiece or mask with a system measuring breathing rate, gas volumes and exchange are attached to a patient before the test [1–3]. Exercise during the CPET initiates after a short warm-up, followed by

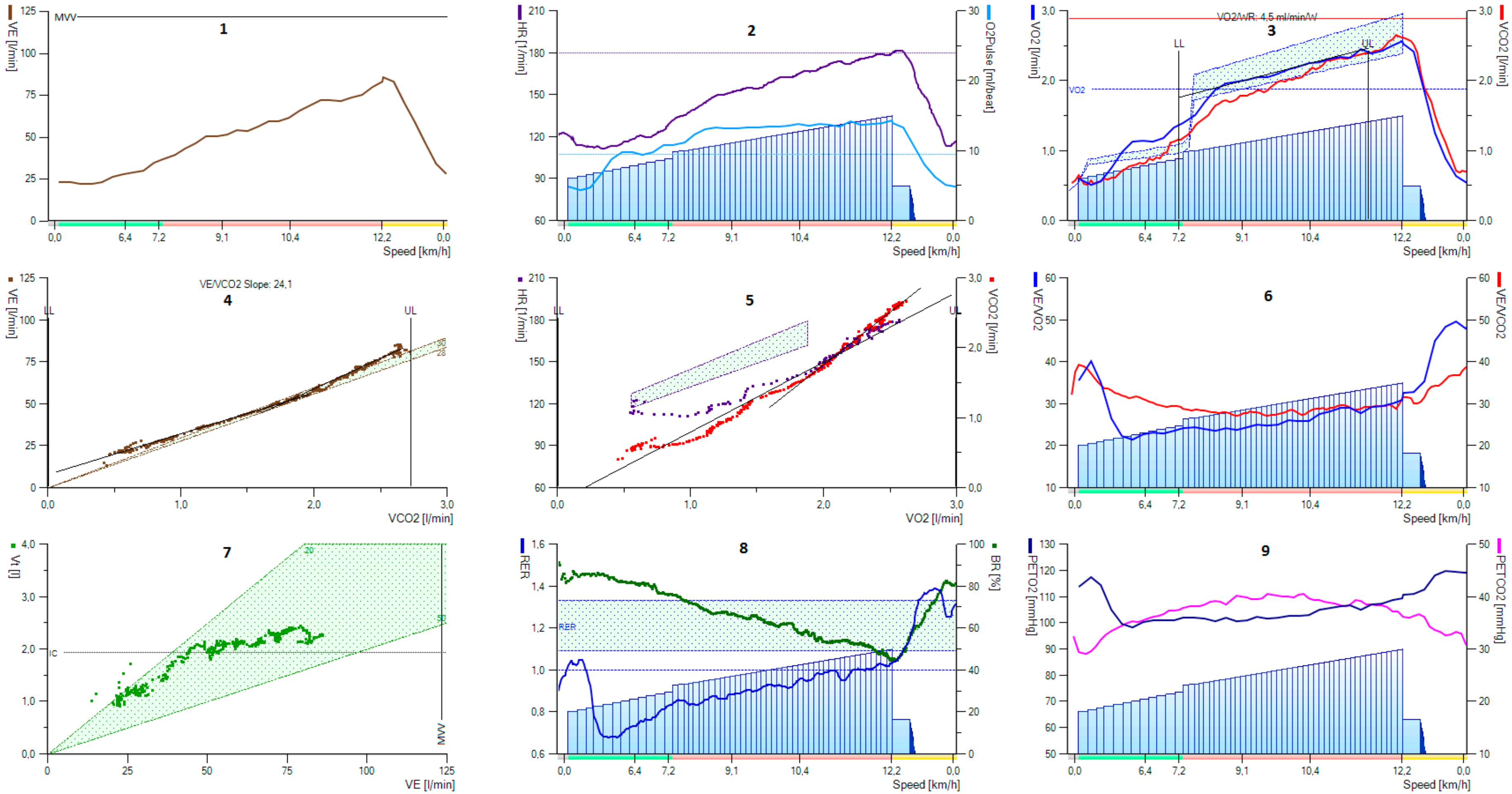

Figure 1. Nine-panel plot graphical display with results of the CPET in a 25-year old female patient with obesity (body mass – 94 kg, body mass index – 31.1 kg/m^2) complaining about exertional dyspnea of unknown origin. The test was terminated when the dyspnea became a limiting symptom; the perceived exhaustion by the 10-grade Borg scale was 9/10 [12]. The maximal value of VO_{2max} was 2.5 l/min but normalized to body mass VO_{2max}/kg was 26.6 ml/kg/min what corresponded to 73% of the predicted VO_{2max}/kg. There was no drop in sO_2. The CPET results were within normal range (with the exception of VO_{2max}), neither cardiac nor pulmonary dysfunction was observed. The patient reached nearly maximal predicted heart rate. There was a short increase of pulse O_2 (Panel 2), mainly during the warm-up and the early phase of the exercise, which then flattened into a plateau. After the premature increase of RER above 1 (due to initial hyperventilation), there was a rapid normalization and RER reached the value of 1 again in the second half of exercise. Neither ST-segment changes suggestive of myocardial ischemia nor cardiac arrhythmias were observed. The final CPET result was normal. Other pulmonary and cardiac tests, including echocardiography and spirometry, were normal as well. Finally, a mildly reduced exercise tolerance due to a sedentary life and obesity was diagnosed. Upper panels: panel 1: VE plotted over time (or treadmill speed); panel 2: heart rate (HR) and oxygen pulse (VO_2/HR) plotted over time; panel 3: VCO_2 and VO_2 plotted over time. Middle panels: panel 4: VE plotted over VCO_2 to determine the change in the VE/VCO_2 slope; panel 5: HR and VCO_2 plotted over VO_2; panel 6: ventilatory equivalents VE/VCO_2 and VE/VO_2 plotted over time. Lower panels: panel 7: VT plotted over VE; panel 8: RER and breathing reserve (BR) plotted over time; panel 9: end-tidal partial pressures of O_2 ($PETO_2$) and CO_2 ($PETCO_2$) plotted over time. For panels with speed on the X-axis, i.e., 1, 2, 3, 6, 8 and 9, different phases of CPET are marked with colors: warm-up with green, exercise with red, and recovery with yellow

a gradually increasing exercise and ending with post-exercise recovery. A list of directly measured or indirectly derived parameters acquired during the CPET is shown in **Table 1**.

The CPET can be used in healthy people, athletes for fitness evaluation or to determine their training loads. In clinical practice, this test is applied in a number of patients suffering from heart and pulmonary diseases such as heart failure or chronic respiratory failure or other diseases of the respiratory system [1–10]. The CPET may be used to distinguish cardiac from pulmonary causes of dyspnea, to assess the response to applied therapy both in cardiac and pulmonary patients, to perform pre-rehabilitation or pre-surgery evaluation in high-risk patients [5, 6]. This test can also be applied in individuals with heart or respiratory failure who are potential candidates for heart or lung transplantation, respectively [1–3, 5–10].

1 V	2 C	3 V + C + M
4 VE	5 C	6 VE
7 V	8 M	9 VE

Figure 2. The nine-panel diagram used to describe the results of the CPET. Panels mainly applied for the evaluation of the function of the respiratory system are 1 & 7 (yellow) for the ventilation and 4, 6 & 9 (blue) for the ventilation efficiency. Panels for the cardiovascular function are 2 and 5 (green). Panel 8 (red) is used to determine metabolic abnormalities, and panel 3 (orange) depends on the function of the respiratory system, cardiovascular system, and metabolic factors [1, 11]

Table 1. Typical signals and parameters measured or derived during a standard CPET [1–9]

	Measured Signals
HR	Heart rate from ECG in beats/minute
Vt	Tidal volume of each breath in ml
BF	Breathing frequency or rate in breaths/minute
VCO_2	The volume of carbon dioxide output in ml/minute
VO_2	The volume of oxygen uptake in ml/minute. An index of aerobic exercise capacity
$PETO_2$	Peak end-tidal oxygen partial pressure in mmHg
$PETCO_2$	Peak end-tidal carbon dioxide partial pressure in mmHg. An index of the ventilation-perfusion matching in the lung and the level of arterial PCO_2
sO_2	Peripheral arterial oxygen saturation in %
Treadmill speed	The speed of the treadmill in km/h
Watt	The workload for cycle ergometer in Watt
	Derived parameters
VE	Minute ventilation — accumulative volume of all tidal volumes during one minute in l/minute
RER	Respiratory exchange ratio, i.e., the ratio of VCO_2 to VO_2 — it shows the balance between VCO_2 and VO_2
Pulse O_2	The ratio of VO_2 to heart rate in ml/beat — it shows how much oxygen is delivered to tissues during one cardiac beat and is proportional to the stroke volume
VE/VCO_2	The ventilatory equivalent for CO_2 — it shows the amounts of air in ml ventilated in a minute (VE) needed to exhale and remove 1 ml of CO_2 (VCO_2) or efficiency for CO_2 pulmonary clearance. It reflects a proper matching of pulmonary ventilation to perfusion
VE/VO_2	The ventilatory equivalent for O_2 — it shows the amounts of air in ml ventilated in a minute (VE) needed to deliver with inhalation 1 ml of oxygen (VO_2) or ventilatory efficiency for oxygen delivery
BR	Breathing reserve, i.e., the difference between the predicted maximal VE and peak VE measured during the CPET
VO_{2peak}	The peak or highest oxygen uptake during CPET — it corresponds to the patient's aerobic capacity
VO_{2max}	The highest VO_2 value that can be attained by the patient regardless of still increasing treadmill speed or workload on a cycle ergometer
VO_{2max}/kg	VO_{2max} divided by body weight in kilograms
AT or VT1	Anaerobic threshold (AT) or the first ventilatory threshold — the point during a CPET beyond which the aerobic metabolism is supplemented with anaerobic metabolism
RCP or VT2	Respiratory compensation point (RCP) or the second ventilatory threshold — the point beyond which there is respiratory compensation for metabolic acidemia generated during an extensive exercise with anaerobic metabolism. After this point, the acidemia becomes an additional (to CO_2) stimulus (through chemoreceptors) for increased ventilation

There are many different reasons to order CPET in patients with respiratory system diseases or symptoms. A list of clinical indications for CPET in such patients is presented in **Table 2**.

Parameters measured during CPET are presented in a graphical display [1–3, 5, 6, 9, 11]. Typically, results of the CPET are presented in 9 separate panels (**Figure 1**) showing either changes of values of measured parameters (e.g. VO_2, pulse O_2, VCO_2, VE/VCO_2, $PETO_2$, RER) during the CPET or mutual relations between different parameters (e.g. VT and VE, VO_2 and VCO_2).

The nine-panel plot was first proposed by Wasserman et al. in 1977, and, with some modifications, is still in use. Each of the nine plots can be assigned to mainly evaluate the respiratory system, circulatory system, their mutual interaction or some features of body metabolism related to energy production [1, 11]. An example of the nine-panel graph with results of a CPET performed in a 25-year old woman with unexplained exertional dyspnea is shown in **Figure 1**. The general rule for reading and interpretation of such nine-panel graphs is given in **Figure 2** — a set of different panels is used to estimate the ventilation, ventilatory efficiency, heart and circulation, or their combined effects. Panel number with RER is used to describe body metabolism related to O_2 and CO_2. The RER shows the balance between O_2 consumption and the total amount of CO_2 which first comes from burning fats and carbohydrates, and later when anaerobic processes also begin from buffering lactic acid by bicarbonate [1, 2, 8, 9, 11].

In practice, out of many possible parameters, only some have earned special attention for their usefulness in the diagnostic and prognostic eval-

Table 2. The most common clinical indications for CPET in patients with confirmed or suspected respiratory system disease or involvement of the respiratory system in other diseases [1–3, 5–10]

Clinical indication	Explanation
Dyspnea of unknown origin	– Diagnostic assessment of possible causes of dyspnea – Differentiation between potential cardiac and respiratory causes of dyspnea
COPD	– Diagnostic assessment of COPD – Prognostic stratification of a patient with COPD – Determination of exercise capacity and its limitation – Monitoring of treatment and therapeutic interventions – Evaluation of the disease progression – Screening for secondary pulmonary hypertension
Pulmonary hypertension (PAH)	– Diagnostic assessment of patients with a higher risk of PAH – Differentiation between the primary and secondary PAH – Prognostic stratification of a patient with PAH – Guiding and monitoring of the applied treatment – Evaluation of the disease progression
Pulmonary surgery	– Pre-operative assessment for risk quantification in moderate- and high-risk patients with cardiac and pulmonary diseases – more accurate than standard pulmonary functional testing – Prediction of postoperative pulmonary complications – Prediction of exercise limitation in patients undergoing lung volume reduction surgery
Interstitial Lung Disease (ILD)	– Diagnostic assessment of ILD – Prognostic stratification of a patient with ILD – Screening for secondary pulmonary hypertension – Detection of pulmonary gas exchange abnormalities – Determination of the O_2 concentration value in the treatment – Evaluation of the disease progression
Exercise-Induced Bronchospasm (EIB)	– Diagnostic assessment of EIB. Pulmonary function tests must be performed before and after the CPET to determine FEV1 and PEF. If FEV1 drops more than 10% compared with the pre-exercise level, then EIB is diagnosed – Evaluation of the disease progression
Cystic Fibrosis	– Prognostic stratification of a patient with cystic fibrosis – Evaluation of the effectiveness of the applied treatment – Guiding and monitoring of the applied treatment – Evaluation of the progression of respiratory system involvement
Heart failure	– Assessment of the contribution of lung disease to the severity of HF – Detection of pulmonary gas exchange abnormalities accompanying HF – Evaluation of the clinical effects of secondary PAH due to HF on the function of the respiratory system

Table 3. Summary of the most common CPET parameters used for the evaluation of the respiratory system with clinical interpretation [1–3, 5–9]

Parameter	CPET result	Interpretation related to pulmonary diseases
VO_{2max}	Low	Lung or airway disease with low capacity of getting O_2 into the lungs or from the lungs into the blood. An unfit patient who cannot reach maximum exercise capacity; The degree of the impairment of the cardiorespiratory function based on VO_{2max}: < 20 ml/kg/min — minor < 15 ml kg/min — moderate; < 10 ml kg/min — severe.
	Normal/high	No lung disease; VO_{2max} >80% of predicted value — low probability of clinically significant pathology of either the cardiovascular or respiratory systems.
HR	Low	Not reaching predicted value with dyspnea or exhaustion suggests lung disease; unfit patient; Bradyarrhythmias (e.g., sick sinus syndrome, 2nd-degree atrioventricular block); Effect of drugs slowing heart rate, e.g., beta-blockers, verapamil, diltiazem.
	Normal/high	Does not suggest lung disease; HR >80% of the predicted maximal HR at peak exercise equals a low HR reserve; A fast increase in HR in patients with heart failure or unfit individuals; Well preserved or high HR reserve if exercise is limited by other than cardiac causes, for example by lung disease.
VE	Low/normal	Excludes lung disease; Should not reach 80% of the predicted value during a CPET in a healthy individual.
	High	Suggests a lung disease, particularly when VE reaches 80% of predicted value (a low ventilatory reserve) and VO_{2max} is low. A flatter Vt/VE slope with a visible plateau in patients with lung disease; Poor or no Vt increase during a CPET suggests a lung disease.
Pulse O_2	Low	A plateau in the O_2 pulse at a low value and during low workload or treadmill speed suggests a limited cardiac output or presence of anemia or pathology within pulmonary circulation;
	Normal/high	O_2 pulse of at least 10 ml/beat at peak exercise should be observed in healthy people;
VCO_2	Low	High VE with low VCO_2 suggests a lung disease
	High	Exclusion of lung disease as CO_2 is effectively eliminated from the blood.
VE/VCO_2	Low	A lack of fall of $VEqCO_2$ below 30 suggests an impaired gas exchange in the lungs — usually in pulmonary vascular disease.
	High	High VE/VCO_2 (>30) suggests poor perfusion of some lung areas not participating in the gas exchange and increased dead space in the respiratory system. Most commonly it translates to the presence of pulmonary vascular disease. In patients with HF indicates a poor prognosis.
RER	Low < 1.0	< 1.0 only in the early and middle part of a CPET. The exercise phase should be near or cross 1 at the end. If CPET ends with RER < 1, then exercise intensity was too low.
	Normal/high > 1.0	If in the latter part of CPET then submaximal or maximal exercise capacity is reached; If at the beginning then probably due to hyperventilation and agitated emotional status; Erratic RER behavior during a CPET (falls and increases) suggests dysfunctional breathing. Value > 1 indicate an intense effort and >1.1 corresponds to exhaustion or near-exhaustion level reached during CPET.
VE/VO_2	Low	Suggests a lung disease or pulmonary vascular disease.
	Normal/high	Excludes a lung disease.
$PETCO_2$	Low	Acute or chronic hyperventilation
	High	Increase by 3–8 mm Hg suggests pulmonary vascular disease
RCP	Not visible or uncertain	Presence of lung disease or poor ventilation is a limiting factor of exercise capacity, and a patient is unable able to exercise until academia develops.
	Normal/high	A clear RCP is a marker of acidemia developed during exercise (an expected physiological response to maximal physical effort). If RCP is present, then ventilation is not a limiting factor of exercise and excludes a lung disease.
BR	Low	When accompanied by low VO_2 then typical for COPD. When accompanied by normal/high VO_2 then typical for people with high cardiovascular capacity, e.g., endurance athletes.
	Normal/High	In patients with cardiac disease, for example, HF.
SpO_2	Low	A fall of more than 4% during CPET suggests a disease of the lungs or the pulmonary circulation accompanied by impaired gas exchange. It may also be present in patients with right-to-left cardiac or aortic-pulmonary shunts.
	Normal	Usually in patients with cardiac diseases and no right-to-left shunts. Should exclude lung disease

uation of a patient with respiratory diseases. For example, VO_{2max} is the most commonly measured single parameter during CPET. When VO_{2max} is less than 80% of the predicted value, then it may indicate some lung pathology [1–3, 5–11]. However, a reduced VO_{2max} can also be found in patients with heart failure, ischemic heart disease, some cardiomyopathies, anemia or unfit individuals. It is worth mentioning that typically VO_{2max} gradually declines with aging. Although VO_{2max} is the most popular parameter in the CPET description, it is not sufficient to describe and diagnose all pathologies responsible for exertional dyspnea or other pathologies from the respiratory system.

Unfortunately, there is no single variable exclusively characteristic for the respiratory system diseases. For this reason, a set of different parameters, including HR, VE, pulse O_2, VE/VCO_2, sO_2, must always be reviewed in concert to make an appropriate clinical decision. **Table 3** summarizes such CPET parameters with their clinical interpretation.

It is worth mentioning that CPET is useful not only as a confirmatory but also in ruling out respiratory diseases and pathologies as causes of exertional dyspnea or poor exercise capacity [2, 3, 5–8]. The probability that dyspnea originates in the respiratory system is low if a patient has achieved at least predicted value of VO_2, HR, pulse O_2, VE/VO_2, and RCP with low to normal VE, no or irrelevant (< 4%) drop in sO_2 and a distinct RCP during this test.

The CPET is a valuable method in the diagnosis and risk stratification of patients with dyspnea, suspected and confirmed respiratory system diseases. It is also helpful in monitoring the progress of respiratory diseases and guiding the applied therapy. This test quantifies an integrative response of the cardiovascular and respiratory systems combined with metabolic factors (hemoglobin concentration, aerobic and anaerobic metabolism) to a controlled exercise. The examination of patients with respiratory diseases during exercise reveals new and clinically significant information which, in another case, might be inaccessible with resting measurements.

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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Acceptance for editing: 2019-05-09
Acceptance for publication: 2019-06-29

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