REVIEW

Cardiopulmonary exercise test in clinical practice, evaluation of myocardial ischemia

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Abstract: In patients presenting cardiovascular, pulmonary, muscular and metabolic diseases, exercise testing continues to be a predictive and diagnosis source of information. Diagnosis and assessment of coronary artery disease (known or suspected) encompass clinical and risk factors evaluation and well-defined non-invasive and invasive tests. Cardiopulmonary exercise test (CPET) is an evidence-based evaluation technique in Europe, USA and other countries. It consists in applying, directly supervised by a physician, a standardized incremental physiological stress (using cycle ergometer or treadmill) until the patient reaches the anaerobic threshold. CPET can assess the presence of myocardial ischemia, by three parameters: oxygen pulse, maximum oxygen uptake curve and elevation and relationship between maximum oxygen uptake variation and load variation. Furthermore, the CPET is useful in assessing the prognosis of cardiac patients, in choosing the most effective treatment, and in evaluating the response to treatment post-acute coronary syndrome, post-primary percutaneous coronary intervention or assessment of unexplained dyspnoea or myocardial ischemia in heart failure patients. CPET has a higher sensitivity, specificity, positive predictive value and negative predictive value as compared to standard ECG stress testing in patients with suspected myocardial ischemia.
In this paper a brief review of current indications, analysis of standardized nine panel plot interpretation of CPET parameters related to myocardial ischemia are depicted.
Keywords: cardiopulmonary exercise test, indications, oxygen consumption, anaerobic threshold, myocardial ischemia.

Rezumat: La pacienții care prezintă afecțiuni cardiovasculare, pulmonare și metabolice, testarea fiziologică la efort continuă să fie o sursă de informație predictivă și diagnostică. Evaluarea factorilor de risc, clinică precum și utilizarea adecvată a metodelor neinvazive și invazive sunt fundamentale în diagnosticul și evaluarea bolii cardiace ischemice (cunoscute sau suspectate).
Testul de efort cardiopulmonar (CPET) reprezintă o metodă bine-definită de evaluare neinvazivă utilizată în Europa, SUA și alte țări. Ea constă în aplicarea, direct supravegheată de către medic, a unui stres fiziologic progresiv standardizat (folosind un cicloergometru sau covor rulant) până când pacientul atinge pragul anaerob. CPET poate evalua prezența ischemiei miocardice, prin trei parametri: pulsul de oxigen, aspectul curbei maxime de absorbție a oxigenului și relația dintre variația maximă a absorbției de oxigen și modificarea încărcăturii la efort. Suplimentar, CPET este util în evaluarea prognosticului pacienților cardiovasculari, în alegerea celei mai eficiente scheme de tratament și în evaluarea răspunsului la tratamentul post sindrom coronarian acut, post intervenție coronariană percutană primară sau în diagnosticul dispneei inexplicabile, a ischemiei miocardice la pacienți cu insuficiență cardiacă. CPET are o sensibilitate, specificitate, valoare predictivă pozitivă și valoare predictivă negativă mai ridicată comparativ cu testul standard de efort ECG la pacienții cu ischemie miocardică suspectată.
În acest articol sunt trecute în revistă indicațiilor actuale, analiza interpretării standardizate a celor nouă panouri a parametrilor testului de efort cardiopulmonar corelați cu ischemia miocardică.
Cuvinte cheie: test de efort cardiopulmonar, indicații, consum de oxigen, prag anaerob, ischemie miocardică.

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List of abbreviations used in text

AT	Anaerobic threshold
CAD	Coronary artery disease
CPET (or CPX)	Cardiopulmonary exercise test
CTEPH	Chronic thromboembolic pulmonary hypertension
CV	Cardiovascular
FEV1	Forced expiratory volume measured during the first second of the forced breath
HF	Heart failure
HR	Heart rate
HR/VO_2	Heart rate – Oxygen uptake relationship
IC	Inspiratory capacity
MVV= FEV1x40	Maximal voluntary ventilation: volume of air expired in a specified period during repetitive maximal effort
PAH	Pulmonary arterial hypertension
Peak VO_2	Oxygen utilisation (mLO_2 x kg-1x min-1)
$PETCO_2$	End-tidal partial pressure of CO_2 (mmHg)
$PETO_2$	End-tidal partial pressures of O_2 (mmHg)
PVOD	Pulmonary Veno-Occlusive Disease
PTP	Pretest probability
RC	Respiratory compensation
RER	Respiratory exchange ratio (respiratory quotient), RER=VCO_2/VO_2
SPTD	Standard conditions: temperature 0 degrees Celsius, pressure 760 mmHg and dry
VC	Vital capacity
VCO_2	Carbon dioxide production/min corrected for STPD conditions
VD/VT	Dead Space to Tidal Volume ratio
VE	Ventilation
VE/VCO_2	Minute ventilation/carbon dioxide production
VO_2	Oxygen consumption/min corrected for STPD conditions
VO_2/HR	Oxygen pulse
VO_{2max}	Maximal O_2 uptake
VT	Tidal volume (mLO_2 x kg-1 x min-1)
WR	Work rate
$\Delta VO_2/\Delta WR$	Oxygen delivery (uptake)

INTRODUCTION

In patients presenting cardiovascular (CV), pulmonary or association of both diseases, exercise testing continues to be a predictive and diagnosis source of information. Diagnosis and assessment of coronary artery disease (known or suspected) encompass clinical and risk factors evaluation and well-defined non-invasive and invasive tests.

Currently, non-invasive tests commonly used to diagnose the presence of coronary artery disease (CAD) can vary in sensitivity (45-97%) and specificity (61-95%), accordingly to different authors[1].

Recommendations for using non-invasive tools need to take into account the pre-test probability (PTP).[1] In patients with stable angina symptoms and PTP at 15% to 65% intervals, an exercise ECG test could be used as an initial evaluation test. Electrocardiogram exercise testing has inherent limits described elsewhere, wide variability in reported sensitivity (45-50%) and specificity (85-90%), respectively[2,3].

Cardiopulmonary exercise testing (abbreviated CPET or CPX) is a non-invasive diagnostic technique used to evaluate the physiologic response of the cardiovascular, pulmonary and muscle-energetic systems to an increase in physical stress, especially in cardiovascular and pulmonary disease suspected or diagnosed patients[4,5]. It is a distinct exercise testing that provides accurate and objective quantification of cardiorespiratory fitness (peak VO_2)[6,7].

CPETs are used, and should be used more and more, with cardiac patients. Indeed, the CPET evaluates the functional capacity and helps to identify the cardiac, pulmonary or peripheral origin of a possible reduced functional capacity.

Furthermore, the CPET is useful in assessing the prognosis of cardiac patients, in choosing the most effective treatment, and in evaluating the response to treatment. The term "cardiac disease" comprises several disorders that show typical and different pattern of gas kinetic during exercise. For this reason, it is im-

portant to know the specific typical behaviour of each cardiac disease before analysing the tests.

Using treadmill or electromagnetically braked cycle ergometer (preferred in most European countries), the progressive incremental workload exercise test (ramp) is frequently used for patients clinical evaluation; it is the most appropriate to obtain data about cardiac and pulmonary function, the functional capacity, the prognosis, and the response to therapy.

In the last two decades, applications of CPET are increasing, being used in diagnostic, appraising therapeutic regimens and prognostic recommendations in heart failure (HF) patients, valvular diseases, hypertrophic cardiomyopathy, pulmonary interstitial and vascular diseases. The use of CPET affords combined data illustrating exercise physiology in addition to non-invasive measurements (especially echocardiographic) of cardiac anatomy and function[8]. Table 1 outline the current indications of CPET.

The combined analysis of several parameters, which are obtained by incremental workload protocols, provides the most accurate information.

Data provided by the CPET relevant to gas exchange measurements (ventilation versus CO_2 output VE/VCO_2 peak, analysis of O_2 pulse and $\Delta VO_2/\Delta WR$ slope) can lead to identifying exercise-induced myocardial ischaemia, especially when conduction of rhythm disturbances are present at rest[13-16].

In a recently published study, Belardinelli et al. present that in patients with chest pain, CPET indicates a better diagnostic and predictive accuracy than standard exercise test in detection or rule-out obstructive CAD[17].

Current guidelines for the management of stable CAD do not include CPET in the diagnostic algorithm of myocardial ischemia[1].

A supervised CPET is recommended to prescribe an adapted physical activity and cardiac rehabilitation programme post-acute coronary syndrome, post-primary percutaneous coronary intervention or assessment of unexplained dyspnoea or myocardial ischemia in HF patients[18-20].

Nevertheless, in patients with diabetes mellitus usefulness of CPET complementary to standard exercise testing needs further evidence, in order to assess functional capacity and exercise-induced ischemia, especially when resting electrocardiogram is normal and interpretable[8]. Presence of anginal symptoms secon-

Table 1. Adapted current indications for CPET[9-12]

1. Evaluation of exercise tolerance
Determination of functional impairment or capacity (peak VO_2)
Determination of exercise-limiting factors and underlying pathophysiologic mechanisms
2. Evaluation of undiagnosed exercise intolerance
Assessing liability of cardiac and pulmonary aetiology in coexisting disease
Symptoms disproportionate to resting pulmonary and cardiac tests
Unexplained dyspnoea when initial CPET is non diagnostic
3. Evaluation of patients with cardiovascular disease
Functional evaluation and prognosis in chronic HF patients
Selection candidates for cardiac transplantation (pre-transplant risk-stratification)
Evaluation of exercise limitation and improvements in exercise tolerance after heart surgery in patients with congenital heart disease
Exercise prescription and monitoring response to exercise training for cardiac rehabilitation
4. Evaluation of patients with respiratory disease
Functional impairment assessment
• Functional and prognostic evaluation of patients with chronic obstructive pulmonary disease • Functional and prognostic evaluation of patients with interstitial lung diseases, including documentation of therapeutic response to potentially toxic therapeutic regimens • Functional and prognostic evaluation of patients with pulmonary vascular disease (PAH, PVOD, pulmonary capillary haemangiomatosis, CTEPH, and other) • Functional and prognostic evaluation of patients with cystic fibrosis • Detection of exercise-induced bronchoconstriction
5. Specific clinical applications
Preoperative evaluation • Lung cancer resection surgery • Lung volume reduction surgery (i.e. for emphysema patients) • Elderly patients undergoing major abdominal surgery (assessing cardiovascular reserve and calculating CV risk) • Evaluation for lung or heart–lung transplantation
Exercise evaluation and a prescription for pulmonary rehabilitation
Evaluation for impairment–disability

dary to abnormalities of coronary artery tract where the presence of ischemia (ST-segment changes) can be assessed using CPET.

CARDIOPULMONARY EXERCISE NINE-PANEL PLOT

Using CPET to evaluate the gas exchange between the body cells and atmosphere through the interconnected cardiovascular and respiratory systems, can delineate the pathophysiology of performance restraint[21]. The nine-panel graphical array describes the cardiovascular, ventilatory, ventilation-perfusion matching and metabolic responses to exercise. Starting from 1997, specific recommendations of graphical CPET panels, panels display and axes, were published. In 2017, Dumitrescu and Rosenkranz presented an update on the graphical data display for clinical CPET[22].

Panel 1 – VO_2 and VCO_2 gas kinetics

Panel 1 is the first panel to be observed in the identification of possible exercise limitation. The VO_2 and VCO_2 gas kinetics analysis could enlighten a possible cardiovascular or respiratory limitation. In healthy subjects performing a 10 minutes CPET, there is a linear increment of workload to O_2 consumption (VO_2). Continuously to workout, VO_2 increases at a standard rate of 10ml/min/W.[22] Within the panel, the parameters and their position, slope, and linearity correspondence should be analysed: VO_2, VCO_2 versus time and work rate.

Panel 2 – Heart rate and oxygen pulse

The oxygen pulse (VO_2/HR) defines the ratio of oxygen consumption to heart rate, inference of the VO_2 normalized for the heart rate (HR). The oxygen pulse is a defined cardiac performance index, particularly of the systolic output. In healthy subjects, the oxygen pulse increases as the workload increases and it reaches a plateau associated with a linear increase in HR. This pattern is a proper demonstration of a well-adjusted and adequate rise of the systolic output, correspondent to the HR and therefore, the cardiac output in response to exercise. A limitation of the systolic output is manifest in anaemia, hypoxemia or in the presence of muscle impairment.

Panel 3 – Respiratory equivalent. VO_2 and VCO_2 relationship (V-slope). The first method of anaerobic threshold (AT) estimation

Heart rate and VCO_2 calculated over VO_2 in panel 3, graphically presents the heart frequency tendency end the relation of VO_2 and VCO_2. Plotting the VO_2 and the VCO_2 with axes using the same scale, allows calculating the anaerobic threshold (AT). Up to the AT, the VCO_2 rises linearly to VO_2. Subsequently to the AT, the VCO_2 increases more rapidly and the slope of the curve depends on the degree of lactic acidosis buffering. The point of inflexion or the change of slope identifies the AT. The AT is reached anticipative in patients with altered cardiac function or muscle deconditioning.

Panel 4 – Ventilatory equivalent for O_2 and CO_2 (VE/VO_2 and VE/VCO_2). The second method of AT estimation

This panel graphically presents the tendency of ventilatory equivalents, the ratio of VE to VO_2 and VE to VCO_2 versus time and work rate. The analysis of ventilatory equivalents provides information to the clinician on the presence of dead space/current volume ratio (VD/VT) alterations, concomitant to the ventilation/perfusion ratio (V/Q) alterations. Furthermore, analysing the ventilatory equivalents, the AT point can be identified. VE/VO_2 slope outline an initial reduction followed by parallel direction to the work axis up to the AT. Therefore, it starts to increase related to ventilation increase, as a consequence of the CO_2 necessary to the lactic acidosis tamponade. During the isocapnic tamponade period, on the other hand, the VE/VCO_2 slope remains constant up to the respiratory compensation (RC) point. Beyond the point of RC also VE/VCO_2 increases, and this is due to the particular acidosis stimulus no longer compensated on the ventilatory drive.

Panel 5 – Ventilation

This panel presents the course of ventilation (L/min) during an increasing workload; an increase in ventilation (change of slope of the curve) at the moment of workload above the anaerobic threshold (AT), is evident. The increase in the ventilatory drive is secondary to the increase in CO_2, as a result of the lactic acidosis buffering and the increase in cellular metabolism. A second and further increase in ventilation is noticeable, which determines a second change in the curve slope, and a point of respiratory compensation is defined. At this moment the buffer systems are no longer able to compensate the pH, so that acidosis appears, being a strong stimulation for hyperventilation. The phase of isocapnic tamponade defines the start phase of the anaerobic threshold up to the point of respiratory compensation. The next phase at the respiratory compensation point is named uncompensated acidosis or respiratory compensation phase.

Panel 6 – Ventilatory efficacy

The VE/VCO_2 report provides indications on the organism's efficiency in eliminating the CO_2 produced during the metabolic processes. The slope of the curve defines the entity of ventilation increase, necessary to eliminate a given carbon dioxide production. A high slope value is associated with inefficient ventilation. There is no linearity of VE and VCO_2 above the respiratory compensation point. VE/VCO_2 relationship is validated as a powerful prognostic parameter for cardiac and pulmonary disease[22]. The *y*-axis intercept derived from the chart is related to the dead space ventilation[23].

Panel 7 – End-tidal partial pressures of O_2 ($PETO_2$, mmHg) and end-tidal partial pressure of CO_2 ($PETCO_2$, mmHg). The third method of AT estimation

The possible presence of ventilation/perfusion mismatch by decreased PET_{CO2} value is recognized in the ventilation/perfusion mismatch, and in case of hyperventilation. A concomitant increase of respiratory exchange ratio (panel 8) confirms and identify a situation of hyperventilation.

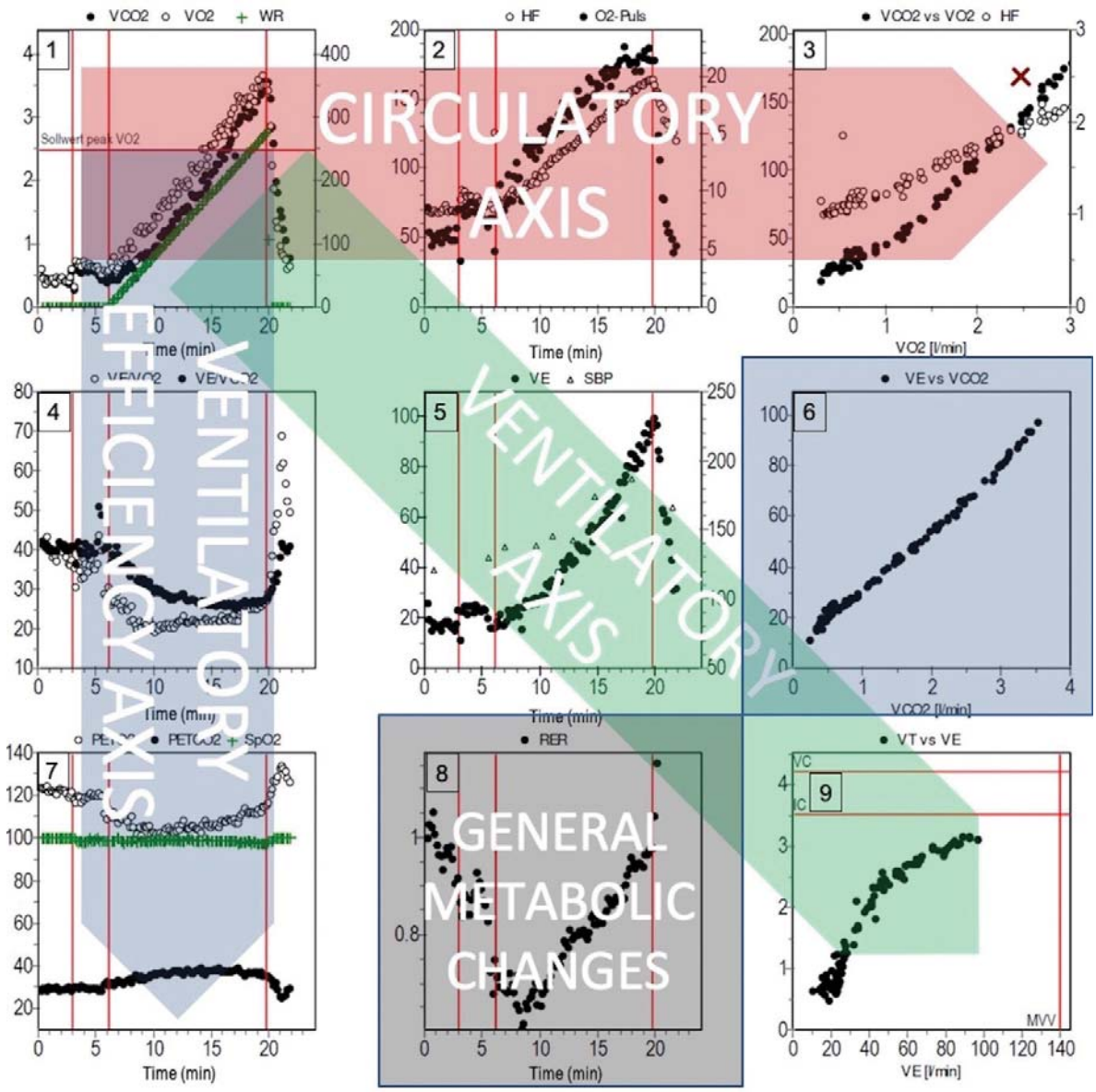

Figure 1. Presents CV, ventilatory, ventilation-perfusion matching and metabolic responses to exercise, displayed in standard nine-panel plot in a 51-year old athlete.

Panel 8 – Respiratory exchange ratio (respiratory quotient) (RER, R); RER=VCO_2/VO_2

The metabolic pathway of chemical energy production involves the use of oxygen for energy substrates oxidation (mainly carbohydrates and lipids) and CO_2 produced by oxidative reactions. In the ATP production when fatty acids are used,[23] O_2 molecules are needed to oxidize a fatty acid molecule and 16 molecules of CO_2 are produced (RER=16/23=0.7) The carbohydrates oxidation involves the utilization of six O_2 molecules and six molecules of CO_2 are produced (RER=6/6=1). During CPET on the y-axis, RER begins at 0.8 and the rise above 1.0 validates a maximal exercise test[21,24].

Panel 9 – Tidal volume, ventilation and respiratory frequency

The behaviour of ventilation is represented by the relation of tidal volume (VT) and ventilation (VE). The patient's vital capacity (VC) and inspiratory capacity (IC) is pictured in a parallel line to the x-axis, and the maximum voluntary ventilation (MVV=FEV1x40) on a parallel line to the y-axis. The origin isogram determines the ventilatory frequency. Breathing reserve is computed as MVV-VE using panel nine parameters[24].

Figure 1. The 9 panel plot data display and interpretation. Cardiopulmonary exercise test of a 51-year old athlete. Ramp test with an increment of 20 W/Min. Nine-panel plot display of the results, with 10-second averaging. Panels marked in red (1,2,3): „Circulatory axis", indicating that these panels show parameters important for the evaluation of circulatory function and circulatory reserve. Panels marked in green (1,5,9): „Ventilatory axis", indicating that these panels show parameters important for the evaluation of ventilatory function and ventilatory reserve. Panels marked in blue (1,4,6,7): „Ventilatory efficiency axis", indicating that these panels show parameters important for the evaluation of ventilatory efficiency and the relationship of ventilation to perfusion during exercise. Panels marked in grey (8): „General metabolic changes" (RER).

(Courtesy of Dr. med Daniel Dumitrescu, Klinik für Allgemeine und Interventionelle Kardiologie/Herz-und Diabeteszentrum Nordrhein-Westfalen, Germany)

FUNCTIONAL CAPACITY LIMITATION

Different cardiac, ventilatory, pulmonary or peripheric vessel abnormalities can induce exercise limitations. CPET focuses on a number of questions related to physiology and pathophysiology workout, though identification of the unique cause of limitation is complex.

By equating the CPET derived parameters, panel analyse, it becomes feasible to identify disorders underlying abnormalities[24,25] (Table 2).

CPET TO ASSESS MYOCARDIAL ISCHEMIA

Systematize clinical exercise test interpretation relays on key CPET variables for diagnostic and prognostic utility in patients with ischemic heart disease. The use of CPET to detected cardiovascular dysfunction induced by mild ischemia was not conclusive in previous studies; still, changes in specific parameters were identified as a response at incremental workload in extended myocardial ischemia.[26] Several case reports and research papers revealed the same exercise-induced left ventricular dysfunction detected by CPET, in both microvascular and macrovascular coronary artery disease (CAD)[27,28]. In particular cases, if the ECG is not accurate for myocardial ischemia (i.e. intraventricular blocks, pacemakers) gas exchange analysis can provide valuable information on O_2 consumption and O_2 supply imbalance in mitochondria[17].

Concomitant use of complementary functional methods with current cardiac imaging studies demonstrated a blunt value in the diagnosis of myocardial dysfunction, secondary to non-obstructive coronary artery disease in symptomatic patients. CPET can

Table 2

Reduced peak VO_2 (all limitations)			
Cardiovascular limitation	Ventilatory limitation	Ventilation-perfusion mismatching	Metabolic substrates abnormality
ECG changes	Ventilation (Panel 5)	VE/VCO_2 (Panel 6)	Respiratory exchange ratio (RER)
VO_2/WR (Panel 1)	Tidal volume, ventilation and respiratory frequency (Panel 9)	Increased ventilatory equivalent (panel 4)	Anaerobic threshold – first (AT1, VT1)
VO_2/HR (Panel 2)	Increase in residual functional capacity		Anaerobic threshold – second (AT2, VT2)
HR/VO_2 (Panel 3)	Exhaustion of ventilatory reserve		

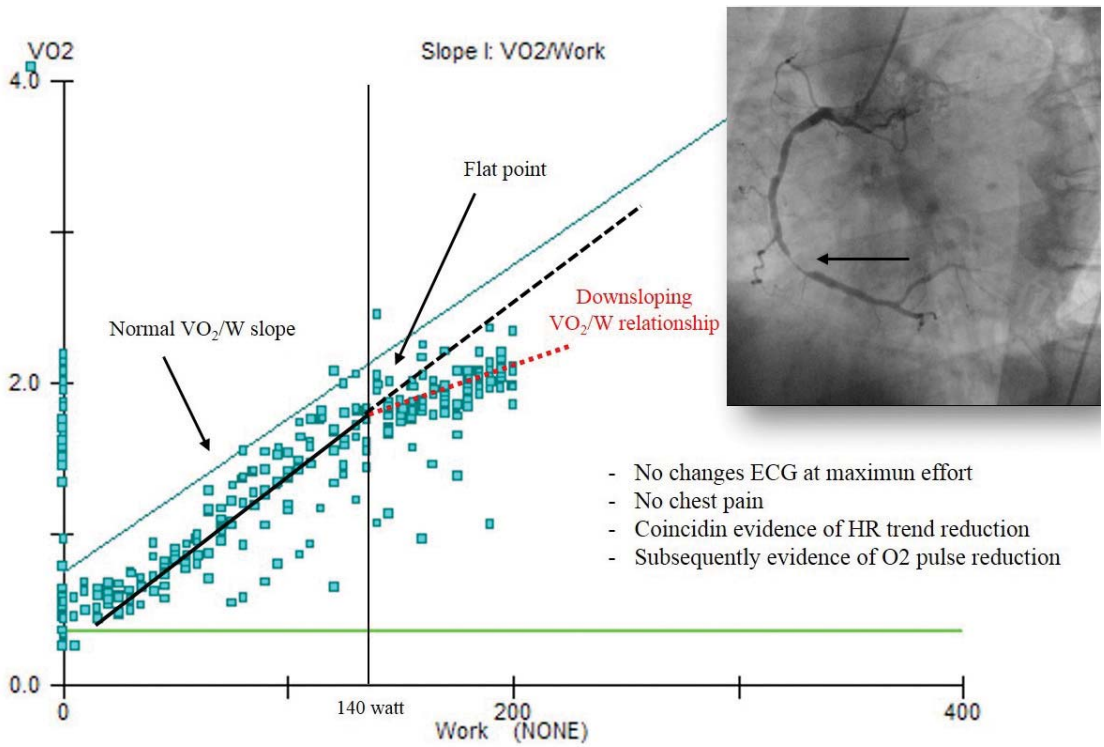

Figure 2. CPET in a patient with unexplained dyspnea and multiple cardiovascular risk factors. During CPET, no ECG changes at maximal effort and no chest pain. Reduction in heart rape and pulse oxygen and down sloping of VO2/W relation is observed in panel 3. Coronary angiogram revealed sever stenosis in the distal-right coronary artery (arrow) (Case of Dr. Pietro Palermo).

detect cardiac dysfunction using specific sets of values identifying the abnormalities in stroke volume and heart rate in this defined subset of CAD[29].

CPET determinants to detect myocardial ischemia: O_2 pulse, VO_2 slope and VO_2/Watts.

Maximal O_2 uptake (VO_{2max}) – Panel 1

In different population, age, sex, fitness exercise level, weight, height, ethnicity and genetic variability influence the average values of VO_{2max}. Depending on these factors, different equations for predicting the standard values of VO_{2max} have been determined, although the equation proposed by Wasserman and Whipp is the most used[24]. In performing exercise test, VO_2 raises at a rate of 10mL/min/W. Maximal oxygen uptake (VO_{2max}) represents the highest O_2 consumption possible to attained during an incremental exercise test as proven by the fall of VO_2 to raise linearly to increasing work rate.

Peak VO_2 – Panel 1

Peak oxygen uptake (peak VO_2) represents the highest O_2 consumption achieved during presumed maximal effort in an incremental exercise; it can equal the VO_{2max}.

As a marker of cardiovascular limitation, in a Finnish population, Khan et al. concluded that maximal O_2 uptake (peak VO_2) reduction is directly associated with non-fatal myocardial infarction and heart failure events[30]. Preserving a high peak VO_2 was demonstrated as a protective prognosis value[31].

Work rate - VO_2 to watt, (VO_2/WR) – Panel 1

Abnormal pattern, reduction or non-linear relationship of work rate in a standardized CPET represents the first signs of exercise limitation, and indices of left ventricular restraint in case of myocardial ischemia. The VO_2/Work rate presents the coupling of external to cellular respiration, graphically represented by the ability of O_2 consumption to track the workout increase. The $\Delta VO_2/\Delta W$ ratio follows a standard course along with the low workload, with a straight decline consecutive to myocardial ischemia inducing myocardial dyskinesis at the AT point. The VCO_2 progress increases abruptly as the VO_2 continues to decline[24]. There is also a documented correlation of the ECG changes at the moment or subsequently to $\Delta VO_2/\Delta W$ decrease.[16] The study of Popovic and collab. validate the $\Delta VO_2/\Delta W$ recumbent cycle-ergometer CPET as an evident additional value in the prognosis of CAD[32].

Oxygen pulse (VO_2/HR), reduce response – Panel 2

Oxygen pulse (oxygen consumption and heart rate, VO_2/HR, mL/heartbeat) and stroke volume (mL/heartbeat, blood volume ejected to the aorta during the systole) are both parameters indicator of left ventricle performance during workload. Decline or flattening of the VO_2/HR curve plotted over workload time indicate the oxygen pulse and stroke volume reduction, as a subtle indicator of myocardial ischemia induced by left ventricular dysfunction[26,33]. Chaudry et al. tested the new mathematical model DHR-WR slope, expressing the changes in HR slope in late exercise plotted to the workload, demonstrating an increased sensitivity and negligible specificity reduction of the undertreated atherosclerosis diagnosis[34].

Heart rate – Oxygen uptake (HR/VO_2) relationship – Panel 3 (V-slope in AT determination)

Progressively increase and concomitant with altering of the linearity of HR to VO_2, will be observed in the panel, in myocardial ischemia pattern[22].

CONCLUSION

CPET demonstrated the role in CAD assessment. Particular CPET parameters and panel analyse, extend possibilities of myocardial ischemia detection outside the limits of using more expensive, harmful and invasive traditional investigating procedures. In patients with suspected myocardial ischemia, CPET has a higher sensitivity, specificity, positive predictive value and negative predictive value as compared to standard ECG stress testing.

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